

**Review article:**

**The role of zinc supplementation for diarrhoea in children: a critical review**

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**Abstract**

**Background:** Nearly 1.7 million children suffer from diarrhoea and around 760,000 die each year. The high prevalence of diarrhoea in the developing countries is closely related to lack of safe drinking water, inadequate sanitation and hygiene, and poor health and nutritional status. These environmental conditions facilitate the spread of infectious disease easily. The great morbidity and mortality of this preventable and treatable disease raise concern on how to save children from this fatal disease by improving management of diarrhoea. Several studies suggest that zinc deficiency contribute towards high morbidity and mortality in diarrhoea. Further, there is an area of uncertainty regarding how significant zinc supplementation will help to reduce the duration and severity of diarrhoea in children compared to the diarrhoea management without zinc? **Objective:** To critically analyse the current evidences of zinc supplementation in diarrhoea. **Data Sources:** Keywords searching through MEDLINE Ovid database and additional references from retrieved articles. **Study Selection:** Limited to randomized controlled trial(RCT) study design and systematic review studies which were conducted from 2006 to 2016. However, there is one prospective cohort study included as it is a follow-up of subjects who participated in the previous double-blind randomized placebo-controlled trial. **Data Synthesis:** This review involves a summary of 10 articles that have been appraised on their relevance in evaluating the role of zinc in reducing severity and duration of diarrhoea in children. Further, the literature found is synthesised through method used in the studies and the effectiveness of zinc therapy **Conclusion:** Zinc is relatively safe to be used and it can improve diarrhoea management especially in developing countries.

**Keywords:** Zinc; zinc therapy; zinc supplemental; diarrhoea; diarrheal disease; gastroenteritis, children; infant; malnutrition; developing country.

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**Overview**

Diarrhoea is the second leading cause of death among children younger than five years globally.<sup>1</sup> Although this disease is preventable and treatable, yet nearly 1.7 million children suffer from diarrhoea and around 760,000 die each year.<sup>1</sup> The causes of diarrhoea may vary, such as malabsorption syndrome, various enteropathies, lactose allergic, and infectious organisms. In children commonly it is caused by infectious organisms such as viruses, bacteria, protozoa, and helminths that are transmitted from contaminated food or drink.<sup>2,3</sup> The high prevalence of diarrhoea in the developing countries is closely related to lack of safe drinking water, inadequate sanitation and hygiene, and poor health and nutritional status.<sup>4</sup> These environmental conditions facilitate the spread

of infectious diseases easily.

Diarrhoea is defined as an increasing defecations more than three times per day and/or loosened stool consistency, and/or increased stool weight (>200 gr/day).<sup>5</sup> The main cause of diarrhoea among children worldwide is rotavirus that responsible for 40% of hospitalizations cases.<sup>2,6</sup> The primary symptoms of rotavirus infection are fever, vomiting, and non-bloody diarrhoea. Viral infection are commonly self-limited diseases, if the immune system of a child is good and supported by adequate treatment, s/he will recover without any complication. However, diarrhoea can be severe due to life-threatening dehydration, and dehydration that is caused by rotavirus is a significant cause of mortality.<sup>6</sup> The great morbidity and mortality of this preventable

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and treatable disease raise concern on how to save children from this fatal disease by improving diarrhoea management.

Meanwhile, several studies suggest that zinc deficiency contribute to the high morbidity and mortality in diarrhoea.<sup>7</sup> Studies claim that zinc can protect the intestinal mucosa and improve immune system. In diarrhoea case, loss of zinc through stool maybe as high as 159 µg/kg/day in acute diarrhoea.<sup>6,7</sup> Therefore, children who suffer from diarrhoea need zinc supplement to replace the zinc loss. Further, there is an area of uncertainty regarding how significant zinc supplementation will help to reduce the duration and severity of diarrhoea in children compared to the diarrhoea management without zinc?

### **The Current Use of Evidence-Based Practice in Diarrhoea Management**

In the late 1970s to 1990s, oral rehydration salts (ORS) and oral rehydration therapy (ORT) have been known as diarrhoea management. This recommendation have been successful in helping diarrhoea management by reducing the number of deaths due to diarrhoea.<sup>4</sup> Further, many researches have been conducted to improve diarrhoea management, and since 2004, World Health Organization (WHO) and The United Nations Children's Fund (UNICEF) have introduced the guideline of diarrhoea management for developing countries. Beside appropriate rehydration therapy, and the use of selective antibiotics, WHO-UNICEF suggest to use zinc supplementation at the dose of 10 mg in infants less than 6 months old and 20 mg in older infants daily for 10-14 days.<sup>8,9,10,11</sup> Zinc is believed could reduce the severity of diarrhoea by three mechanism, first is immune system stimulation, second is enhancement of intestinal mucosa regeneration, and the last is that zinc could perform as anti-secretory agent in the gastrointestinal tract.<sup>6,8</sup> Supplementation of zinc is likely to be a promising option in diarrhoea management. A series of studies has actually been conducted to assess the effectiveness of zinc therapy in diarrhoea. However, due to the high heterogeneity amongst the findings, the advance study is still required.<sup>10</sup>

In the last decade, WHO recommendation for diarrhoea management has been implemented in Indonesia. Adopted from WHO, a guideline that is released by Indonesian Paediatrician Association explains five comprehensive diarrhoea management that are rehydration, zinc, nutrition, selective antibiotics, and education.<sup>13</sup> Zinc supplementation is used as adjunct therapy in acute diarrhoea.<sup>14</sup> Meanwhile, in the most cases, zinc has not been used

to treat diarrhoea as its effects are still questionably by some clinicians.<sup>11</sup> They argue that high zinc intakes inhibits other micronutrients (iron and calcium) absorption that may lead to unintended impact of children's health and development. Apparently, not all developing countries have applied the current guideline from WHO. Moreover, research findings regarding the benefits of zinc are also diverse. It is obvious that even though there is an evidence-based recommendation from internationally well-respected health organisation, the role of zinc in diarrhoea management is still arguable amongst health practitioners and researchers.

### **Literatures Synthesis**

This review involves a summary of 10 articles that have been appraised on their relevance to evaluate the role of zinc in reducing severity and duration of diarrhoea in children. There are 2 systematic reviews, 2 systematic reviews with meta-analysis, 5 randomised clinical trials, and 1 prospective cohort study. The search terms used were 'children', 'infants', 'zinc therapy', 'zinc supplemental', 'diarrhoea', and 'gastroenteritis'. Further, the literature found was synthesised through method used in the studies and the effectiveness of zinc therapy.

### **Method Used in the Studies**

Among 10 articles, 8 articles found that zinc is beneficial to reduce the duration and severity of diarrhoea in children.<sup>15,17</sup> While, the other two did not find any significant effects of zinc in the diarrhoea management. The latest systematic review conducted by Galvao et al (2013) used comprehensive search strategy by gathering both published and unpublished studies. The search strategy used by Galvao et al (2013) is also not limited only in specific language (i.e English) which can be the strength of the study. Another systematic review conducted by Lamberti et al (2013) even included a large proportion of Chinese studies (89 studies out of 104 papers of zinc therapy) as China experiences a significant portion of the global burden of diarrhoea. This large proportion of Chinese studies could be the positive value to Lamberti et al (2013) study. It will enrich and widely encompass the findings so that the result is expected to represent the true picture of zinc effects in many developing countries. However, several limitations in Galvao et al (2013) study have been found such as unclear allocation concealment in almost 50% studies and high heterogeneity in duration of diarrhoea that may lead to bias. Heterogeneity is found in almost all systematic reviews and meta-analysis. High heterogeneity is also occur in Lukacik,

## Literature Summary Table:

No.	Author/ Title	Aim	Method	Sample	Key Findings	Limitations
1	Galvao et al. 2013	To update the available evidence on zinc efficacy for treating acute diarrhoea in children and to investigate the effect of zinc supplementation on malnourished children	Systematic review	18 randomised control studies as samples	Oral zinc supplementation significantly decreases diarrhoea duration and has a greater effect on malnourished children. The broad data sources and no language restriction in search strategy are the strengths of the study.	The limitation of this study is that almost 50% of the studies were unclear for allocation concealment
2	Bhandari et al. 2008	to evaluate the effectiveness of education and provision of zinc supplements to caregivers in the treatment of acute diarrhoea and whether this strategy adversely affects the use of oral rehydration salts	cluster randomized trial	six clusters of 30,000 people each located in India	This study found that diarrhoea is more effectively treated when caregivers receive education on zinc supplementation and have access to oral rehydration salts and zinc	The confounding factors had not been analysed. i.e., the engagement of private health providers in this trial may influence the result. If the private providers were not engaged in giving access to zinc and ORS, the effect may be less than was observed in this trial.
3	Lukacik, Thomas & Aranda. 2008	to examine the efficacy and safety of oral zinc therapy during recovery from acute or persistent diarrhoea	meta-analysis	22 randomized control trials studies	This study reported that zinc supplementation reduces the duration and severity both acute and persistent diarrhoea	There were five RCT studies were not double-blind (either clinicians or patients know the intervention given) that may lead to bias. It should also be considered that the heterogeneity ( $I^2 = 84.3\%$ ) of this meta-analysis is statistically significant.
4	Karamyyar et al. 2013	to compare the severity and duration of diarrhoea between patients with acute diarrhoea who received zinc plus oral rehydration solution (ORS) and those who received only ORS	double-blind randomized clinical trial	379 samples of children aged 9 months to 5 years old	There is beneficial effects of zinc treatment on disease duration and severity in children with acute diarrhoea and moderate dehydration in Iran.	The baseline characteristic were not clearly described. This may lead to minor bias.
5	Patel et al. 2010	to assess the therapeutic benefits of zinc supplementation in diarrhoea management and to examine the causes of any heterogeneity of response to zinc supplementation	systematic review	There were 26 studies of acute diarrhoea and 6 studies of persistent diarrhoea	This study suggest that zinc supplementation reduced the mean duration of acute diarrhoea by 20%, and persistent diarrhoea by 15-30%, but there is no significant effect on stool output	The limitation of this study is that multivariate meta-regression analyses cannot be conducted due to only few studies reported information of the predictor variables simultaneously. Thus, important factors were unknown in the multivariate context.
6	Crisinel et al. 2015	to analyse the effectiveness of zinc treatment in paediatric population of a high-income country (Switzerland).	double-blind randomized clinical trial	148 children aged 2 months to 5 years suffer from acute diarrhoea	This research claims that zinc treatment decreases the frequency and severity of diarrhoea in children living in Switzerland	There are several weaknesses found in this research, such as the large number of patients lost to follow-up (40%); lack of compliance from patients and parents to administer the treatment given; and insufficient of sample (the goal was 200 patients).
7	Lamberti et al. 2013	to combine evidence across regions to generate global estimates of the effect of oral zinc supplementation on children with acute diarrhoea.	systematic review and meta-analysis	There were 104 papers included in the study including 15 non-chinese countries and 89 chinese	This study confirm and highlight the benefits of zinc supplementation for diarrhoea among children under five years of age in low- and middle-income countries. Zinc treatment reduces the duration, stool output, and length of hospitalization.	Lack of placebo-controlled groups in Chinese studies and various zinc dose may lead to minor bias.
8	Patel et al. 2009	to evaluate the efficacy of zinc and copper supplementation to children with acute watery or bloody diarrhoea.	double-blind randomized controlled clinical trial	There were 808 children aged 6 months to 59 months involved randomly in the trial in India	there is no significant different in duration and stool output between supplemented and placebo groups	There is 11% of patients lost to follow-up that may lead to minor bias.
9	Boran et al. 2006	to evaluate the effect of daily zinc supplementation for 14 days on diarrhoea duration, severity, and morbidity in children	randomized open-label non-placebo control trial	There were 280 of children randomly assigned to zinc and control groups	there is no significant effect in severity and duration of diarrhoea between zinc and control groups	The limitation of this study beside open-label trial, the baseline characteristics were less similar.
10	Roy et al. 2007	to explore whether supplementation of zinc to children during persistent diarrhoea has any subsequent effect on morbidity and growth	prospective follow-up study	190 samples of children aged 3 to 24 months who participated earlier in a double-blind randomized placebo-controlled trial	Supplementation of zinc to children during persistent diarrhoea reduce subsequent diarrhoea episodes and their duration in all children and overcoming growth faltering among underweight children.	Recall method used to obtain morbidity data from the mother is less valid.

Thomas & Aranda (2008) meta-analysis study, there are 5 out of 16 acute diarrhoea studies and 2 of 5 persistent diarrhoea studies found no statistically significant differences of duration between zinc and placebo. Meanwhile, there were significant degree of heterogeneity in effect sizes in all five systematic reviews and meta-analysis studies about zinc effects in Patel et al (2010) study. Therefore, it may impact to the reliability of zinc therapy assessment.<sup>18</sup>

Four randomised control trials and one prospective cohort study agree that zinc is effective in reducing the duration and severity of diarrhoea in children. Four studies were conducted in developing countries such as Bangladesh, India, and Iran, where zinc supplementation is recommended by WHO-UNICEF. The research findings about zinc effects in these countries certainly support WHO-UNICEF recommendation of zinc supplementation for children with diarrhoea. Karamyyar et al (2013) study found that zinc is beneficial to reduce the frequency and duration of diarrhoea. The distinctive method of this study is that they excluded all probable infectious diarrhoea cases and only children with watery diarrhoea and moderate dehydration were enrolled in this study.<sup>16</sup> It is important to consider dehydration level (mild, moderate, and severe) as it is a crucial factor to determine the outcomes of the disease. Meanwhile, there is study conducted in Switzerland to assess the effectiveness of zinc in diarrhoea management in developed country. Although the result indicate that zinc has beneficial effects, however the limitation of this study such as the small number of sample, the 40% lost to follow-up and the compliance issue should be considered as bias and validity issue.<sup>8</sup>

On the contrary, Patel et al (2009) and Boran et al (2006) studies argue the benefits of zinc in diarrhoea management. A double-blind RCT conducted by Patel et al (2009) in India shows that there is no significant effects of zinc in diarrhoea management ( $P= 0.64$ ). In this study, there is 11% of patients lost to follow-up that may lead to minor bias but still acceptable to be valid. However, it should be noted that this study used lower dose of zinc than WHO recommendation. Instead of using fixed dose 20 mg, they used 13.9 mg zinc per day. This will impact to the failure of achieving therapeutic dose. Similarly, Boran et al (2006) study in Turkey shows that there is no improvement in duration and severity after supplementing children in 14 days as recommended by WHO. Nevertheless, this study used open-label trial that may weaken the accuracy of the result. Additionally, the baseline characteristic

of the subjects were less similar that may lead to bias. Inconsistency of evidences regarding zinc supplementation for diarrhoea management may be derived from various aetiologies of diarrhoea, disease severity, treatment options (tablets, syrup, and dosage), different age groups, study populations, study designs (field based or hospital based), comorbidity factors, monitoring methods, and outcomes measured.<sup>19</sup> These may affect the observed outcomes of zinc supplementation studies. In *in vivo* study, zinc has less impact on rotavirus and *Escherichia coli* heat-stable enterotoxin but it has beneficial effect on enteropathogenic *E. coli*.<sup>20</sup> Meanwhile, the most common causes of diarrhoea is rotavirus (40% hospitalisations cases). Hence, a complete examination of causative infectious agents should be included at baseline of study. Identification of specific organisms in developing countries is a dilemma situation and complicated due to lack of access to laboratory test.<sup>9</sup>

#### **The Effectiveness of Zinc Supplementation**

Zinc is one of the most important micronutrients in human body that play in protein synthesis, cell growth and differentiation. It plays an important role in accelerating water and electrolytes flow in the intestinal. Zinc could also increase the number of enterocyte brush border enzymes in intestinal.<sup>10,11,16</sup> The benefits of zinc supplementation to malnourished children who suffered from persistent diarrhoea in Bangladesh has been clarified by Roy et al (2007) in their study. This result confirmed the community-based study in India by Bhandari et al (2008), where communities who received zinc education and zinc provision have significantly better outcomes. In Iran, Karamyyar et al (2013) state that the addition of zinc supplements to routine ORS is associated with more favourable clinical and economic outcomes.<sup>16</sup> The dose of zinc they used is based on the weight of children (1 mg/kg/day), thus it is expected to be more accurate than fixed dose given to children. However, it is imperative to be concerned regarding the precise beneficial dose for children since zinc may also has negative effects to human body. Zinc supplementation alone may augment the deficiencies of other minerals and inhibits phagocytic and fungicidal activity in malnourished infants.<sup>14</sup> Another awareness is that the mental development index scores of a zinc treated group were slightly lower than those of placebo group.<sup>14</sup> Despite its benefits to diarrhoea management proven in many studies, there are several drawbacks that should be considered regarding the uncertainty of the long-term effects of zinc. Thus, advance

research should be undertaken both in developed and developing countries through high quality study.

### **Comparing the Studies**

The result from this review show that zinc supplementation can improve diarrhoea management. All four systematic reviews state that zinc can reduce the duration and severity of diarrhoea in children. The quality of those studies and its level of evidence are generally high. It can be seen from the methodology and appropriate study design. Almost all studies in this review had large sample studies and large number of subjects/participants that can also be the strength of these studies. Additionally, all systematic reviews which are analysed in this paper provide consistent finding regarding the beneficial of zinc therapy. A good point from systematic reviews is that there is no limitation of language and publication status (both published and unpublished paper are included) in search strategies so that the possibility of undetected studies is slight. However, the high heterogeneity in systematic reviews still the main limitation. This is due to the diversity of the diarrhoea duration.<sup>6</sup> The strengths of the two studies that oppose WHO recommendation are the large sample they used, and small number of patients lost to follow-up. While, their limitations are the lower dose of zinc used in the study; the open-label trial and unequal baseline characteristics.<sup>14,19</sup>

### **Rationale for Decision Making**

The majority of studies show that zinc play significant role in children with acute diarrhoea by accelerate intestinal mucosa regeneration and help electrolytes transport.<sup>8,19</sup> Related to the area of uncertainty, evidences show that zinc is significantly beneficial in children with acute diarrhoea. However, there are several considerations regarding the recommendation of zinc usage as adjunct therapy in diarrhoea. First, there is an urgency to establish the optimal dosage and appropriate indication whether all types of diarrhoea should receive zinc treatment or particular types only (non-rotavirus caused diarrhoea).<sup>11</sup>

Second, further research in other developing country (i.e. Indonesia) is required to assess the effectiveness of zinc. Indonesia has different climate and environment that may turn to different aetiology (i.e. more variation of organisms as well as its virulence). Third, further research regarding zinc interaction with other antibiotics or vitamins is needed to assess whether it will impede or promote them. Fourth, it should also be considered regarding the long effects of daily zinc usage particularly in children growth and development. Fifth, there should be an advanced study investigating zinc effects on diarrhoea caused by rotavirus since rotavirus is responsible for 40% of inpatient diarrhoea cases, while the beneficial effects of zinc to rotavirus has not been proven yet. In conclusion, zinc is relatively safe to be used and it can improve diarrhoea management especially in developing countries. It should also be highlighted that zinc is not the only assurance in diarrhoea management. Comprehensive management in diarrhoea is absolute to achieve better outcomes. Comprehensive management consist of provision of safe drinking water, healthy sanitation, good nutritional status, adequate public education, sufficient rehydration, selective antibiotics, and zinc supplemental. A standard guideline from WHO-UNICEF should be followed as it is an evidence-based recommendation at this moment. However, further research should be conducted particularly on zinc usage in other developing country; zinc interaction with antibiotics or vitamins; and the effectiveness of zinc in diarrhoea caused by rotavirus. These may improve the management of diarrhoea in children.

### **Conflict of interest**

We declare none of conflict of interest in this research

### **Authors' Contribution:**

Data gathering and idea owner of this study, study design, data gathering, writing and submitting manuscript & editing and approval of final draft all have done by Wulandari Berliani Putri

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