

## Meta-Analysis: Effect of Probiotics on the Frequency and Duration of Diarrhea in Children Under Five

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### ABSTRACT

**Background:** Digestive tract disease is still a health problem around the world, currently there are 2,544,084 cases of diarrhea in Indonesia in 2016. In the Central Java region, there are an estimated of 911,901 cases of diarrhea, while 95,635 cases of diarrhea have been handled. This study aims to estimate the magnitude of the effect of probiotics on the frequency and duration of diarrhea among toddler based on the results of a number of similar previous studies.

**Subjects and Method:** This study was a systematic study and meta-analysis, with PICO as follows: Population= children under five. Intervention= Probiotics. Comparison= Not Probiotic. Outcome= Frequency and Duration of Diarrhea in toddlers. The articles used in this study were obtained from several databases including PubMed, Springer Link, Cochrane Database, Hindawi, Elsevier, JBBA, LWW, Google Scholar. The keywords for searching articles are as follows: "Probiotic", OR "frequency", OR "diarrhea", "kid", OR child "AND" Randomized Controlled Trial (RCT). The articles included in this study were full text

articles with a randomized controlled trial study design. Articles were collected using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.

**Results:** A total of 12 articles reviewed in this meta-analysis study originated from India, Canada, Indonesia, America, Iran. Studies showed that the effect of probiotics decreased the frequency (Standardized mean difference - 0.32; 95% CI= -0.67 to 0.03 p= 0.070). The effect of probiotics reduced the duration of diarrhea in children under five (Standardized mean difference= -0.74; 95% CI= -1.60 to 0.12 p= 0.090).

**Conclusion:** Probiotics reduced the frequency and duration of diarrhea in toddlers.

**Keywords:** Probiotics, Frequency, Diarrhea, Toddlers

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### BACKGROUND

Diarrheal disease is one of the health problems with a high degree of morbidity and mortality in various countries, especially in developing countries such as Indonesia, where morbidity and mortality are still high, and is one of the main causes of high morbidity and mortality rates for children in Indonesia (Vrese and Marteau, 2020).

Acute diarrhea is still a major cause of child morbidity and mortality in developing countries. In the world there are nearly 1.7 billion cases of diarrhea in children every year (WHO, 2017).

There are 6 million children die each year because of diarrhea and most of these occurrences occur in developing countries. In Indonesia, it is estimated that about 60

million people with diarrhea are found each year, most (70-80%) of these sufferers are children under 5 years of age ( $\pm$  40 million cases)(Rajagukguk, 2013).

Probiotics are a mucosal defense, a protective function and defense of gastrointestinal immunity such as the epithelial layer, mucus layer, peristalsis, and epithelial desquamation, as well as the secretion of immunoglobulin A (IgA), which greatly affect the attachment of pathogenic bacteria and also for modulation of the local and systemic immune system (Htwe, 2008).

Probiotics in children aged 36 months old did not decrease the duration of diarrhea with less frequency of defecation, but the difference was not significant (Waspada, 2012) with 1 month – 5 years old compared to those without probiotics. (Hatta et al., 2011).

Giving probiotics to children aged 6 - 36 months did not decrease the duration of diarrhea with less frequency of defecation, but the difference was not significant (Waspada, 2012).

Based on the high number of diarrhea patients in children and the need for patient care based on strong evidence about the use of appropriate probiotics, it is necessary to conduct study to determine whether the addition of probiotics to standard diarrhea therapy will have a better effect on reducing the frequency and duration of diarrhea in children (Hatta et al., 2011).

Probiotics are non-digestible fibers that can stimulate the growth of microorganisms in the colon such as Lactobacillus and bifidobacteria. Some examples of prebiotics are oligosaccharides, maltodextrin, inulin and others (Pandey et al., 2013).

Currently, more and more people claim the beneficial effects of probiotics, including improving intestinal health, increasing immune response, lowering

serum cholesterol, and preventing cancer. This advantage is specific to the bacterial strain (SKRT, 2011).

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Giving probiotics and zinc to children aged 1 month – 12 years old had a significant effect on feces consistency, frequency of diarrhea, duration of diarrhea, and length of stay (Lolopayung et al., 2014).

Giving probiotics to children aged 6 - 36 months did not decrease the duration of diarrhea with less frequency of defecation, but this difference was not significant (Waspada, 2012).

Appropriate use of probiotics to standard diarrhea therapy will have a better effect on reducing the frequency and duration of diarrhea in pediatric patients (Hatta et al., 2011).

## SUBJECTS AND METHOD

### 1. Study Design

This study was a systematic and meta-analysis study. The articles used in this study were obtained from several databases including PubMed, Springer Link, Cochrane Database, Hindawi, Elsevier, JBBA, LWW, Google Scholar. The keywords for finding articles are as follows: “Probiotic”, OR “frequency”, OR “diarrhea”, “kid”, OR child “AND “Randomized Controlled Trial (RCT).

### 2. Inclusion Criteria

The article included in this study is a full paper article with a randomized controlled trial study design. The subject of the study was diarrhea sufferers in toddlers. Selected articles discussed the effects of probiotics on the frequency and duration of diarrhea

in toddlers. The intervention given in the article is in the form of probiotics.

### 3. Exclusion Criteria

Articles published in this study are articles with research designs with non-RCT studies, articles are not full text, articles published before 2010 and the articles are not published in English.

### 4. Operational Definition

The article search was carried out by considering the eligibility criteria defined using the PICO model. The population in the study of diarrhea sufferers among children under five, intervention was a probiotic comparison, which was no probiotic and the outcome was reducing the frequency and duration of diarrhea in toddlers.

**Microbial probiotics** that stimulate the growth of other microbes, live microorganisms which, when administered in adequate quantities.

**Frequency** is a measure of the frequency of discharge per day with abnormal consistency with a categorical scale.

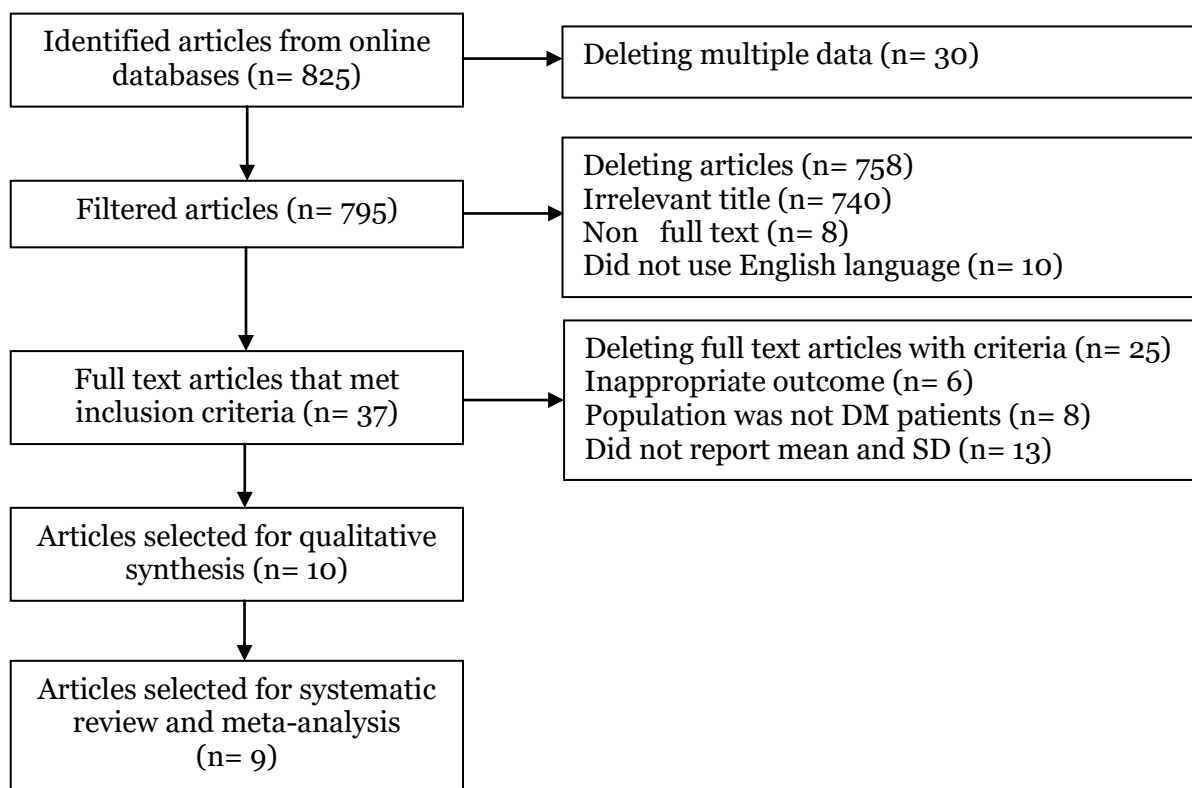
**Diarrhea** is how often the feces is passed over a certain period of time with an abnormal consistency.

### 5. Data Analysis

Data processing was carried out by the Review Manager (RevMan 5.3) by calculating the mean difference to determine the research model that was combined and formed the final meta-analysis result.

## RESULTS

The process of searching for articles done by searching through a database with journals can be seen in Figure 1. Articles obtained from 2 continents, namely America and Asia.



**Figure 1. PRISMA flow diagram**



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**a. The effect of probiotics on reducing the frequency and duration of diarrhea in toddlers**

9 articles proved the effect of probiotics on the frequency and duration of diarrhea in toddlers

<b>Author (Year)</b>	<b>Country</b>	<b>Study Design</b>	<b>Sample</b>	<b>P (Population)</b>	<b>I (Intervention)</b>	<b>(Con)</b>
Bhat et al., (2018)	India	RCT	Oral and zinc = 40 Probiotics = 80	6 months – 5 years	Assess the overall physical examination, assessment	Not assessing physical examination of vitamin and severity
Rajagukguket al., (2013)	Indonesia	RCT	Probiotics = 20 Synbiotics = 20	1 year – 14 years	Synbiotics (mixed) in children with acute diarrhea.	Did not see duration and diarrhea
Putra et al., (2007).	Indonesia	RCT	Probiotics = 35 Placebo = 35	1 month – 12 months	Compared the effects of probiotic and placebo supplementation on the duration and frequency of acute diarrhea in infants.	Did not see biotic and p mentation o frequency.
Sharif et al (2016)	Iran	RCT	Probiotics = 100 Placebo = 100	6 months – 6 years	Comparing the effects of <i>S. Boulardi</i> and placebo administration on the duration and frequency of acute diarrhea in infants.	Did not see boulardi and probiotics.
Sharif et al (2017)	Iran	RCT	Probiotics = 60 Placebo = 30	1 year – 5 years	Comparing the effects of probiotics and placebo on the duration and frequency of diarrhea	Did not see biotics and p duration and diarrhea.

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Schnadow er et al., (2018)	USA	RCT	Probiotics = 55 Placebo = 60	3 months – 4 years	Seeing the effectiveness of the probiotic <i>L. rhamnosus</i> GG, and placebo in children suffering from acute gastro- enteritis in children	Did not see of the probi <i>rhamnosus</i>
Freedman et al., (2020)	Canada	RCT	Probiotics = 108 Placebo = 102	3 months – 4 years	Evaluating the effectiveness of the probiotics of <i>L. rhamnosus</i> and <i>L. helveticus</i> in children aged 3 to 48 months in acute gastroenteritis.	Did not see of the probi <i>rhamnosus</i>

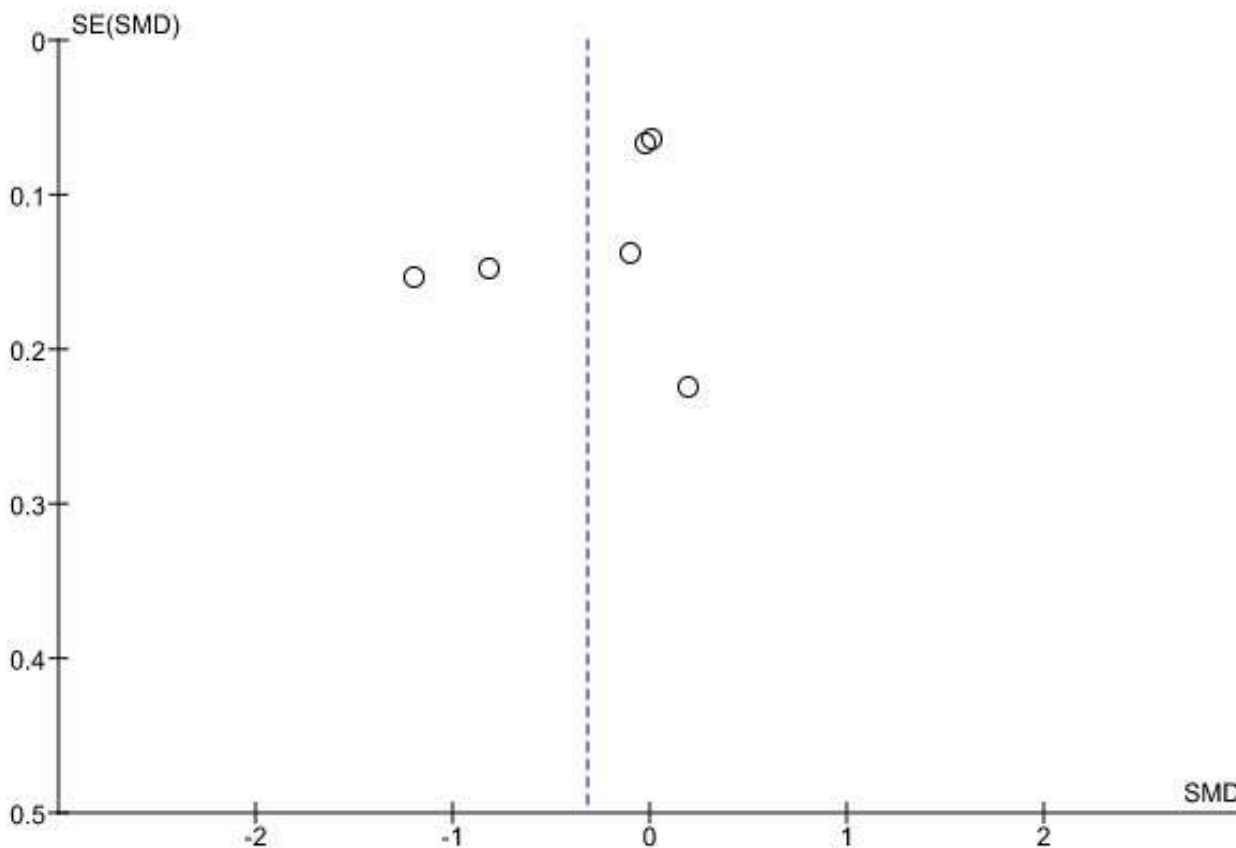
**b. Forest Plot**

Study or Subgroup	Probiotics			Non-probiotics			Weight	Std. Mean Difference IV, Random, 95% CI	Std IV
	Mean	SD	Total	Mean	SD	Total			
Bhat 2018	1.28	2.09	40	0.35	0.66	40	16.8%	0.59 [0.15, 1.04]	
Misra 2009	2.03	2	106	2.1	2	105	17.3%	-0.03 [-0.30, 0.24]	
Rajaguguk 2013	2	1.27	15	2	1.73	13	15.6%	0.00 [-0.74, 0.74]	
Sharif 2016	1.5	0.73	100	3.2	1.04	100	17.2%	-1.88 [-2.22, -1.55]	
Sharif 2017	2.13	0.27	30	3.98	1.12	30	16.0%	-2.24 [-2.90, -1.59]	
Sudha 2019	3.46	0.66	59	4.57	1.59	60	17.1%	-0.90 [-1.28, -0.53]	
<b>Total (95% CI)</b>			<b>350</b>			<b>348</b>	<b>100.0%</b>	<b>-0.74 [-1.60, 0.12]</b>	

Heterogeneity: Tau<sup>2</sup> = 1.09; Chi<sup>2</sup> = 129.36, df = 5 (P < 0.00001); I<sup>2</sup> = 96%

Test for overall effect: Z = 1.70 (P = 0.09)

**c. Funnel Plot**



**Figure 3. Funnel plot of the effect of probiotics on frequency of diarrhea in children under five**

Based on the results of the forest plot (Figure 2) 4, it was shown that probiotics decreased the duration of childhood diarrhea by -0.32 times higher compared to placebo and it was not statistically significant ( $p = 0.07$ ). The heterogeneity of the research data shows  $I^2 = 94\%$  so that the distribution of the data is heterogeneous (random effect model).

The funnel plot shows a publication bias which is indicated by asymmetry of the right and left plots where 4 plots are on the right and 2 plots are on the left. The plot on the left of the graph has a standard error between 0.1 and 0.2 and the plot on the right has a standard error between 0.1 and 0.3. Bias also occurs from an imbalance between the distance between studies on

both the right and left of the funnel plot. And do not form an inverted funnel triangle. Based on the results of the forest plot (Figure 3) 4, it was shown that probiotics decreased -0.32 times the duration of childhood diarrhea compared to placebo and it was not statistically significant ( $p = 0.07$ ). The heterogeneity of the research data shows  $I^2 = 94\%$  so that the distribution of the data is stated to be heterogeneous (random effect model).

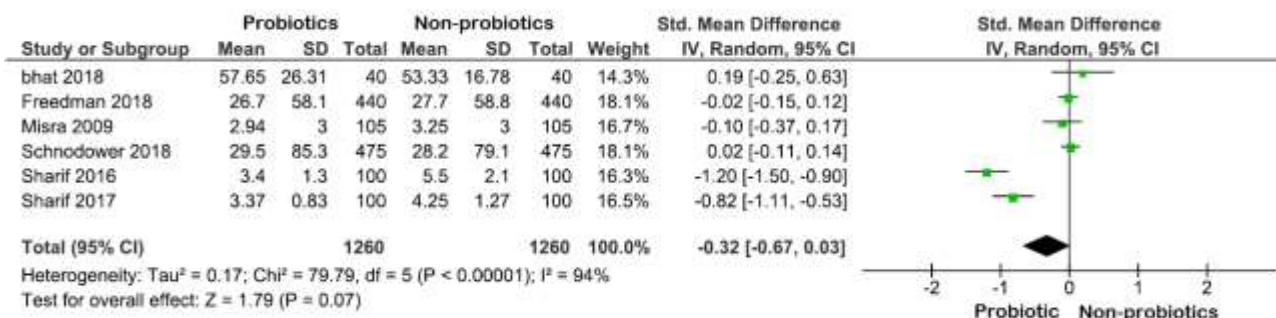
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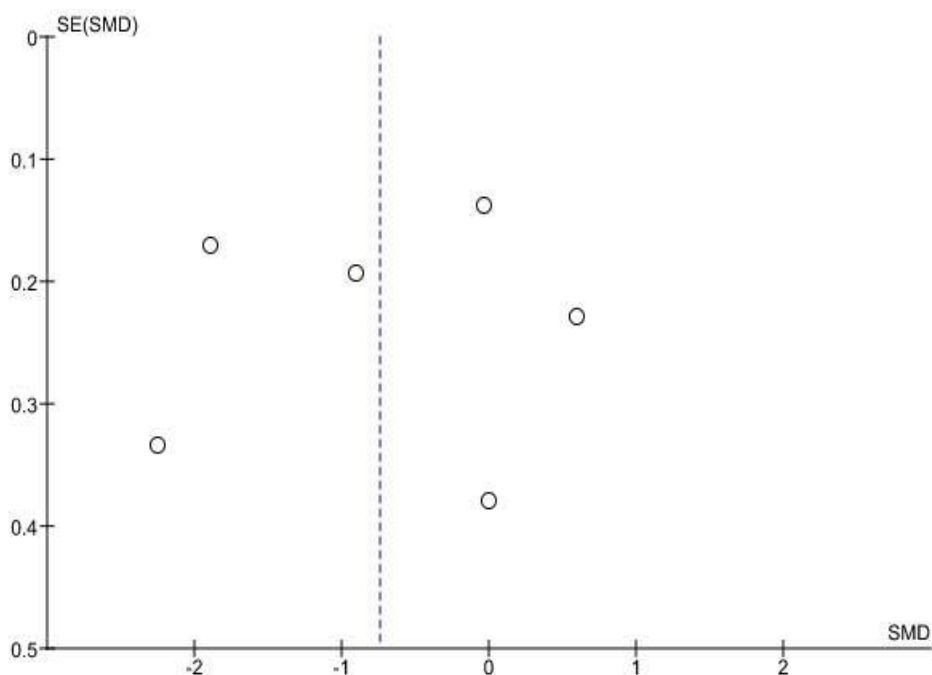
form an inverted funnel triangle.

**d. Forest Plot**



**Figure 4. Forest plot effect of probiotics on duration of diarrhea in children under five**

**e. Funnel Plot**



**Figure 5. Funnel plot of the effect of probiotics on duration of diarrhea in children under five**

**DISCUSSION**

This systematic study and meta-analysis research raised the theme of the effect of probiotics on the frequency and duration of diarrhea in toddlers. This study discussed data about probiotics that were considered to have a positive effect on the frequency and duration of diarrhea in toddlers. The number of relevant research published and

accessible was still small and also has data access problems (data duplication) (Murthi, 2018).

Confounding factors affected the relationship or effect of exposure to the occurrence of the disease estimated (estimated) by the study was not the same as the relationship or effect that actually



occurred in the target population, it lead to invalid study results (Murti, 2018).

The combined estimates were processed using RevMan 5.3 with the Continuous method. This method was used to analyze the effect size or standardized mean difference in the bivariate data of two groups that had been controlled for confounding factors by randomization. The results of the systematic study and meta-analysis were presented in the form of a forest plot and a funnel plot. The forest plot provided an overview of information from each of the studies examined in the meta-analysis, and estimates of the overall results (Murti, 2018).

The results of the systematic study and meta-analysis were presented in the form of a forest plot and a funnel plot. Forest plots provided an overview of information from each of the studies examined in the meta-analysis, and estimates of the overall results (Murti, 2018). The forest plot showed the amount of variation (heterogeneity) between study results visually (Akobeng in Murti, 2018).

A funnel plot is a diagram in a meta-analysis used to demonstrate possible publication bias. The funnel plot shows the relationship between the effect size of the study and the sample size or standard error of the effect size of the various studies (Murti, 2018).

Systematic review and meta-analysis in this study were carried out with the aim of increasing the generalizability of the findings and obtaining convincing conclusions from various similar studies regarding the effects of probiotics on the frequency and duration of diarrhea in toddlers.

This study is in line with the study that was conducted for 15 months involving 120 toddlers aged 6 months - 5 years who were randomly selected and divided into 3 groups. Group 1 received oral rehydration

therapy and zinc. 2nd group with *Bacillus clausii*. Group 3 with *Saccharomyces boulardii*.

This study was supported by a study done by Rajagukguk et al., (2013) which was carried out for 3 months involving 40 children aged 1-14 years, with a sample of more men (52%) than women (48%) and divided into probiotic groups and the synbiotic group. The probiotic group received probiotics.

#### **AUTHOR CONTRIBUTION**

Wahyu Agustin is the main researcher who selected topics, explored and collected research data. Bhisma Murti, Setyo Sri Raharjo, played a role in analyzing data and reviewing research documents.

#### **CONFLICT OF INTEREST**

There was no conflict of interest.

#### **FUNDING AND SPONSORSHIP**

This study used personal funds from the main researcher.

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