

Meta-Analysis: The Effectiveness of Zinc on Diarrhea and Pneumonia in Children Under Five

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ABSTRACT

Background: Diarrhea and pneumonia together account for 29% of all child deaths globally, resulting in the deaths of more than two million children each year. Zinc deficiency is associated with decreased immunity and an increase in serious infectious diseases. Zinc deficiency is likely to be a major cause of increased mortality of malnourished infants in developing countries. Numerous studies have shown that zinc supplementation reduces the duration and severity of diarrhea. In addition, zinc administration can also prevent pneumonia, and is effective in recovering fever, shortness of breath and respiratory rate. This study aims to analyze the effectiveness of zinc on the incidence of diarrhea and pneumonia in children under five.

Subjects and Method: This research is a systematic review and meta-analysis conducted with PRISMA flow diagram. Article searches through journal databases include: PubMed, Science Direct, and Google Scholar. The keywords used were (“Zinc” OR “Diarrhea”) AND (“Zinc” OR “Pneumonia”) AND “randomized controlled trial”. Inclusion criteria were full paper articles with Randomized Controlled

Trial (RCT) research methods, the relationship measure used was Mean SD and Odds Ratio, the intervention given was zinc, research subjects had an age range of 0-6 years. Eligible articles were analyzed using the Revman5.3 application.

Results: Meta-analysis of 14 articles showed that zinc administration reduced diarrhea duration 0.73 days statistically significantly (MD= -0.73; 95% CI-1.22 to -0.24, p<0.003, zinc administration reduced pneumonia duration 0.58 days more rapidly and significantly statistically not significant (MD -0.58; 95% CI-0.32 to -1.04, p<0.001) than placebo.

Conclusion: Zinc is effective in reducing the duration of diarrhea and treating pneumonia in children under five.

Keywords: Zinc, Diarrhea, Pneumonia, Meta-analysis

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BACKGROUND

Diarrhea and pneumonia together account for 29% of all child deaths globally, resulting in the deaths of more than two million children each year (WHO, 2017). Deaths from diarrhea occur among children less

than 2 years of age living in South Asia and Sub-Saharan Africa (UNICEF, 2018) and pneumonia is the leading cause of death in children under five worldwide with an estimated 1.6 million deaths per year (WHO, 2018). 2017).

Diarrhea is a change in bowel habits, indicated by an increase in the frequency (defecation more than 3 times a day) marked by changes in stool from solid to liquid. In addition, this disease also depletes fluids and electrolytes in the body through the liquid stool. If the fluid is not replaced immediately, the patient with diarrhea will become dehydrated. Severe dehydration can cause death (Lukacid et al, 2018).

Pneumonia is a form of acute respiratory infection that attacks the lungs. The lungs are made up of tiny sacs called alveoli, which fill with air when a healthy person breathes. When a person has pneumonia, the alveoli are filled with pus and fluid, which causes pain when breathing and limits oxygen intake (Kliegmanetal, 2011).

Zinc deficiency is associated with decreased immunity and an increase in serious infectious diseases. Zinc deficiency is likely to be the main cause of increased mortality of malnourished infants in developing countries, zinc deficiency results in serious health impacts including a weakened immune system as a result of which there is an increase in the prevalence of infectious diseases in children (Bhuta, 1997).

The gluconad and sulfate/acetate-soluble zinc salts are used as supplements in tablet or syrup form to prevent zinc deficiency and to treat diarrhea in children (Wegmuller et al, 2014), zinc administration has been investigated as a tool for treatment and prevention from pneumonia (Marni, 2014).

Based on the high mortality rate due to diarrhea and pneumonia that occurs and the need for appropriate treatment, the researchers are interested in studying the effectiveness of zinc on the incidence of diarrhea and pneumonia. Researchers will conduct a systematic review and meta-analysis on the effectiveness of zinc on the

incidence of diarrhea and pneumonia in children under five.

SUBJECTS AND METHOD

1. Study Design

The study design used in this study was a systematic review and meta-analysis, using the PRISMA diagram flow guidelines. Article searches were carried out using a journal database which included: PubMed, Science Direct, and Google Scholar by selecting articles published in 1998-1998. The keywords used were (“Zinc” OR “Diarrhea”) AND (“Zinc” OR “Pneumonia”) AND (“Zinc OR “Randomized Controlled Trial”). The inclusion criteria were full paper articles using the Randomized Controlled Trial (RCT) research method. The study design used in this study was a systematic review and meta-analysis, using the PRISMA diagram flow guidelines. Article searches were carried out using a journal database which included: PubMed, Science Direct, and Google Scholar by selecting articles published in 1998-1998. The keywords used were (“Zinc” OR “Diarrhea”) AND (“Zinc” OR “Pneumonia”) AND (“Zinc OR “Randomized Controlled Trial”). The inclusion criteria were full paper articles using the Randomized Controlled Trial (RCT) research method.

2. Inclusion Criteria

In this study, the inclusion criteria were full paper articles with Randomized Controlled Trial (RCT) research methods, the size of the relationship used with Mean SD (diarrhea), Odds Ratio (pneumonia) the intervention given was zinc, research subjects had an age range of 0- 6 years.

3. Exclusion Criteria

Exclusion criteria in this study included articles published other than in English, cross-sectional studies, case control (case control), quasi-experimental, research subjects were children > 72 months, therapy

was given zinc or other supplements (vitamin A, probiotics), non-placebo comparison group.

4. Operational Definition of Variable

In formulating research problems here using PICO. Population is children aged 0-6 years. Intervention is zinc, with comparison that is placebo and outcomes are diarrhea and pneumonia.

Zinc is an important micronutrient in humans and has been shown to be important for the immune system. Zinc deficiency causes serious health impacts, including a weakened immune system as a result of which there is an increase in the prevalence of infectious diseases in children. Insufficient zinc consumption will interfere with overall immune function and resistance to infection due to suppression of thymus function, T lymphocyte development, lymphoproliferation, and T cell dependent B cell function (Bhuta, 1997).

Diarrhea is a change in bowel habits, indicated by an increase in the frequency of changes in stool from solid to liquid. In addition, this disease also depletes fluids and electrolytes in the body through the liquid stool (Lukacid et al, 2018).

Pneumonia is a form of acute respiratory infection that attacks the lungs. The lungs are made up of tiny sacs called alveoli, which fill with air when a healthy person breathes. When a person has pneumonia, the alveoli are filled with pus and fluid, which causes pain when breathing and limits oxygen intake (Kliegmanetal, 2011).

5. Instruments

The instrument used in this study was a published article that tested the effectiveness of the use of zinc with a placebo on the incidence of diarrhea in children.

6. Data Analysis

Data analysis in this study used the Review Manager application (RevMan 5.3). Data were analyzed based on variations between studies by determining the use of random effects analysis models. In this study, I^2 was used to quantify the dispersion. The results of data analysis are in the form of the effect size value of the heterogeneity of the study which later the results of the analyzed data are interpreted in the form of forest plots and funnel plots.

RESULTS

Research from primary studies related to the effectiveness of zinc on the incidence of diarrhea and pneumonia in children under five, there were 9 articles (diarrhea) with a total sample of 1,012 participants for the intervention and 999 participants for comparison, 5 articles (pneumonia) with 1,852 participants for the intervention and 1,879 participants for comparison. Articles were obtained from 3 continents, namely, 11 studies from the Asian continent, 1 study on the African continent, and 2 studies on the South American continent. Outcomes for some of the articles mentioned that there was a reduction in the duration of diarrhea and faster recovery in pneumonia after zinc intervention was given.

The article search was carried out using a database based on the PRISMA flow diagram, which can be seen in Figure 1. The study quality assessment was carried out qualitatively and quantitatively. After assessing the quality of the study, a total of 14 articles included in the quantitative synthesis process of the meta-analysis were analyzed using RevMan 5.3.

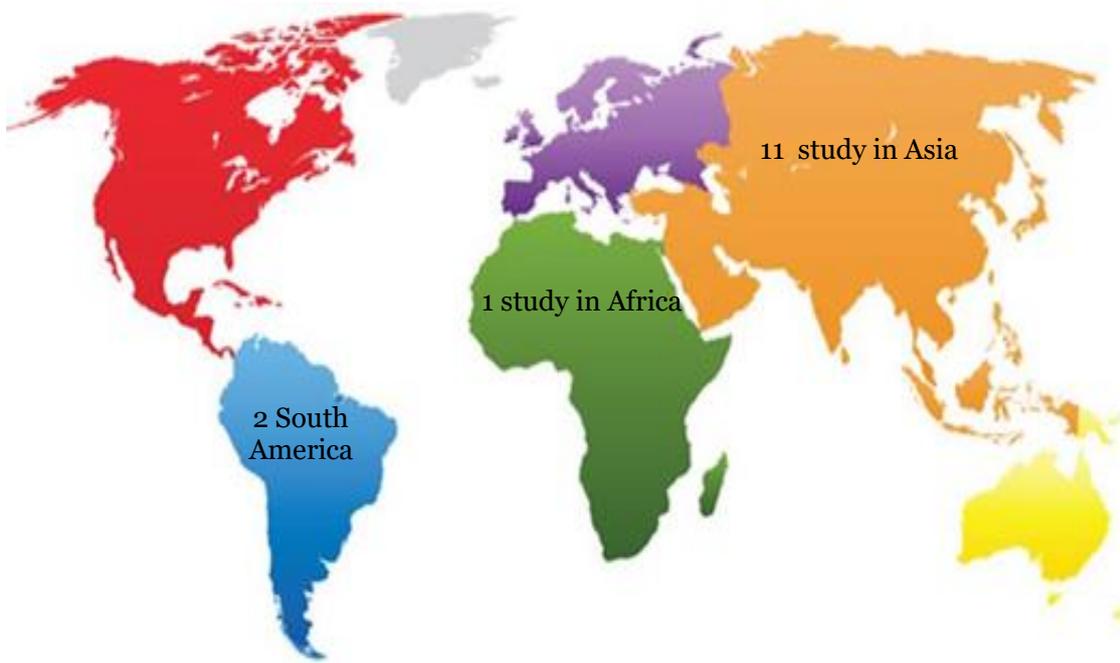


Figure 1. Map of the study area

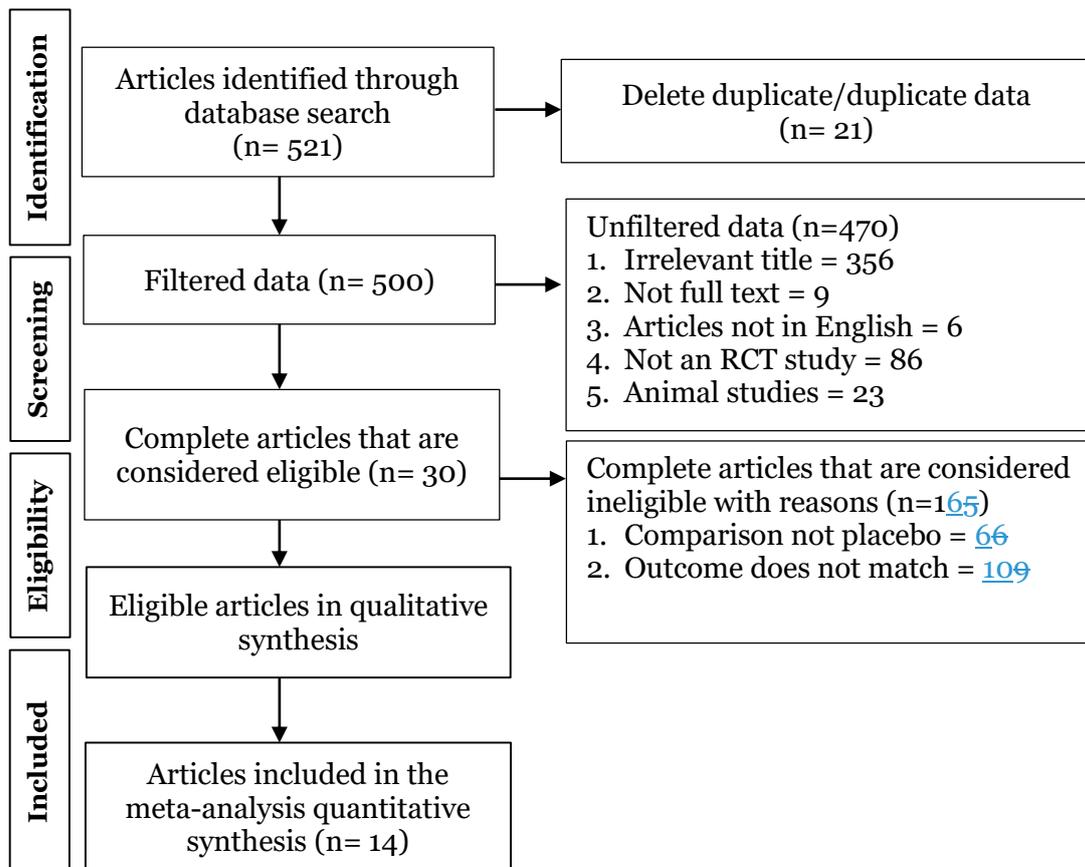


Figure 1. PRISMA flow diagram

Forest Plot

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 based on the analysis of 9 articles on the duration of diarrhea on the use of zinc and placebo reported that zinc administration is one way to reduce the duration of diarrhea in children. Based on the results of the analysis, there was a high heterogeneity between experiments ($I^2=95\%$; $p<0.003$) so the Random Effects Model (REM) was used. Zinc administration was able to reduce the duration of diarrhea 0.73 days faster than placebo, statistically

significant (MD= -0.73: 95% CI= -1.22 to -0.24).

Funnel Plot

A funnel plot is a plot that represents the approximate size of the effect of each study on the estimate of its accuracy, which is usually the standard error. Figure 3 funnel plots the effectiveness of zinc on the incidence of diarrhea, the plots on the right and left are not symmetrical to each other to form the best funnel, indicating that in this study there was a publication bias of research, which overestimated the effect of zinc.

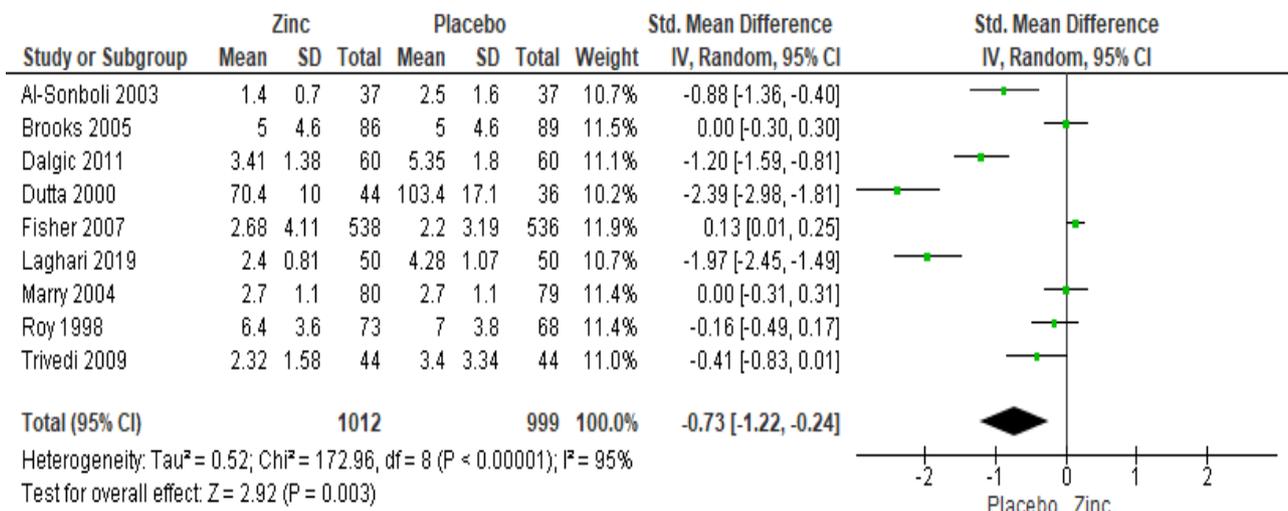


Figure 2. Forest plot of zinc on the incidence of diarrhea

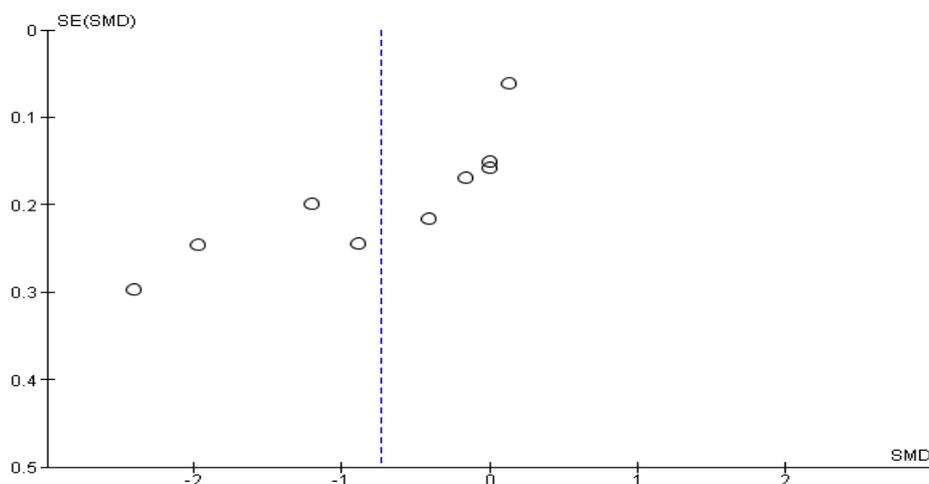


Figure 3. Funnel plot of zinc on the incidence of diarrhea

Forest Plot

Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 based on the analysis of 5 articles regarding the duration of pneumonia on the use of zinc and placebo reported that zinc administration is one way to reduce the duration of pneumonia in children. Based on the results of the analysis, there was a high heterogeneity between experiments ($I^2= 92\%$; $p<0.001$) so the Random Effects Model (REM) was used. Zinc administration was able to reduce the duration of diarrhea 0.58

faster than placebo, statistically not significant (MD -0.58; 95% CI -0.32 to -1.04).

Funnel plot

A funnel plot is a plot that represents the approximate size of the effect of each study on the estimate of its accuracy, which is usually the standard error. Figure 3 funnel plot funnel plot the effectiveness of zinc on the incidence of pneumonia, the plots on the right and left sides are symmetrical to each other and form the best funnel, indicating that in this study there was no publication bias.

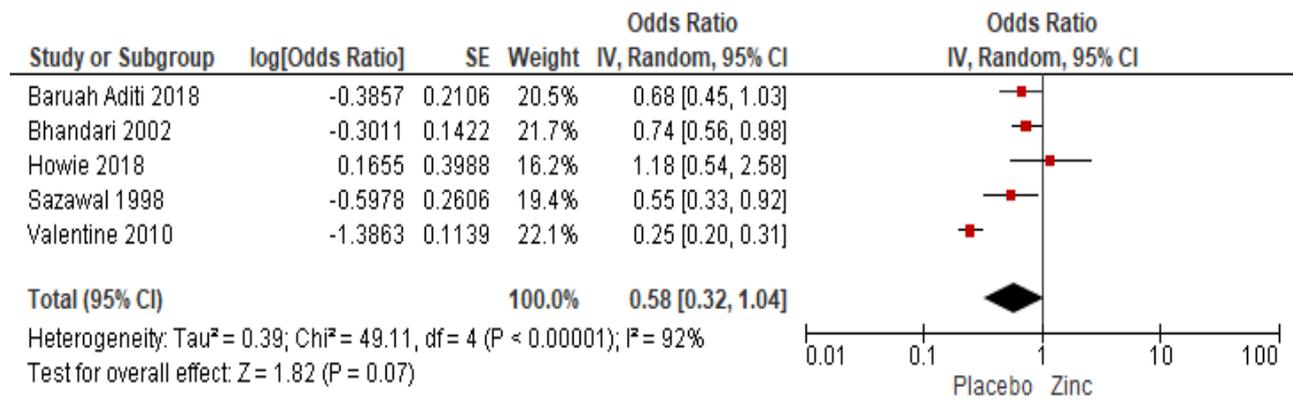


Figure 2. Forest plot of zinc on the incidence of pneumonia

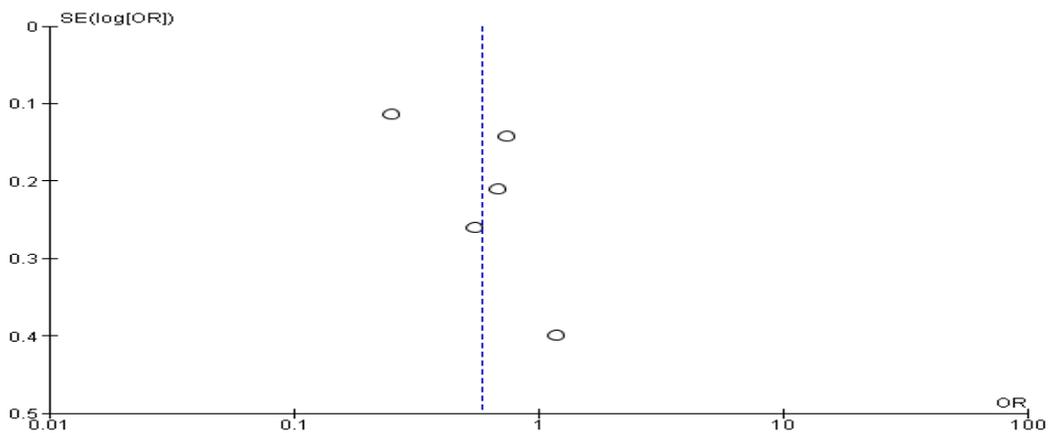


Figure 3. Funnel plot of zinc on the incidence of pneumonia

RESULTS

Diarrhea is the second leading cause of death for children under the age of five worldwide. In developing countries, children under five experience an average of three

episodes of diarrhea each year. Each episode of diarrhea deprives children of the nutrients necessary for growth and development. Zinc supplementation (10-20 mg per day until diarrhea stops) significantly

reduces the severity and duration of diarrhea in children younger than 5 years. Additional studies have shown that supplementation with zinc (10-20 mg per day for 10 to 14 days) reduces the duration of diarrhea by 25% and reduces stool volume by 30% (WHO, 2017).

Pneumonia is inflammation of the lungs caused by viruses, bacteria or other microorganisms, giving zinc 20 mg/day in children can prevent pneumonia in children. Pneumonia is the leading cause of death in children under five worldwide with an estimated 1.6 million deaths per year. More than 99% of pneumonia deaths occur in low- and middle-income countries. South Asia and sub-Saharan Africa have more than half the number of pneumonia cases among children under five worldwide (WHO, 2013).

Zinc supplementation in children in developing countries is associated with marked reductions in diarrhea and pneumonia. Zinc is an important micronutrient in humans and has been shown to be important for the immune system, many children, especially in developing countries, are zinc deficient (Bhuta, 1997).

In this systematic review, there were 14 articles of intervention studies identified worldwide from 1998 to 2019. This study analyzed articles using the Mean, SD (diarrhea) and Odds Ratio (pneumonia) measures. The results of the systematic review and meta-analysis are presented in the form of forest plots and funnel plots. 11 research articles with randomized controlled trials study design as a source of meta-analysis of the effectiveness of zinc on the incidence of diarrhea and pneumonia

The forest plot results showed that zinc was able to reduce the duration of diarrhea 0.73 days faster than placebo, statistically significant (MD= -0.73; 95% CI-1.22 to -0.24, $p < 0.003$).

The results of this study are in line with Yoga (2006) which states that the use of zinc as a medicine in diarrhea is based on scientific reasons that zinc has an effect on the immune function of the gastrointestinal tract and affects the function of the structure of the gastrointestinal tract and accelerates the epithelial healing process during diarrhea. Zinc has been known to play a role in metallo enzymes, polyribosomes, cell membranes, cell function, where this will stimulate cell growth and improve cell function in the immune system. It should also be noted that during diarrhea, zinc is lost along with diarrhea, so this can spur zinc deficiency in the body.

This study is also in line with Artana (2005) which states that the effect of giving zinc to patients with acute diarrhea is shortening the duration of diarrhea. This is probably because zinc accelerates regeneration and improves the function of the intestinal villi, so that it will affect the formation of disaccharide enzymes, namely lactase, sucrose, and maltase, in addition zinc also affects the transport of Na and glucose, and enhances the immune response that leads to the clearance of pathogens from the intestine so that zinc can affect the healing process.

Brown (1998) showed that the zinc required from supplementary food is different from the zinc that is fulfilled daily (estimated 2.8 mg/day for ages 6-24 months) and the intake of zinc from breast milk, from this analysis. They suggest zinc supplementation or zinc fortification during infancy because infants and children in developing countries are unlikely to meet their zinc requirements from food.

The forest plot results showed that zinc reduced pneumonia duration 0.58 days faster than placebo, statistically not significant (MD= -0.58; 95% CI= -0.32 to -1.04; $p < 0.001$).

The results of this study are in line with research conducted by Qasemzadeh et al. (2014) which states that zinc can accelerate recovery from pneumonia and quickly overcome symptoms in children suffering from this disease. Overall, the use of zinc along with antibiotic therapy is recommended in this group of children. Zinc therapy can also reduce drug resistance caused by various antibiotic therapies. Therefore, to improve the clinical course and duration of symptoms, it is recommended to give zinc supplementation to children suspected of having respiratory symptoms when they arrive at the hospital.

In line with this, Brooks et al. (2005) argue that treatment with 20 mg zinc per day accelerates the recovery of severe pneumonia in children. Giving zinc supplements will reduce 45% of the incidence of acute lower respiratory tract infections in children.

Aggarwal et al. (2007) confirmed that daily and weekly oral zinc supplementation routinely for three months significantly reduced the incidence of acute lower respiratory tract infections. To examine the effect of zinc supplementation on the outcome of childhood pneumonia, in our study the cure rate for pneumonia was determined by calculating the time of fever, shortness of breath, improvement of respiratory rate back to normal, cough during hospitalization, and length of stay.

FUNDING AND SPONSORSHIP

This study is self-funded.

AUTHOR CONTRIBUTION

Anastasia Dwi Anggraeni is the main researcher who selects the topic, searches and collects research data. Bhisma Murti and Yulia Lanti Retno Dewi analyzed data and reviewed research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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