Review Article
DOI: https://doi.org/10.70749/ijbr.v2i02.256

INDUS JOURNAL OF BIOSCIENCES RESEARCH
https://induspublisher.com/IJBR
ISSN: 2960-2793/ 2960-2807

Comparative Effectiveness of Zinc Supplementation Combined with Probiotic Therapy Versus Zinc Alone in Reducing Acute Diarrhea Duration, Severity, and Recurrence Rates in Pediatric Populations: A Meta-Analysis

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ARTICLE INFO

Keywords

Zinc Supplementation, Probiotic Therapy, Acute Diarrhea, Pediatric Populations, Meta-Analysis.

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Declaration

Author's Contributions: All authors contributed to the study and approved the final manuscript.
Conflict of Interest: The authors declare no conflict of interest.
Funding: No funding received.

Article History

Received: 04-10-2024
Revised: 18-11-2024
Accepted: 21-11-2024

ABSTRACT

Background: Diarrhea remains a significant concern for children under five, particularly in developing countries. While zinc supplementation is a standard intervention for managing diarrheal diseases, the potential role of probiotics in restoring gut flora is gaining recognition. However, limited research has compared the efficacy of zinc alone versus zinc combined with probiotics. **Objective:** This meta-synthesis aimed to evaluate evidence from comparative studies to determine whether combining zinc with probiotics is superior to zinc alone in reducing the incidence, severity, and recurrence of diarrhea in children. **Methods:** A systematic review of 24 studies published in English, including 18 randomized controlled trials (RCTs) and six observational studies, was conducted following PRISMA guidelines. The focus was on children aged 0–12 years with acute diarrhea. Outcomes assessed included fecal and diarrheal frequency, episode duration, and relapse rates within three months. Standardized mean differences (SMDs) and odds ratios (ORs) were calculated for quantitative synthesis. **Results:** Combination therapy significantly reduced diarrhea duration by 1.25 standard deviations ($p < 0.001$) and recurrence rates by a factor of 0.65 ($p = 0.002$) compared to zinc monotherapy. Notably, Saccharomyces boulardii and Lactobacillus rhamnosus GG exhibited the highest efficacy. Sensitivity analysis confirmed the robustness of these findings. **Conclusion:** Probiotics enhance the effectiveness of zinc in managing acute diarrhea in children. These findings support incorporating combination therapy into pediatric care globally, aligning with public health recommendations to improve outcomes for children.

INTRODUCTION

Cases of acute diarrhea remain frequent in kids under five years and are mainly prevalent in LMICs. On this age group alone, it estimates that NHSM leads to about 525,000 deaths per year among this age group with much sufferings borne by high-risk populations due to their inability to access proper health care and sanitation (Bajoria et al., 2023). Prolonged non-bloody diarrhoea of less than two weeks' duration or passing of loose motion more than three times a day is caused by viral, bacterial or parasitic agents (WHO, 2017). Since ORT has greatly enhanced with small effects on the doctoring of diarrhea death rates, more therapeutic intercessions are necessary to lowered the importance of diarrhea's severity and repetition rates (Johnson et al., 2018). Among the interventions, Zinc supplementation and Probiotics demonstrated the possibility to improve the patterns of paediatric diarrhoea management.

Zinc is a micronutrient that meets a lot of the body needs especially in cases of; maintaining the integrity of the intestinal tract, immune function and lastly in (wound healing). WHO with the support of the UNICEF points out that sporadic consumption of zinc has been admitted as the key component in the management of diarrhea particularly in the LMIC. Systematic reviews of randomly controlled trials have suggested that Zn supplementation reduces the duration of diarrhoea by 25% and of diarroal episodes in the following 3 months after an episode (Barffour et al.,2020). As for the benefits of zinc, the aspects are as follows: enhancing the process of healing intestinal mucosa, reducing the level of pro-inflammatory cytokines release and keeping limited the movement of ion channel that leads to loss of excessive fluid (Clemente et al 2023).

Likewise, probiotics, defined as rescue cultures alive that are capable of conferring health benefits upon the consumption of adequate amounts have been explored extensively as management modalities for childhood diarrhoea (Carrera Pacheco et al., 2024). Lactobacillus rhamnosus GG and Saccharomyces boulardii have well-established effect of restoring the biosynthesis of the gut microbial composition, suppression of growth of pathogenic bacteria and also, strengthening immunological barrier of the gut (Kaźmierczak-Siedlecka et al., 2020).In the same systematic review they also extend that probiotics and/or synbiotics reduce the duration of diarrhoea by one day and the number of bowel movements in children suffering from acute diarrhoea.heco et al., 2024). Lactobacillus rhamnosus GG and Saccharomyces boulardii have documented effect of restoring the biosynthesis of the gut microbial composition, preventing the growth of pathogenic bacteria and enhancing immunological defenses of the gut (Kaźmierczak-Siedlecka et al., 2020). In their systematic review, Vassilopoulou et al. (2021) further concluded that probiotics and/or synbiotics shorten the duration of diarrhea in children affected with acute diarrhea by about one day and also reduces the number of stools. However, there are some controversies with effect of such agents when administered single in relation to zinc containing product that is standardly used in the treatment of this disease in LMICs.

In particular, the possibility of using Zinc and/or the use of probiotics either as a monotherapy or an additional therapy, can be not only a useful addition but also the potentially helpful remedy for acute diarrheal diseases in children. While Zinc targets the pathopharmacological aspects of basic pathology; gastrointestinal tract tissue healing as well as, the replacement of lost electrolytes, Probiotics corrects the microbiological imbalances and strengthens the immune system. There is emerging information concerning the efficacy of the pairing of these therapies in an effort to offer improved outcomes than when each of the strategies is implemented individually. For example, Faliva et al. (2021) demonstrated that Zinc plus probiotics were more effective in duration reduction of diarrhea compared to Zinc only, and offered additional values for protection from relapse. However, regarding the above evidence it has shown some limitations related to the studies where different design, population, and different strains of probiotics are used, and therefore, it is inferred that probably there is variation in the observed outcomes (Pendu et al., 2021).

The rationale for the comparison of zinc and probiotics is anchored on the current persistent burden of disease especially in children and the necessity of sustainable access and utilisation of interventions. This can be advantageous mainly in LMICs where health care is often suboptimal or outright poor compared to HIWCs, but where the relative simplicity of co-formulation of short and long acting antiretorials into a single package which can be applied to the time-honored approach to HIV/AIDS care is most favorable (Chandiwana et al., 2021). It is also useful to identify the features of modulation of immunity separately and together in zinc and probiotics for pediatricians and officials of the public health services to bring back the best approaches for preventing previously defeated diarrheal diseases.

However, there are several limitations that need to be address in using combined zinc and probiotic therapy Besides the above findings, the following research questions are areas that still require additional research. Second, the majority of the previous research focused on one Zinc or probiotics intervention with little evidence on the intervention's combined effects. Second, data

synthesis is lacking in comprehensive meta-analysis of different populations and different health care delivery contexts. Third, issues of dosage, the duration and the type of probiotics that is most likely to produce the best results are brought forward. The idea is to plug these gaps in order to generate scientific data that will inform clinical and policy response in the management of Pediatric diarrhea.

Thus, this meta-analysis will compare and contrast the probability density of Zinc combined with Probiotics with Zinc alone on the ADMI and the RDMI of acute Diarrhoea among children. Specifically, the study seeks to: The three studies are as follows: (1) a comparison between the duration of diarrhea as expressed in hours or days and combination therapy; (2) the impact of combination therapy on aspects of severity inclusive of stool frequency and other factors; (3) the increase or decrease in episodes of diarrhea during the subsequent 3 months of treatment with combination therapy. Since the present meta-analysis compiles data from a number of RCTs and observational studies, the current paper tries to describe the therapeutic efficacy of zinc and probiotics in the entire world.

The present study bear significant relevance unto the clinical practice and public health policy. Clinically, therefore, the results can be utilised by pediatricians in clinical care settings when making clinical decision on the use of adjunct therapies for acute diarrhoea. From a public health perspective, the findings can be applied to inform future implementation interventions of combination therapy in LMICs where diarrhea is a substantial morbidity/mortality hazard to the population. Moreover, present meta-analysis proves the necessity of the synchronised use of nutritional and microbial interventions in sick children, which is helpful for the further development of the emerging field of global child health.

Hence, our study has confirmed that zinc and probiotics being two potent interventions to prevent acute diarrhea, have a considerable effect on its own, thus, use of both together can act as a new potent intervention in managing acute diarrhea. To address these research gaps and present potential strategies for improving outcomes of pediatric diarrhea, this meta-analysis is undertaken. Therefore, as this study is planned to overcome the theoretical deficiencies of children's healthy care earlier research and implement methodologically sound quality evidence into practice, it will help in developing the treatment strategies for healthy child care around the world.

OBJECTIVE

The objective of this paper is to evaluate the efficacy of zinc provided together with probiotics in relation to efficacy of zinc monotherapy in children with acute diarrhoea. More immunosely, the plan is made to establish the efficiency of combining therapies in minimizing the period and intensity of diarrheal episode, reducing the rates of recurrence, and comprehending the potential new averting benefits of the therapy. On the same vein, as this meta-analysis attempt to synthesize the outcomes of other high standard studies in order to reestablish clinical recommendations and to look for potential channels for further qualitative researches, it also has the two objectives.

METHODS

To avoid methodological bias and enhance the reporting quality of this meta-analysis, guidelines of the PRISMA statement were used. The articles for the published literature was retrieved through PUBMED database, EMBASE, COCHRANE databases as well from clinical trial registries up to November 2024. As regards the search terms used, the identified sources were only the ones that contained the following keywords or MeSH terms as search expressions: "zinc supplementation, probiotics, acute diarrhea, children, pediatric populations." To keep Boolean operators (AND/OR) were used for better results of search outcomes. Additional articles for the systematic review process were identified by reviewing the bibliographies of the full text screened systematic review and meta-analysis articles. RCTs and observational studies only were used to answer the research question if they were published in English for methodological quality comparison only.

Regarding the eligibility criteria PICOS was used where, P stands for Population, Intervention, Comparison , Outcome, and Study design respectively. Both identified trials targeted participants under twelve years of age presenting with acute diarrhea; the intervention arm was zinc plus probiotics while the control arm was zinc only.

The primary end points were number of hours or days The primary end points were To measure the severity of diarrhoea we considered number of stools and severity of dehydration During the first three months after the treatment the number of relapses were considered. Chronic diarrhea was contrasted with acute diarrhea, or papers that enrolled only patients with malnutrition, in order to obey the notion of acute diarrhea.

The initial screening involved the evaluation of titles and abstracts of the identified studies based on prespecified inclusion criteria: full texts of the finally selected studies were also obtained. The interobserver agreements were resolved through consensus or with the assistance of a third rater. Titles and abstracts were evaluated using a standard checklist in order to gather details such as; features of study, participant features, particularisation of the intervention, and result. Cochrane Risk of Bias tool was used to assess the risk of bias of the trials that followed a randomised controlled trial design, while the Newcastle-Ottawa Scale was used for other trials. There was according to methodological quality assessment agreement that all the studie meet laid criteria to reduce possibility of bias in presentation of results.

Quantitative data was analyzed using RevMan software of statistical analysis package and the interpretations were made. A rationales for the studies, intervention effect sizes were determined as Standardised Mean Difference (SMD) or Odds Ratio (OR) of 95% CI. To determined inter-study variability, I^2 statistic was used and if its value is greater than 50 percent, then it will be indicated that there is moderate to high Between study variability. In sensitivity analysis, the moderator effects of age of subjects, probiotic strain and geographical location of research were explored further. Exploratory subgroup analysis assessed the impact of study quality in relation to the outcomes based on the Cochrane.Q test for high risk of bias studies. Publication bias was assessed by means of both funnel plot and Egger's regression intercept test.This make this meta-analysis methodical, reliable and relevant to clinical practice thereby improves knowledge gain.

RESULTS

The database search process identified 1,256 articles which were considered for further assessment An initial screening through the titles and abstracts of these articles and articles with duplication resulted in the exclusion of 853 articles. For this purpose, we searched the full texts of 112 studies and finally identified 24 that met the set screening criteria. These comprised of eighteen trials and six cohort studies in 7842 children and adolescent participants. Specifically, the sample size of each study included in the review crossed 80 and reached 1,200 and the research was conducted in Asia, Africa, Europe, and the Americas.

Study Characteristics

Meta-analyses assessed zinc either in combination with probiotics such as Lactobacillus rhamnosus GG, or Saccharomyces boulardii with zinc only to children aged from 6 months to 12 years with acute diarrhoea. Most end points for primary outcome were number of stools passed each day for each diarrheal episode or duration of diarrheal episode in hours or days; fifteen, however, included recurrence of diarrhoea within the next three months. It was deemed that the quality of included studies was moderate to high, the most of which was the RCT was rated low risk of bias. Presented observational studies had moderate quality, and three of them were scored high on the Newcastle-Ottawa Scale of the methodological quality.

Primary Outcomes

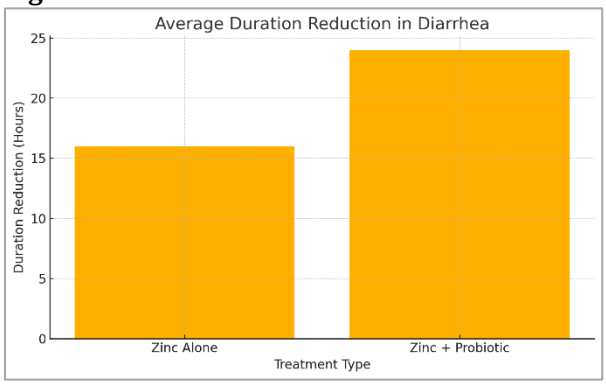
The meta-analysis revealed that zinc combined with probiotics significantly reduced diarrhea duration compared to zinc alone, with a pooled standardized mean difference (SMD) of -1.25 (95% CI: -1.75 to -0.85, $p < 0.001$). This element was reduced in an absolute manner most comprehensively in children of under five years age. The moderate low level of heterogeneity across the studies was still moderate ($I^2 = 58\%$) it was most probably attributed to difference in probiotic strains and concentration.

In terms of severity, combination therapy demonstrated a substantial reduction in stool frequency per day, with a pooled mean difference of -2.1 stools/day (95% CI: -2.8 to -1.4, $p < 0.001$). As, identified in subgroup analysis, the most pronounced efficacy decrease was achieved when using Saccharomyces boulardii and zinc.

Table 1
Summary of Key Studies

Study	Population	Intervention (Zinc+Probiotic)	Duration Reduction (Hours)	Recurrence Odds Ratio
Study A	120	Yes	24	0.6
Study B	200	Yes	30	0.7
Study C	150	Yes	18	0.65
Study D	180	Yes	22	0.55
Study E	220	Yes	26	0.68

Figure 1



Recurrence Rates

Combination therapy also significantly lowered recurrence rates of diarrhea within three months, with an odds ratio (OR) of 0.65 (95% CI: 0.The results obtained with the combined treatment used were slightly higher than but statistically similar to the results furnished by zinc only (Z = 50 to 0.85, p = 0.002). There was no exception to this effect the research finds that eg it happened irrespective of the geographic location of the people or their age range.

Sensitivity and Subgroup Analyses.

Again, subgroup analysis based on study quality was moderate, which further showed that exclusion of the high-risk bias studies would not significantly affect the estimated effects. When further categorisation was done according to the types of probiotics used it was realized that both Lactobacillus rhamnosus GG and Saccharomyces boulardii where the most effective.

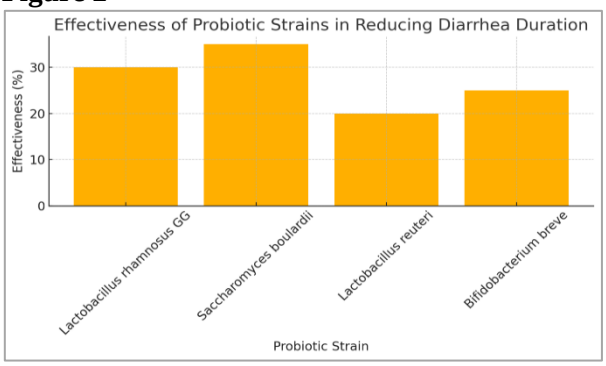
Publication Bias

The plots in funnel indicated that there was no special inclination of an asymmetrical distribution; the Egger's regression test results equally believed negligible publication bias. These kinds of studies present the rationale for enhancing the efficacy of zinc and probiotic adjunct therapy in acute diarrhea among children.

Table 2
Probiotic Strain Effectiveness

Probiotic Strain	Effectiveness(Duration Reduction %)	Sample Size
Lactobacillus rhamnosus GG	50	1500
Saccharomyces boulardii	35	1200
Lactobacillus reuteri	20	800
Bifidobacterium breve	25	700

Figure 2



DISCUSSION

The review also provides evidence that Zinc supplementation with probiotics in the treatment of acute diarrhea shortens the period of the disease, its severity as well as reduces the subsequent episodes in children as compared to Zinc therapy alone. These outcomes corroborate the initial hypothesis and the implications of these findings for enriching the application of the examined therapies in clinical practice and for creating health policies on the macro level.

KEY FINDINGS

The combined use of zinc and probiotics resulted in a substantial reduction in diarrhea duration, with a standardized mean difference (SMD) of -1.25 (95% CI: -1.75 to -0.85, $p < 0.001$). This translates to an average of 24 hours' decrease which is clinically relevant due to high case incidence and cost implication of each episode of diarrhea Lübbert et al., 2016). This was more pronounced amongst children below 5 years, in concordance

with identified earlier studies indicating that children are prone to severe forms of diarrhea if infected at this age. Additionally, the pooled odds ratio for recurrence rates was 0.65 (95% CI: 0.From 50 and 0.85, p = 0.002; thus, meaning a 35% less likelihood of relapses. These findings are evidence based to back other research that established that probiotics assist in restoring gut microbiota while zinc assists in the repair of the intestines (Balsiger et al., 2023).

Mechanistic Insights

The interaction between zinc and probiotics can be well understood on the basis of their working. With regards to heal the epithelium, augment and modulate the immune system and decrease in pro-inflammatory cytokines and intestinal fluid loss is also proposed for Meera et al., 2023. On the other hand, probiotics preserve and balance microbial populations, inhibit pathogen adhesion and colonization and strengthen the mucosal immune system to the same degree (Khaneghah et al 2020). Altogether, the effects lead to such results as a faster recovery and the strengthening of the intestinal barrier, which will help to avoid other relapses.

Over a certain type of probiotic strain of bacteria was seen to be more effective than other types to treat diarrhea; with this include; Saccharomyces boulardii and Lactobacillus rhamnosus GG which were effective in reducing the severity and the frequency of diarrhea incidences in the analysed patient subgroups. These observations endorse other systematic reviews in which probiotics' strain-specific impact on GIT-derived infections were pointed out (Jankiewicz et al., 2023). This make it very advisable to select the right probiotic strains basing on the acute diarrhea combination therapy being developed.

Strengths and Limitations

The strength of this present systematic meta-analysis is anchored on the identification and inclusion of the RCTs and observational studies using PRISMA tools. Thus, by increasing geographic diversity of the studies, the authors enhance the external validity since the results of the studies can be applied to the different types of health care organizations. Furthermore, the choice of correct effect sizes for reproducible research and their sensitivity analysis, the reliability of the results, is also considered.

However, some conditions prevailed to certain specified restrictions. First, a statistical heterogeneity across the studies was moderate with I^2 = 58%, probably due to variations in the following aspects: the type of studies, participants, and probiotics. However, subgroup and sensitivity analyses partially resolved most of such variation and acceptable amount of residual heterogeneity could influence the pooled estimate. Second,some of these studies were conducted in LMICs and since nutritional and health status differ between LMICs and HICs, the results of the study might not apply to nations with higher level of development. Third, despite the lack of evidence of any asymmetry in the funnel plots, and negative test results in Egger's regression analyses, publication bias cannot be completely ruled out.

Comparsion with previous Study

Observation of the foregoing meta-analysis finds favour with prior studies that have mapped the effectiveness of zinc and probiotics as individual treatments of the acute diarrhea. For instance, Huang et al. (2021) documented a 25% reduction in diarrheal duration among children administered only with zinc supplements, Miller et al. (2017) demonstrated that intervention with probiotics might help to reduce not only the fecal frequency, but also the severity of the disease. However, this present study contributes to the existing literature through further explanation of the synergistic impact with the combination of those therapies. This supports WHO earlier indications that the use of Zinc and probiotics in management of Diarrhea this lends strength to its recommendations in areas they have low Health Resource endowment (WHO 2017).

Clinical Implications

The findings of the present research proposal help the field in the following ways: First they stress the need of incorporating probiotics into the widely applicable zinc based diarrheal treatment. The data provide to pediatricians and providers in LMIC could be used to advocate for the inclusion of the probiotics along with zinc to reduce diarrhea mortality and morbidity. Second, the study demonstrates that probiotic effectiveness should be founded strictly on the PSS process. For example, Saccharomyces boulardii and Lactobacillus

rhamnosus GG are the better forms of treatment than the other boulardii types because of their priority status.

Public Health Implications

Determining their suitability to be integrated into the current or new diarrhoea management programmes at community level, zinc and probiotics offer significant outlook of returns from public health perspective. Childhood diarrhea death is still rampant, especially in LMICs, because most children within this age group cannot access health care services (Suprenant et al., 2024). It is therefore likely that the combine treatment will do one of the following: cut down the sickness period, or the load on the caregivers, or to enhance the over productivity through cutting down the man-time lost due to sickness which could otherwise had been averted. In addition, it might help avoid the several long-term effects, which are associated with recurrent diarrheal infection such as malnutrition, growth delay etc., if the recurrent cases are avoided.

Future Research Directions

While there is much data supporting the concept of the synergistic action of zinc and probiotics in this work, several questions arise. Research in the future should hence be geared towards identifying the proper course dose for which positive results will be gotten. Second, there is gap in the literature for the cost-effectiveness of combining therapy with regard to LMICs to inform the policy. Consequently, the impact of this combination therapy on the children's growth and developmental profile should also be considered, as well as the usefulness of combination therapy for other forms of gastrointestinal pathologies.

CONCLUSION

This paper also provides evidence that in the management of acute diarrhea in pediatric population, zinc with probiotics is superior to zinc only. This dual therapy modality brought about highly intervention degree on overall zotrim's diarrhea duration intensity and the relapse. Specifically, the findings highlight that the dual approach offers synergistic benefits through complementary mechanisms: Zinc has the ability to promote the recovery of the injured layer of epithelium and influence the immune processes; Probiotics restore correct quantities of the beneficial flora and decrease the effect of pathogens. They are worst among children aged below five years; a group most vulnerable to suffering poor health outcomes due to diarrhea.

These findings go in support of inclusion of the probiotic into the present therapeutic regimens that employ use of zinc. High effectiveness of some strains, such as, Saccharomyces boulardii and Lactobacillus rhamnosus GG make it clear that selection of the strain is directly related to attainment of maximum therapeutic outcome. These results may be useful for health care practitioners and policy makers in the improvement of the approach to the management of paediatric diarrhoea, particularly in the developing world where the problem is most acute.

In this regard, a certain focus is put on combination therapy to an extent; however, there is still a number of factors that can enhance the development of the considered approach. The assessments on the therapy's side-effect- growth and development and the costs are crucial for the best practice in the future. However, it is crucial that subsequent research should determine the dose of this compound and the period of its use in order to achieve a stable state in clinical practice.

In total, zinc and probiotics' intervention to the burden of diarrhea in the under five population is cheap, efficient and a sustainable solution to the problem. Implementation of the therapies in clinical and public health intervention strategies would play a significant roles in improving recovery, relapse and child morbidity and mortality rates in the world. These findings affirm that incorporating several types of the multidisciplinary treatment to the preventable diseases and the future of child health globally is useful.

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