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Masters Program in Public Health, Universitas Sebelas Maret

Meta-analysis

Probiotics and Its Effects on the Cognitive Development in Children: A Meta-Analysis

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ABSTRACT

Background: Due to its high morbidity and mortality rate, diarrhea is still a major health problem among children, particularly toddlers, in developing countries. One of the causes of diarrhea in children is the side effect of antibiotics or known as antibiotic-associated diarrhea (AAD). Evidences of studies conducted in several countries indicated the high use of antibiotics among children that put the group at a high risk of enduring AAD. Probiotics has shown efficacy in preventing and curing various medical conditions, especially those involving digestive tract in children.
Subject and Method: It was a systematic review and meta- analisis study. Data collection was conducted by obtaining from databases, namely: Google Scholar, PubMed, Scopus and Science Direct. The study was analyzed by using RevMan 5.3 software. Inclusion criteria used were full paper in English with Randomized controlled trial design during the period of 2000-2022. Keywords used were "Probiotic" AND "Antibiotic Associated Antibiotic" AND "Child" AND "Randomized Controlled Trial".
Results: Meta-analisis was conducted to 9 primary studies from several countries such as Poland, Italy, Korea, Iran, and Australia. Mata-analysis concludes that there were effects of probiotics toward antibiotic-associated diarrhea. Children who were given probiotics had one-third time risk of diarrhea episodes compared to those who were not given probiotics (RR= 0.32; 95% CI= 0.23 to 0.44; p<0.001). Heterogeneity of between-study effect estimates of the meta-analysis data was (I^2= 0%; p= 0.096) therefore, calculation of effect estimates was written by using fixed effect approach. Funnel plot did not identify the occurrence of publication bias out of the meta-analysis. Therefore, the funnel plot did not identify the occurrence of publication bias.
Conclusion: Probiotics have effects in reducing antibiotics-associated diarrhea incidences in children.

Keywords: probiotics, diarrhea, antibiotics.

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BACKGROUND

Due to its high morbidity and mortality rate, diarrhea is still a major health problem among children, particularly toddlers, in developing countries. Around 80% deaths from diarrhea occur to children under 2 years old. Acute diarrhea is generated by a lot of factors such as infections (bacteria, parasite, virus), food poisoning, drug effects, and others. One of the causes of diarrhea in children is the effect of antibiotics use or known as antibiotic-associated diarrhea (AAD). Probiotics works naturally by using beneficial microbes.

Probiotics works in several methods, among others is microbes that serve as the

probiotics are capable to feed on organisms that are harmful for their host such as parasite or pathogenic microbes (Abbadi et al., 2018). The benefit of probiotics was initially discovered in 1997 by a Nobel laureate Elie Matchnikoff, who observed Bulgarian farmers that frequently consumed fermented milk that contained lactobacillus. Apparently, they had good health condition and relatively longer age. Later, probiotics consumption spread all over Europe and subsequently all over the world (Olivia et al., 2004).

Probiotics currently are getting more popular both globally and in Indonesia. The trend is aligned with the increased public awareness toward the importance of health. It is indicated from the increased consumption of functional food products. Probiotics is one of the functional foods that has been commercialized for quite a while. Along with the increased public awareness of health, probiotics foods are also getting more in demand (Jenie., 2019). Bifidobacterium administration seems to be promising as the therapy regiment for growth disorder symptoms development. However, evidences based on clinical trial are still limited, and indicate heterogenous results (Suryawan and Sekartini., 2021).

Probiotics have shown efficacy in preventing and curing various medical conditions, particularly those that are involving digestive tract in children. There are several specific strains of probiotics, such as Lactobacillus GG, L. Reuteri, Saccharomyces boulardii, Bifidobacterium species, known to significantly play important role in overcoming acute diarrhea problem in children, particularly reducing duration and severity of diarrhea (Dewi et al., 2021).

Based on the causal factor of diarrhea, that is medications, and the trend of probiotics development, the researchers were interested to analyze the effect of probiotics toward antibiotics-associated diarrhea in children. Obtained data were analyzed by using systematic review and meta-analysis as the attempt to obtained comprehensive result by conducting synthesis toward the results of primary studies involving probiotics interventions toward children's cognitive development.

SUBJECTS AND METHOD

1. Study Design

It was a systematic review and meta-analysis study. The data were collected from the databases, namely: PubMed, Science Direct, BMJ, Cochrane, Scopus, and Google Scholar. Study analysis was conducted by using RevMan 5.3 software. The articles employed were in full paper in English with randomized controlled trial, published during the period of 2000 to 2022, the effect size used was Risk Ratio (RR), the subjects were children given probiotics intervention.

The keywords were "Probiotic" AND "antibiotic associated diarrhea" AND "child" AND "randomized control trial".

2. Steps in Conducting Meta-Analysis

Meta-analysis was conducted through five steps, as follow:

a. Defining the research questions with PICO (Population, Intervention, Comparisson, Outcome) form.
b. Searching for primary study articles from various electronic databases such as Google Scholar, PubMed, Cochrane, Scopus and Science Direct as well as non-electronic.
c. Conducting screening and Critical Appraisal toward the primary studies articles.
d. Conducting data extraction and synthesizing the effect estimates into RevMan 5.3.
e. Interpreting and making conclusion.

3. Inclusion Criteria and Exclusion Criteria

The inclusion criteria of the study were

articles with randomized controlled trial study design, the effect size used was Risk Ratio (RR), the articles were in English and full paper version. The study subjects were children given probiotics intervention, the comparison was the placebo or non-probiotics. The exclusion criteria were articles published in non-English language, and before the year of 2000.

4. Study Variables

The independen variables is Probiotcs and the dependen variable is Antibiotics associated diarrhea.

5. Operational Definition of Variables

Probiotics was live microorganisms.

Antibiotics associated diarrhea was a medical condition characterized by loose and watery stools three or more times a day after consuming antibiotics**.**

6. Study Instrument

The instrument used in the study was Critical Appraisal Checklist Center for Evidence Based Management (CEBMa).

The following are indicators in critical appraisal:

1. Did the study discuss a distinct focus of study?
2. Was Randomized Controlled Trail appropriate to answer research questions?
3. Were there enough subjects in the study to determine that the findings were not coincidence?
4. Were subjects randomly allocated into experiment and control groups? If, they were not, could it generate any bias?
5. Were inclusion/exclusion criteria used?
6. Were both groups equivalent initially?
7. Were the objective and unbiased result criteria used?
8. Did the study use objective and validated measurement method to measure the result? If it did not, did someone who did not know the groups' task measure the result (blinding measurement)
9. Was effect size practically relevant?
10. How accurate was the estimation of the given intervention effect? Was there any confidence interval?
11. Was there any unpredictable confounding factor?
12. Was the result applicable into your study?

7. Data Analysis

The articles were collected based on PRISMA flow diagram and Critical Appraisal. The study used Review Manager 5.3 for data analysis. The data were subsequently analyzed based on the effect size and heterogeneity calculation result, based on several relevant studies with various methodologies and characteristics and in accordance with inclusion criteria. The final result of data analysis and processing was calculating effect size and heterogeneity values to determine the model of research integration and defining the final result of meta-analysis in the form of forest plot and funnel plot.

RESULTS

Based on the result of searching for relevant articles from several databases the study identified 564 articles. After conducting screening there were 11 doubled articles, which were subsequently de-duplicated resulting in 553 articles. There were 12 articles that met the inclusion criteria and considered eligible for full text review. The final result of article review was 6 articles that met quantitative requirements for meta-analysis, the effect of probiotics toward children's cognitive development. The studies related to the effect of probiotics toward cognitive development in children consisted of 4 articles from Poland, 1 article from Italy, 1 article from Bulgaria, 1 from China, 1 from Iran, and 1 from Australia. The quality and design of the study analyzed in meta-analysis is very critical since it may influence the result. The assessment for study quality was conducted quantitatively and qualitatively. The study employed Critical Appraisal Checklist for

Cross-Sectional Study by the Center for Evidence Based Management (CEBMa).

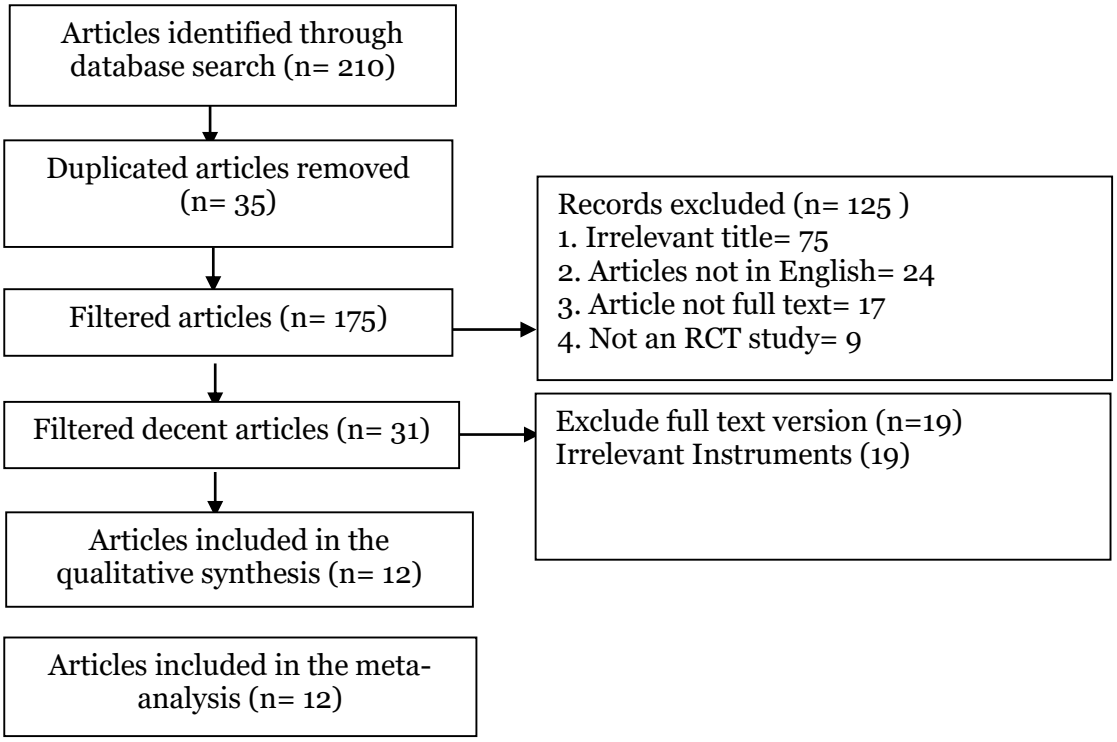

Figure 1. PRISMA Flowchart

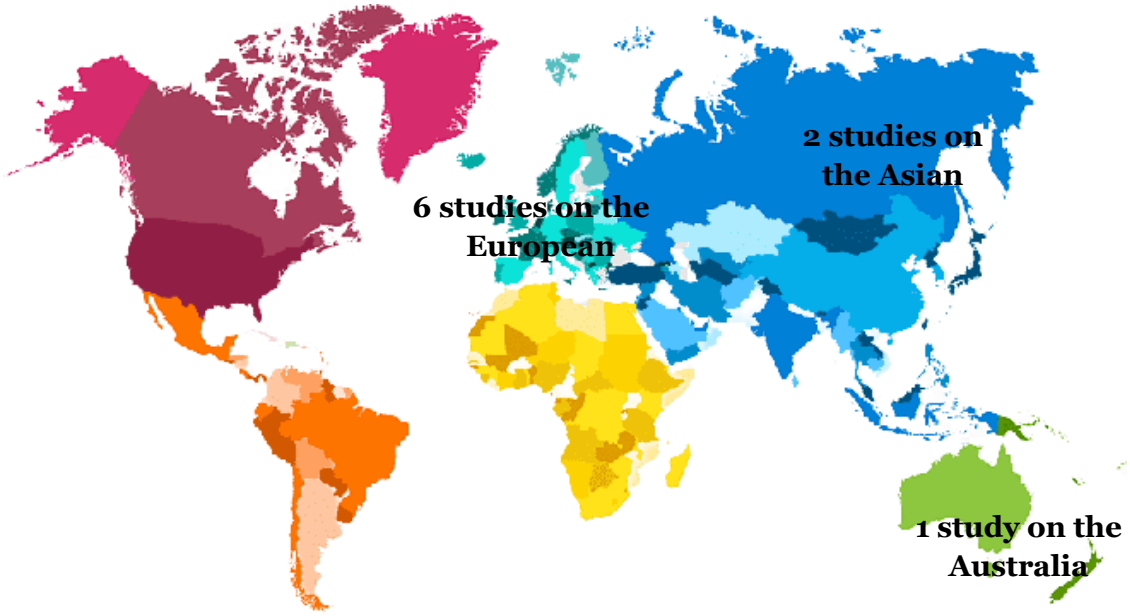

Figure 2. Study Map Area Probiotics and Its Effects on the Cognitive Development in Children: A Meta-Analysis

Table 1. Description of Primary Studies included in Meta-analysis

Author (Year)	Country	Design Studies	Sample Size	Population	Intervention	Comparison	Outcome
Shan et al. (2013)	China	RCT	278	Children of 6 months - 14 years	Saccharomyces boulardii	Non Probiotics	diarrhoea was caused byClostridium difficile
Kolodziej et al. (2019)	Iran	RCT	66	Children < 18 years	Lactobacillus reuteri	Non Probiotics	prevention of diarrhoea and antibiotic-associateddiarrhoea
Kodadad et al. (2013)	Poland	RCT	247	Children 3-14 years	Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis and Bifidobacterium breve	Non Probiotics	Diarrhea akibat antibiotics
Esposito et al. (2018)	Italy	RCT	60	Children 11-36 months	Lactobacillus rhamnosus GG	Non Probiotics	Diarrhea akibat antibiotics
Georgieva et al. (2015)	Bulgaria	RCT	97	Children 1-12 years	Lactobacillus reuteri	Non Probiotics	diarrhoea and Clostridiumdifficile infection
Szymanski et al. (2008)	Poland	RCT	78	Children 5 months-16years	Bifidobacterium longum PL03, Lactobacillus rhamnosus KL53A, and Lactobacillus plantarum, PL02	Non Probiotics	Diarrhea akibat antibiotics
Ruszczykski et al. (2008)	Poland	RCT	120	Children 3 months-14 years	Lactobacillus rhamno sus	Non Probiotics	diarrhoea caused by Clostridium diffificile or otherwise unexplained diarrhoea
Kotowska et al. (2005)	Poland	RCT	246	Children 6 months–14 years	Saccharomyces boulardii	Non Probiotics	antibiotic-associated diarrhoea (diarrhoea caused by Clostridiumdiffificile
Fox et al. (2015)	Australia	RCT	70	Children 1-12 years	Lactobacillus rhamnosus GG (LGG), Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5)	pasteurised yogurt(placebo)	antibiotic-associateddiarrhoea in children.

Table 2. Assessment of research quality of Aquatic Therapy on Functional Ability in Patients with Knee Osteoarthritis

No	Questions	Shan et al., 2013	Kodadad et al., 2013	Kolodziej et al. (2018)	Esposito et al (2017)	Georgieva et al (2015)	Szyma et al. (2008)	Ruszczykski et al. (2008)	Kotow et al. (2008)	Fox et al. (2015)
1	Did the study discuss a distinct focus of study ?	1	1	1	1	1	1	1	1	1
2	Was Randomized Controlled Trail appropriate to answer research questions?	1	1	1	1	1	1	1	1	1
3	Were there enough subjects in the study to determine that the findings were not coincidence?	1	0	1	0	1	0	1	1	1
4	Were subjects randomly allocated into experiment and control groups? If, they were not, could it generate any bias?	1	1	1	1	1	1	1	1	1
5	Were inclusion/exclusion criteria used?	1	1	1	1	1	1	1	1	1
6	Were both groups equivalent initially?	1	1	1	1	1	1	1	1	1
7	Were the objective and unbiased result criteria used?	1	1	1	1	0	1	1	1	1
8	Did the study use objective and validated measurement method to measure the result?	1	1	1	1	1	1	1	1	1
9	Was effect size practically relevant?	1	1	1	1	1	1	1	1	1
10	How accurate was the estimation of the given intervention effect? Was there any confidence interval?	1	1	1	1	1	1	1	1	1
11	Was there any unpredictable confounding factor?	0	0	0	0	0	1	1	1	1
12	Was the result applicable into your study?	1	1	1	1	1	1	1	1	1
	Total score	11	10	11	10	10	11	12	12	12

Answer: 1=Yes, 0=No.

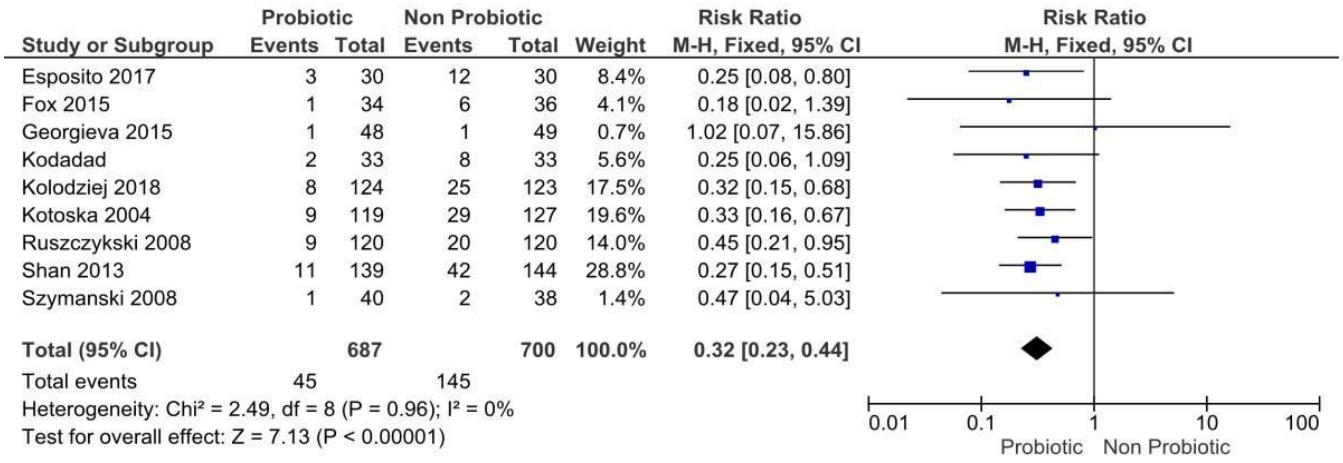

Figure 3. Forest Plot

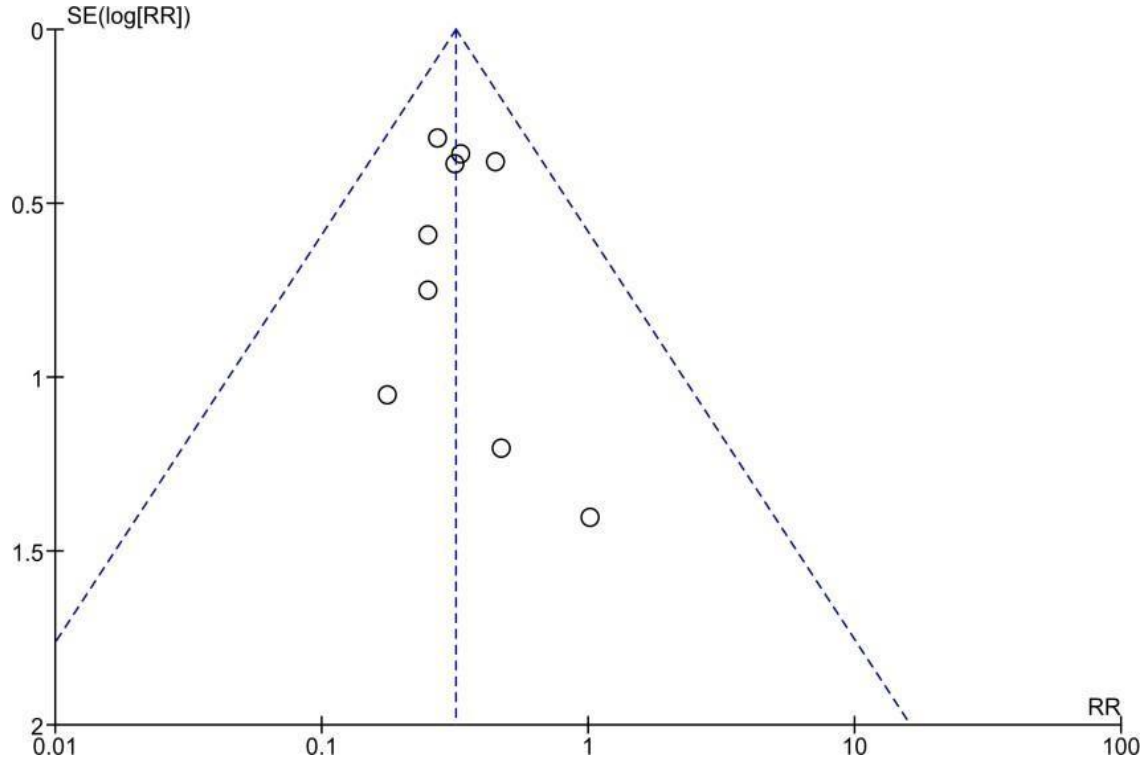

Figure 4. Funnel plot

a. Forest Plot

Forest plot in Figure 3 indicates that there was an effect of probiotics toward antibiotics-associated diarrhea episodes. Children given probiotics had one third time risk of diarrhea episodes (RR= 0.32; 95% CI= 0.23 to 0.44; p<0.001). Forest plot in Figure 3 also indicates the low heterogeneity of between-study effect estimates in this meta-analysis (I^2= 0%; p= 0.096) therefore, the effect estimates measurement was conducted by using fixed effect.

b. Funnel plot

Funnel plot in figure 4 indicates the distribution of effect estimates of all primary study in the meta-analysis that was relatively symmetrical due to the average effect estimates in the right and left side of vertical line. Therefore, the funnel plot did not identify the occurrence of publication bias.

DISCUSSION

One of the supporting factors of nutrient absorption by intestine in children is the occurrence of gut microbiota. Instead of to be cured, diarrhea can be prevented by implementing self-hygiene and nutritious diet. In addition, probiotics can also be utilized as one of the prevention and medication toward diarrhea due to dysbiosis condition within the gut microbiota composition in patient with diarrhea. There are various probiotics species used for diarrhea management.

It was a meta-analysis study. The study aims to obtain a conclusion of various similar study results that examined the effect of probiotics toward cognitive development in children. Primary studies involved in the study were studies conducted in various countries around the globe, therefore it could make a conclusion that may be implemented as a base of an intervention. The result was presented in the forms of forest plot and funnel plot. Forest plot is a tool that represented information related to result estimates of respective study to be analyzed. Whereas funnel plot is a visual tool to investigate publication and other bias in meta-analysis. They are simple scatter plots of medication effect estimates of individual studies against some measure of study's size. Funnel plot is based on the precision in the estimation of the underlying treatment increasing as the sample size of component studies increasing.

Meta-analysis was conducted toward 12 primary studies from several countries such as Poland, Italy, Korea, Iran, and Australia. Meta-analysis concludes that there is an effect of probiotics toward episodes of antibiotics-associated diarrhea. Children given probiotics had one-third time risk of diarrhea compared to those not given probiotics, and the effect was statistically significant (RR = 0.32; 95% CI= 0.23 to 0.44; $p<0.001$). Heterogeneity of between study effect estimates of the meta-analysis was ($I2 = 0\%$; $p= 0.096$) therefore the effect estimates measurement was written by using fixed effect. Funnel plot did not indicate any publication bias in the meta-analysis, therefore funnel plot did not identify any publication bias.

The result of the study is in line with a study by Bin et al (2018) that elaborates that overall S. boulardii has a beneficial effect in preventing and treating diarrhea during H. Pylori eradication in children. Although S. boulardii only slightly increases the eradication rates of H. pylori, the compliance of eradication treatment is also increased. The study stated that probiotics certainly preventing diarrhea related to H. Pylori standard eradication by using proton pump inhibitor and two antibiotics. S. Boulardii intervention during diarrhea development reduces severity and duration, and it leads to the increased compliance toward H.pylori eradication therapy. The findings of the trial should be confirmed by using double blind prospective study with histology and culture-based diagnosis (Bin et al., 2015).

Zhao et al. (2014) stated that in total, 240 children confirmed with Helicobacter pylori (Hp) participate in the study. The eradication level of Hp is 75.8% (91/120) among therapy group and 85% (102/120) in probiotics group ($p>0.05$). Compared to therapy group, probiotics group had three times insignificantly lower incidences of nausea, vomiting, and stomachache ($p>0.05$) and significantly lower incidences of stomatitis, constipation, and diarrhea ($p<0.05$). Therapy combined with Saccharomyces boulardii cannot significantly increase Hp eradication rate however it significantly reduces stomatitis, constipation, and diarrhea incidences during the treatment. It is similar with this study that the effect of probiotics toward antibiotic associated diarrhea in children was significant in reducing the

incidences. Our cumulative meta-analysis strengthens the evidence that the use of prophylaxis probiotics is a non-antibiotics option that may be effective in reducing incidences in critically ill patients with ventilation. However, long term effect of probiotics safety in individuals also requires further study, particularly in critically ill patients such as neonates/ children, patients with immunity disorder, and extremely feeble.

Based on the study it is discovered that probiotics have a significant result in affecting the reduction of antibiotics-associated diarrhea incidences in children. Diarrhea is one of the causes of children mortality, it is important to prevent the incidences to reduce children mortality rate from diarrhea. It also requires a development in the studies related to the exogenous of the results obtained to get the more significant results. The final results indicates that probiotics have an effect of 0.32 times better in reducing antibiotics-associated diarrhea incidences in children compared to children without probiotics.

AUTHORS CONTRIBUTION

Anggraini Ambarsari was the main researcher who selected topic, searched and collected study data. Bhisma Murti and Setyo Sri Rahardjo analyzed the data and studied research documents.

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The study was self-funded by the researcher.

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CONFLICT OF INTEREST

There is no conflict of interest in the study.

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