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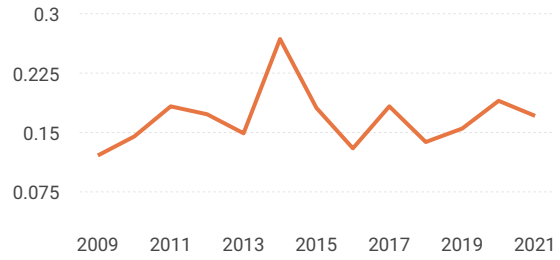

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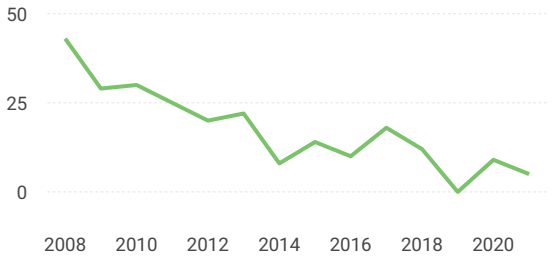

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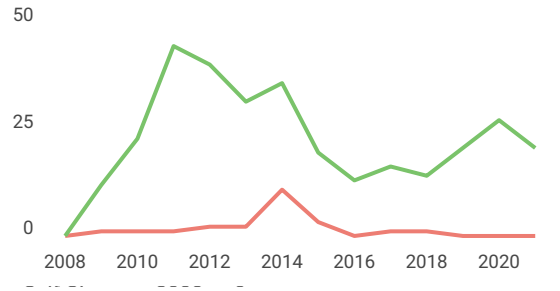

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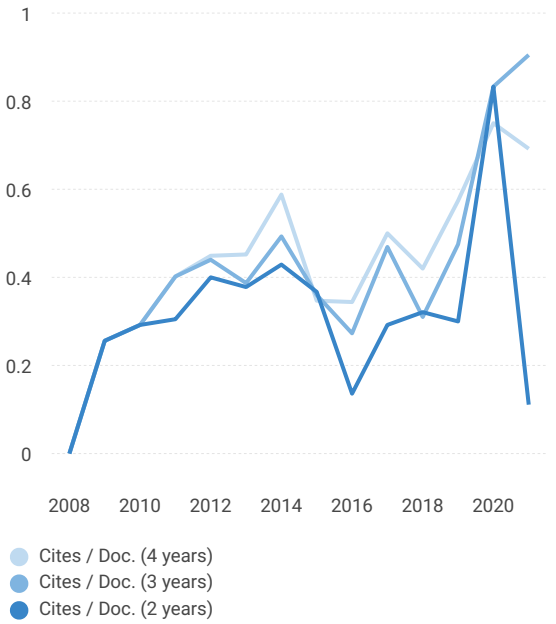

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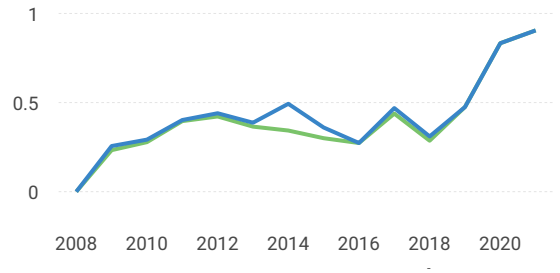

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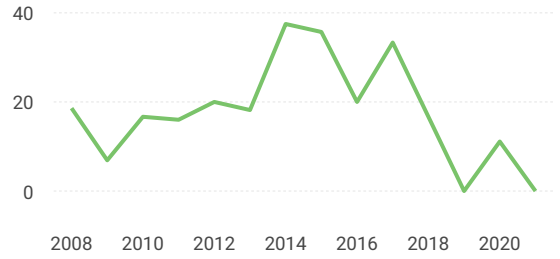

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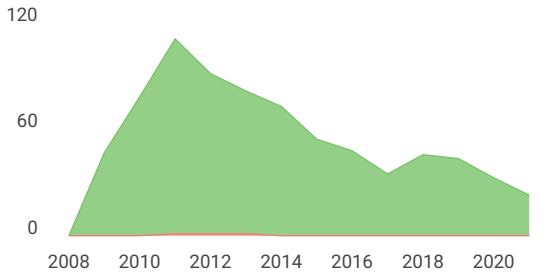

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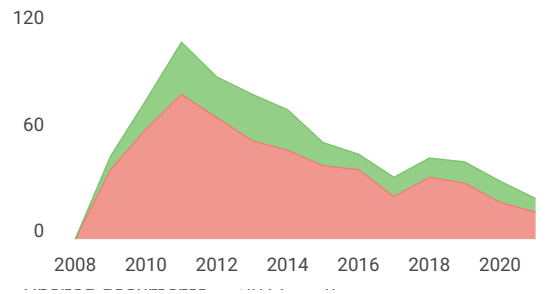

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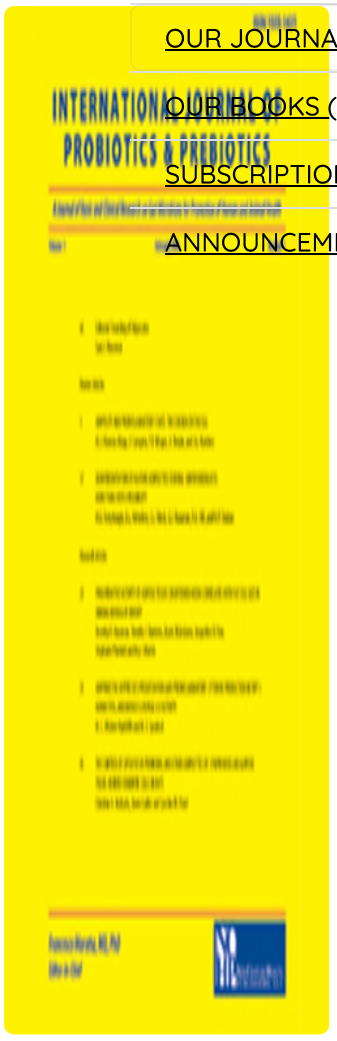

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Clinical Research

The Effects of Probiotic and Prebiotic Administration in Children with Acute Diarrhea at Day-Care Centers

Subijanto Marto Sudarmo, Reza Gunadi Ranuh, Alpha Fardah Athiyyah, Andy Darma, Virany Diana, Boerhan Hidajat, Siti Nurul Hidayati and Anang Endaryanto

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Prevention of diarrhea needs an appropriate immune system supported by normal microbiota composition. This study aimed to determine whether probiotic or prebiotic enriched *Growing-Up Milk* could significantly reduce incidence of acute diarrhea. The randomized, double-blind, placebo-controlled clinical study was conducted in Surabaya, Gresik, and Sidoarjo cities, East Java–Indonesia, between July 2007 and January 2008. This study involved healthy children aged 1–5 years at day-care centers and were randomized to receive three different *Growing-Up Milk* containing probiotic, prebiotic, or placebo groups (containing neither probiotic nor prebiotic). The day-care staff and parents reported the amount of milk consumed, symptoms, and duration of acute diarrhea during the observation time. A total of 162 participants were divided into probiotic (55), prebiotic (54), and placebo groups (53). The incidence of diarrhea in all the participants was 1.2%, which was the least incidence from the prebiotic group and the highest in the placebo group and significantly different (P = 0.001). The mean duration of diarrhea in all the intervention groups was lower than the placebo group, although neither was statistically nor clinically significant (P = 0.254). Administration of *Growing-Up Milk* enriched with probiotics or prebiotics appears to be a great opportunity in reducing the incidence of acute diarrhea in children aged 1–5 years.

Keywords: Acute diarrhea, Day-care center, Prebiotic, Probiotic

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INTRODUCTION

Diarrhea is a major health problem among children that places tremendous health burden on patients and their families, and also an enormous economic burden on the society (Cheng et al., 2005). Day-care attendance is a significant risk factor for infections in children. Child-care centers are increasingly contributing to this situation, as a growing number of children are cared for out of home and exposed to the surroundings lacking appropriate hygienic practices (Jaakkola and Ruotsalainen, 1997; Zomer et al., 2016). The normal indigenous microbiota with an intact epithelium creates a barrier (colonization resistance) against pathogens (Cieza et al., 2012). Commensal microbes are in close "cross-talk" with the epithelial cells and can induce an immunological response that may prevent gastrointestinal infection (Okumura and Takeda, 2017). Environmental pressures, such as changes in the diet or the use of antimicrobials, can dramatically alter microbiota composition, leading to enhanced growth of pathogens or opportunistic pathogens (Hasan and Yang, 2019).

In developing the immune system in infants and children, the gastrointestinal tract plays an essential and dominant role. The microflora changes with introduction of complementary food and decrease in breastfeeding (Ma et al., 2020). Profound changes occur in the intestinal ecosystem when young children are weaned from their mother's milk with a decrease in *Bifidobacterium* dominance. At 2 years of age, the fecal microflora will be similar to the adult microflora profile predominating in anaerobic and need improving in the colonization of normal microflora (Caicedo et al., 2005; Thursby and Juge, 2017).

Supplementation of *B. lactis* in milk formula administered to children aged 1–23 months with acute diarrhea has been shown to significantly decrease the frequency, duration, and hospital stay during acute diarrhea than usual treatment (El-Soud et al., 2015). In another study, the *Lactobacillus casei* variety *rhamnosus* has

been shown to decrease the severity of acute diarrhea by modulating the intestinal microbiota and enhancing immunoglobulin A level, reducing intestinal inflammatory reactions such as lactoferrin and calprotectin (Lai et al., 2019). The growth of probiotic bacteria in the intestinal tract needs specific nutrition such as short-chain galactooligosaccharides (GOS) and long-chain fructooligosaccharides (FOS), which are usually called prebiotic that are degraded by microbiota, which can feed the intestinal microbiota. Their degradation products are short chain fatty acids released into blood circulation, consequently affecting the gastrointestinal tract (Davani-Davari et al., 2019). The observational study of 342 infants proved that FOS and GOS in the milk formula reduced intestinal infection in healthy infants, especially during the first year (Bruzzese et al., 2009).

We have recognized the possible health benefits of either a probiotic or prebiotic in the acute diarrheal incidence in children. A systematic review by the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) concluded that there were no safety concerns regarding feeding probiotic- and/or prebiotic-supplemented formula to healthy infants. However, there are insufficient data to recommend the routine use of probiotic- and/or prebiotic-supplemented formula (Ackerberg et al., 2012). Therefore, this study aimed to determine whether probiotic (*Bifidobacterium* and *Lactobacillus*) or prebiotic (FOS and GOS) was better at achieving the more optimal preventive effect on acute diarrhea.

MATERIAL AND METHODS

Study Design

This randomized, double-blind, placebo-controlled clinical study was carried out in 12 day-care centers, with similar socioeconomic status, in Surabaya, Gresik, and Sidoarjo cities. The Ethics Committee of Medical Faculty, Airlangga University, Surabaya, Indonesia approved the study protocol with the No. 03/EC/KEPK/FKUA/2007 and the subjects' parents provided written informed consent before initiation of any study-related procedures. Enrolled subjects were randomly assigned to receive three different *Growing-Up Milk* containing probiotic (group X), prebiotic (group Y), and placebo *Growing-Up Milk* as a control containing neither probiotic nor prebiotic (group Z). The probiotics added to *Growing-Up Milk* were *B. animalis* subsp. *lactis* BB12 (*B. lactis*) and *L. casei* CRL 431 1×10^9 CFU per 200 mL. The prebiotic added to the *Growing-Up Milk* was GOS 840 mg per 200 mL. Each of the types of milk was served with different packaging colors: purple (group 1), yellow (group 2), and blue (group 3). The day-care staff, parents, children, and investigators were unaware of which packaging contained the study materials. Before intervention began, all the study participants received the placebo *Growing-Up Milk* for 2 weeks, to give time to adapt to the taste of the *Growing-Up Milk* that we used in this study. Subsequently, the selected formula in each group was administrated and observed within 6 months (24 weeks).

The day-care staff served the selected *Growing-Up Milk* thrice a day, 6 days a week, from 9 am until 5 pm. At home, parents or caregivers served the formula. The day-care staff and parents reported the amount of milk consumed by each child day by day. This information was collected once a week, concurrently with the routine weekly examination by the physician team of this study. The target volume of milk consumption was 600 mL (3×200 mL), with a minimum volume of 270 mL per day. The *Growing-Up Milk* formula was distributed once a week at the day-care center. Other prebiotic or probiotic products were prohibited for consumption during the study period. The contact number of the physician team was given to all the parents for being called in case the participant got sick during the study. If there were any emergency cases, they would be referred to a designated health facility. All episodes of diarrhea or other diseases will be recorded closely. Study flow is described in Figure 1.

Research Participants

Eligible subjects were healthy children aged 1–5 years in the designated day-care center. The parents of the participants were voluntarily involved in this study. Exclusion criteria were (i) children with a history of lactose intolerance, (ii) history of cow's milk allergy, (iii) children who were not in healthy condition since 1 week prior to the study took place, (iv) children with a history of prebiotic and probiotic consumption 2 weeks before participating in the study, (v) exclusively breastfed children, (vi) total volume of *Growing-Up Milk* consumption less than 270 mL during the 2-week period of placebo *Growing-Up Milk,* and (vii) intolerance to the *Growing-Up Milk*. Dropout criteria consist of (i) parents refused to continue their involvement in the study and (ii) the participant moved to another day-care center or untraceable before the end of the study.

Randomization

The separated team carried out the randomization, and the results were submitted to the researcher team for respondents' number and each group form. A block random sampling method was used in each day-care center. Thus, the samples from each day-care center were divided into three groups of *Growing-Up Milk* consumption.

Data Collection

The parents and day-care staff recorded any diarrhea daily during the study period. If there were any symptoms of diarrhea, the parents or daycare staff would contact the physician team. The diagnosis of diarrhea was established based on their examination and assessment. Acute diarrhea was defined as three or more loose or watery stools per day, which occurred for no more than 7 days. The assessment regarding acute diarrhea included the incidence and duration of diarrhea. The incidence of diarrhea was calculated using the following formula:

$$\frac{\text{Total diarrhea episode in each group}}{26 \times \text{Number of participant in each group}}$$

The episode of diarrhea was defined as the frequency of diarrhea during 6 months of observation. Twenty-six came from the total time of observation in "weeks". The number of participants included in this formula was all who completed all observations until the end of the study. The duration of diarrhea was described as the number of days since the diarrhea symptoms appeared until declared fully recovered by the physician team. The recovery

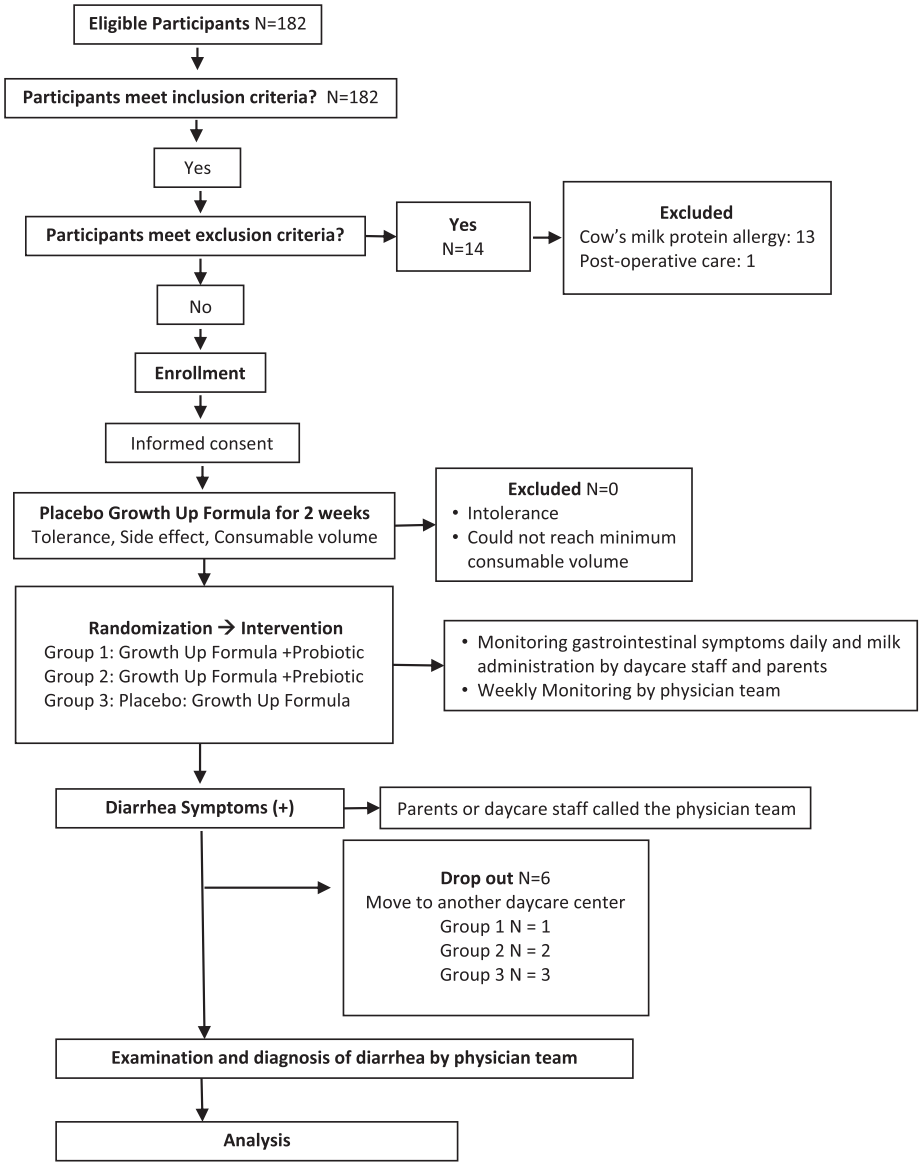

FIGURE 1 | Study flow and assessment chart.

criteria were normal stools consistency with frequency less than three times per day. It was compared between groups using mean diarrhea duration per episode using the following formula:

$$\text{Mean duration of diarrhea} : \frac{\text{Sum of diarrhea duration in each group}}{\text{Number of episodes in each group}}$$

Statistical Analyses

The differences in baseline characteristics between groups were analyzed using ANOVA, Chi-square, and Kruskal–Wallis tests according to the kind of variable and its data distribution. The mean incidence and duration of diarrhea was presented as mean ± standard deviation (SD). The Kruskal–Wallis and Mann–Whitney tests then compared the differences of diarrhea incidence and duration between the groups. Statistical analysis was performed using SPSS version 22.0.

RESULTS

From July 2007 to January 2008, 168 children were randomized into three groups, consisting of 56 participants in each group. Six participants were dropped out because they moved to another daycare center and were not traceable (Fig. 1). At the end of the study, there were 55 participants in the probiotic group, 54 participants in the prebiotic group, and 53 participants in the control group. The baseline characteristics of the participants were described in Table 1. The distribution of age, gender, nutritional status, and volume of consumed milk between the groups were not significantly different. In this study, the total incidence of diarrhea in all the groups was 1.2%. The Kruskal–Wallis test revealed that diarrhea incidence was significantly different between the groups (Table 2).

The post hoc analysis with the Mann–Whitney test was described in Table 3. The difference in diarrhea incidence either

TABLE 1 | Baseline characteristics of the study participants.

Characteristics	Probiotic	Prebiotic	Placebo	P-values
Age (months)	35 ± 13.73	34.8 ± 12.25	38.87 ± 11.56	0.186
Gender				
Male	27	22	31	0.185
Female	28	32	22	
Nutritional status				
Normal	47	49	47	0.688
Malnutrition	8	5	6	
Volume of consumed milk (milliliters)	1353.4 ± 619	1269.7 ± 525	1313.6 ± 535	0.874

The data are presented as mean ± SD.

TABLE 2 | Incidence of diarrhea in the probiotic, prebiotic, and control groups.

Groups	*N*	Incidence	Incidence (%)	P-values
Probiotic	55	0.011	1.1	
Prebiotic	54	0.006	0.6	0.001
Placebo	53	0.019	1.9	

The data are analyzed by the Kruskal–Wallis test.

TABLE 3 | The result of Mann–Whitney analysis among groups.

Groups	Incidence	P-values
Probiotic vs Placebo	1.1% vs 1.9%	0.014
Prebiotic vs Placebo	0.6% vs 1.9%	0.000
Probiotic vs Prebiotic	1.1% vs 0.6%	0.274

TABLE 4 | Estimation of the size of probiotic or prebiotic administration effect to diarrhea compared with control group.

Groups	ARR	RRR	NNT	RR
Probiotic vs. Placebo	0.008 (95%CI: −0.001–0.018)	42.9% (95%CI: −5.5%–69.1%)	119 (95%CI: −1239–55)	0.566 (95%CI: 0.304–1.055)
Prebiotic vs. Placebo	0.013 (95%CI: 0.005–0.022)	67.3% (95%CI: 30.7%–84.6%)	76 (95%CI: 207–45)	0.322 (95%CI: 0.151–0.689)

in the probiotic or prebiotic group compared to the control group was statistically significant. Although the incidence of diarrhea in the prebiotic group was lower than the probiotic group, the post hoc analysis confirmed that the difference was not statistically significant. Subsequently, the relative risk reduction (RRR) showed that the prebiotic group would reduce the risk of diarrhea by 67.3% compared to the control group. On the other hand, the probiotic group will only reduce the risk of diarrhea by 42.9% compared to the control group. The ability of the probiotic *Growing-Up Milk* formula in this study to reduce the risk of diarrhea was less than the prebiotic *Growing-Up Milk* formula, although it was not statistically significant (Table 3). Relative risk of diarrhea in the prebiotic and probiotic group was 0.322 and 0.566 times, respectively, compared to the control group (Table 4). The mean duration of diarrhea per episode in the probiotic group was 4.18 ± 3.2 days, in the prebiotic group was 3.63 ± 1.5 days, and in the control group was 4.92 ± 2.6 days. After confirmation with the Kruskal–Wallis test, the mean of diarrhea duration in all the intervention groups was lower than the control group but neither statistically nor clinically significant (P = 0.254).

DISCUSSION

B. lactis secretes 74 distinct proteins that have several potential functions including attachment to mucin and intestinal cells as well as induction of immunomodulative responses (Yan and Polk, 2011). The other probiotic strain used in this study was *L. casei* that induces mucosal response involving regulation of Th1 and Th2 balance (Lee et al., 2017). *L. casei* promotes a shift in Th1/Th2 balance to a Th2 type and/or Th17 type, with upregulation of IL-17D and IL-21, which improves the development of natural killer cells (Lee et al., 2017; Yan and Polk, 2011). However, the role of both strains in the number of diarrhea episodes and duration from previous research is still controversial, especially if they had been consumed for a short period (Fox et al., 2015; Schnadower et al., 2018; Souza and Jorge, 2012). The clinical trial by Korpela et al. (2018) revealed that probiotic supplementation that was given during pregnancy and continued to the baby for 3 months after delivery, which means long-term consumption, was possible to correct undesired changes in microbiota composition and function caused by antibiotic treatments or cesarean birth. Nevertheless, the effect depended on the infant's diet. Breastfeeding and formula feeding are the dietary factors associated with the infant's intestinal microbiome. The supplementation of probiotics in formula-fed infants is expected to prevent dysbiosis (Savage et al., 2018).

In the present study, the growth milk formula supplemented with probiotics reduced the incidence of diarrhea significantly compared to the control group. This result was in line with the previous findings using formula supplemented with *B. lactis* or *L. reuteri* to prevent diarrhea episodes, although *L. reuteri* showed a more prominent effect (Weizman et al., 2005). The same results were also shown using another probiotic strain, *L. fermentum* CECT 5716, which was isolated from breast milk (Gil-Campos et al., 2012). On the contrary, the result of a systematic review from 10 probiotic studies showed that the probiotics in the formula failed to significantly affect growth, lower the diarrhea incidence, or other functional gastrointestinal disturbances, such as colic, regurgitation, restlessness, or vomiting, in infants (Mugambi et al., 2012).

In the present study, the prebiotic group showed the least total incidence of diarrhea compared to the probiotic and control groups. The differences were statistically significant if compared with the control group but were not statistically significant if compared with the probiotic group. Our result supports several previous studies. Bakker-Zierikzee et al. (2005) confirmed that feeding infants a formula containing the prebiotic FOS/GOS mixture resulted in high relative amounts of fecal acetate, high concentration of fecal lactate, and a low fecal pH than the probiotic group and standard formula group. This group receiving only prebiotic had a similar metabolic activity of the intestinal flora with the breast-fed group.

Another study also showed that the FOS/GOS administration through milk formula reduced intestinal and possibly respiratory infection in healthy infants during the first year of age (Bruzzese et al., 2009). Furthermore, Chatchatee et al. (2014) showed that

the *Growing-Up Milk* supplemented with the prebiotic reduced the occurrence of upper respiratory tract infection and gastrointestinal infection significantly than the control group in children aged 11–29 months. With prolonged consumption of the growing-up formula supplemented with the prebiotic up to 52 weeks, the number needed to treat (NNT) in Chatchatee's study was 17 with RR 0.93 [95%CI: 0.87–1.00], which was higher than our result (Chatchatee et al., 2014). On the contrary, the systematic review of 12 prebiotics studies concludes that the prebiotic in the formula increased weight gain and stool frequency but had no impact on stool consistency. There was also no impact on infection and gastrointestinal microflora (Mugambi et al., 2012). Vaisman et al. (2010) also showed that the FOS and GOS administration in short duration during acute diarrhea episodes in children aged 1–2 years would have no significant clinical effect. However, a study by Arslanoglu et al. (2007) showed that long-term consumption still provides protection against infections during the first 6 months of life.

No significant effect of probiotic or prebiotic on diarrhea duration in this study could have resulted due to the short duration of diarrhea experienced by the participants so that it could cure quickly without any treatment. Our result has several limitations. The research did not describe the changes in microbial balance by probiotic or prebiotic administration and had not explained effects on immune system. Thus, the specific mechanism for preventing this infection was not clearly described. However, our study supported other previous results that have proven the role of consuming formula supplemented with probiotics or prebiotics may have a positive effect on preventing infection.

CONCLUSION

The administration of growing-up formula enriched with probiotics or prebiotics has been a great opportunity in clinically and statistically reducing the incidence of acute diarrhea in children aged 1–5 years at the day-care centers. There was no significant difference in diarrhea incidence between prebiotic and probiotic administration. Follow-up studies with thorough examination on fecal microbiota composition before and after intervention might prove prebiotic or probiotic administration's role in rebalance of microbial dysbiosis.

CONFLICT OF INTEREST DECLARATION

The authors state that there are no conflicts of interest to disclose.

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