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Effect of Probiotic Supplementation on the Duration and Severity of Acute Childhood Diarrhoea: A Double-Blind, Randomized, Placebo-Controlled Trial

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ABS TRAC T

***Background*:** Acute diarrhoea remains a leading cause of childhood morbidity and mortality in Indonesia and other low- and middle-income settings. Probiotics—particularly Lactobacillus rhamnosus GG (LGG) and Saccharomyces boulardii—have been proposed as adjuncts to oral rehydration therapy, but heterogeneous evidence and limited data from Indonesian children call for further investigation. This trial evaluated the effect of probiotic supplementation on the duration and severity of acute diarrhoea in Indonesian children. ***Methods*:** A single-centre, prospective, double-blind, parallel-group, placebo-controlled randomized trial was conducted between January 2024 and December 2025. A total of 150 children aged 6 to 60 months with acute watery diarrhoea of <72 hours' duration were enrolled and randomized 1:1 to LGG 10^{10} CFU twice daily plus standard care (n = 75) or matching placebo plus standard care (n = 75) for 5 days or until resolution. The primary outcome was the duration of diarrhoea from randomization to resolution. ***Results*:** Baseline characteristics were comparable. The mean duration of diarrhoea was significantly shorter in the probiotic group than in the placebo group (54.6 ± 16.8 vs 78.4 ± 22.4 hours; mean difference 23.8 hours, 95% CI 17.2–30.4; $p < 0.001$). Mean stool frequency on day 2 was lower (3.8 ± 1.4 vs 5.6 ± 1.8 per day; $p < 0.001$) and the proportion of children with diarrhoea resolution by day 3 was higher (60.0% vs 28.0%; $p < 0.001$). Vomiting episodes (1.2 ± 1.0 vs 1.9 ± 1.4; $p = 0.001$), need for intravenous rehydration (12.0% vs 26.7%; $p = 0.024$) and length of hospital stay (3.2 ± 1.1 vs 4.4 ± 1.3 days; $p < 0.001$) all favoured the probiotic arm. No serious adverse events were recorded. ***Conclusion*:** Adjunctive Lactobacillus rhamnosus GG supplementation significantly reduced the duration and severity of acute watery diarrhoea in Indonesian children, with a favourable safety profile, supporting its consideration as an adjunct to standard oral rehydration therapy and zinc supplementation.

Keywords: *Probiotics, Lactobacillus Rhamnosus GG, Acute Diarrhoea, Children, Randomized Controlled Trial, Indonesia.*

INTRODUCTION

Acute gastroenteritis is one of the leading causes of paediatric morbidity and mortality globally and continues to account for a substantial proportion of under-five deaths in low- and middle-income countries. The Global Burden of Disease estimates that diarrhoeal disease is responsible for approximately 9% of all deaths among children under five years of age worldwide, with the majority of this burden concentrated in South Asia and sub-Saharan Africa, although Southeast Asian countries including Indonesia also bear a meaningful share [1]. In Indonesia, acute diarrhoea remains among the top three causes of paediatric outpatient and inpatient morbidity, with viral pathogens—particularly rotavirus and norovirus—accounting for the majority of severe episodes in children under five [2].

The cornerstones of management of acute diarrhoea in children have been clearly defined by the World Health Organization and UNICEF and consist of low-osmolarity oral rehydration solution (ORS), continued feeding, and zinc supplementation for 10 to 14 days; antibiotics are reserved for specific bacterial aetiologies such as cholera and dysentery [3]. Although these measures are highly effective in reducing mortality, they do not consistently shorten the duration of diarrhoea or substantially alleviate the symptom

burden, leaving room for adjunctive interventions that can reduce diarrhoea duration, hospitalisation length, and parental and societal costs [3, 4].

Probiotics—live microorganisms that, when administered in adequate amounts, confer a health benefit on the host—have attracted considerable interest as adjuncts in the management of acute diarrhoea. Mechanistically, probiotic strains are thought to act through competitive exclusion of enteropathogens for adhesion sites on the gut mucosa, secretion of antimicrobial substances, restoration of disturbed intestinal microbiota, enhancement of mucosal barrier function, modulation of mucosal and systemic immune responses, and competition for luminal nutrients [4, 5]. Different probiotic strains differ substantially in mechanisms, dose–response and clinical efficacy, and strain- and indication-specific evidence is therefore essential.

Of the various probiotic strains studied, Lactobacillus rhamnosus GG (LGG) and Saccharomyces boulardii have the most robust evidence base in acute paediatric diarrhoea. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group on probiotics, in its updated 2014 and 2020 position papers, gave a positive recommendation (low to moderate quality of evidence, strong recommendation) for the use of LGG and S. boulardii in the management of acute gastroenteritis in children, while emphasising that benefit is strain-specific and that other strains should not be assumed to share the same efficacy [5]. A Cochrane systematic review pooling more than 60 randomized trials concluded that probiotics shortened the duration of diarrhoea by an average of approximately 25 hours and reduced the risk of diarrhoea lasting ≥4 days [6].

However, this conclusion has been challenged by two large, high-quality randomized trials published in 2018—the North American PERC (LGG) trial led by Schnadower and colleagues, and the Canadian PROGUT (Lactobacillus rhamnosus R0011 and L. helveticus R0052) trial reported by Freedman and colleagues—both of which found no significant clinical benefit of probiotics over placebo in children with acute gastroenteritis presenting to emergency departments [7, 8]. These contrasting findings have generated considerable debate, with proposed explanations including differences in pathogen distribution, baseline severity, timing of probiotic initiation, dosing, strain specificity and concomitant standard of care. The debate underscores that probiotic efficacy is unlikely to be uniform across settings and populations and that locally relevant randomized evidence remains valuable [9].

Data on probiotic efficacy from Indonesian children, who face a different pathogen mix, baseline nutritional status and standard-of-care landscape than children in high-income settings, are limited and heterogeneous. A small number of Indonesian and broader Southeast Asian trials have suggested benefit from LGG and S. boulardii in reducing diarrhoea duration and hospital stay, but methodological limitations have constrained definitive conclusions [10]. Given the substantial paediatric diarrhoeal burden in Indonesia and the affordability of LGG-based probiotic preparations in the local market, additional well-conducted randomized evidence in this population is needed to inform clinical practice.

Accordingly, the present single-centre, prospective, double-blind, placebo-controlled randomized trial was designed to evaluate whether adjunctive Lactobacillus rhamnosus GG supplementation, added to standard WHO-recommended care, would shorten the duration of acute watery diarrhoea and reduce its severity in Indonesian children aged 6 to 60 months.

Aims and Objectives

The principal aim of the trial was to determine whether adjunctive Lactobacillus rhamnosus GG supplementation, given for up to 5 days in addition to standard WHO-recommended care, shortened the duration of acute watery diarrhoea in Indonesian children aged 6 to 60 months.

The primary objective was framed as the comparison of the duration of diarrhoea from randomization to resolution between the probiotic and placebo groups. Secondary objectives included the comparison of stool frequency on days 1, 2 and 3 after randomization; the proportion of children with diarrhoea resolution by day 3; the frequency of vomiting episodes; the need for intravenous rehydration; the length of hospital stay; and safety and tolerability of the intervention. An exploratory objective examined whether the benefit was modified by aetiology (rotavirus vs non-rotavirus) and by age.

Materials and Methods

Study design and setting

A single-centre, prospective, parallel-group, double-blind, placebo-controlled randomized trial was conducted at the Department of Paediatrics of Udayana University, Indonesia, between January 2024 and December 2025. The study protocol was approved by the Institutional Ethics Committee in accordance with the Declaration of Helsinki, and written informed consent was obtained from a parent or legal guardian of every participating child. The trial was prospectively registered on a publicly accessible clinical trial registry and reported in accordance with the CONSORT 2010 statement.

Sample size estimation

The sample size was calculated based on the

primary outcome, namely the duration of diarrhoea. Assuming a mean duration of 75 hours in the placebo arm with a standard deviation of 24 hours, and considering a clinically meaningful between-group difference of 12 hours, a two-sided α of 0.05 and power of 80%, a minimum of 64 children per arm was required. To compensate for an anticipated 15% attrition, the final target sample size was set at 75 children per arm, yielding a total of 150 participants.

Eligibility criteria

Children aged 6 to 60 months who presented within 72 hours of the onset of acute watery diarrhoea (defined as ≥3 loose or watery stools in a 24-hour period) and who were either hospitalised or scheduled for observed in-clinic management were eligible. Exclusion criteria included bloody diarrhoea, severe dehydration requiring immediate intensive intravenous resuscitation, suspected dysenteric or cholera-like illness requiring empirical antibiotics, severe acute malnutrition (weight-for-height z-score < –3 or mid-upper-arm circumference <11.5 cm), concurrent significant comorbidity (including known immunodeficiency, chronic gastrointestinal disease, congenital heart disease), use of probiotics or antibiotics within the preceding 7 days, suspected nosocomial diarrhoea, known allergy to any component of the study product, and inability to attend follow-up.

Randomization, allocation concealment and blinding

Eligible children were randomly assigned in a 1:1 ratio to receive either LGG or matching placebo, using a computer-generated block randomization sequence with variable block sizes prepared by an independent statistician. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes opened by the dispensing pharmacist. The probiotic and placebo sachets were identical in appearance, smell, taste and packaging. Participants, parents, treating clinicians, outcome assessors and the analysing statistician all remained blinded to allocation.

Interventions

All enrolled children received standard WHO-recommended care, including assessment of dehydration, low-osmolarity oral rehydration solution, continued age-appropriate feeding (including breastfeeding where applicable), zinc 20 mg/day for 10 days (10 mg for infants <6 months at the discretion of the treating physician), and counselling. Antiemetics and antibiotics were administered only when clinically indicated. Children in the intervention arm received Lactobacillus rhamnosus GG 10^{10} colony-forming units (CFU) twice daily for up to 5 days or until resolution of diarrhoea, whichever came first. Children in the placebo arm received matching maltodextrin placebo sachets on an identical schedule.

Outcome assessment and follow-up

Children were assessed at baseline, at 24, 48 and 72 hours, and at discharge or 5 days, whichever came first. A structured proforma recorded the time and characteristics of every stool and vomiting episode, the volume of ORS and intravenous fluids administered, oral intake, body weight, hydration status (Clinical Dehydration Scale), and any adverse event. Telephone follow-up was conducted at day 7 and day 14 to capture late events. A stool sample obtained within 24 hours of admission was tested for rotavirus by enzyme immunoassay and screened for bacterial pathogens by routine culture in a subset of cases.

Outcomes

The primary outcome was the duration of diarrhoea from randomization to resolution, defined as the time of the last loose or watery stool prior to passage of either no stool or two consecutive formed stools for at least 24 hours. Secondary outcomes comprised stool frequency on days 1, 2 and 3; proportion of children with diarrhoea resolution by day 3; total vomiting episodes during the study period; need for intravenous rehydration; length of hospital stay; treatment failure (defined as persistence of diarrhoea beyond 7 days or worsening clinical course requiring escalation); and adverse events.

Statistical analysis

Data were analysed on an intention-to-treat basis using SPSS version 27.0. Continuous variables were summarised as mean ± standard deviation when normally distributed and as median (interquartile range) otherwise. Categorical variables were presented as frequencies and percentages. Between-group comparisons for continuous variables used the independent samples t-test or Mann–Whitney U test, and for categorical variables used the chi-square test or Fisher exact test. Kaplan–Meier analysis with log-rank testing was used to compare time to diarrhoea resolution. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Participant disposition and baseline characteristics

Of 178 children screened, 150 fulfilled the eligibility criteria and were randomized; 75 were allocated to the probiotic arm and 75 to the placebo arm. All children completed the primary outcome assessment. The two groups were well matched at baseline with respect to age, sex, anthropometric status, duration of diarrhoea prior to enrolment, baseline stool frequency, hydration status and rotavirus positivity (Table 1, all $p > 0.05$). The mean age of the cohort was 18.4 ± 11.2 months, with male predominance of 55.3%. Rotavirus was detected in 56.0% of stool samples.

Table 1: Baseline demographic and clinical characteristics

Variable	Probiotic (n=75)	Placebo (n=75)	p-value

Age (months), mean ± SD	18.6 ± 11.4	18.2 ± 11.0	0.827
Male, n (%)	42 (56.0)	41 (54.7)	0.870
Weight (kg), mean ± SD	9.8 ± 2.6	9.6 ± 2.4	0.625
Weight-for-age z-score, mean ± SD	–0.86 ± 1.02	–0.92 ± 0.96	0.713
Diarrhoea duration before enrolment (h), mean ± SD	32.4 ± 14.6	31.8 ± 13.8	0.797
Stool frequency at baseline (per 24 h)	7.4 ± 2.2	7.6 ± 2.4	0.595
Vomiting present, n (%)	44 (58.7)	46 (61.3)	0.738
Mild dehydration, n (%)	48 (64.0)	46 (61.3)	0.736
Moderate dehydration, n (%)	20 (26.7)	22 (29.3)	0.717
Severe dehydration excluded, n (%)	0 (0.0)	0 (0.0)	—
Rotavirus positive, n (%)	42 (56.0)	42 (56.0)	1.000
Exclusive breastfeeding history, n (%)	32 (42.7)	30 (40.0)	0.737
Zinc supplementation initiated, n (%)	75 (100.0)	75 (100.0)	—

Primary outcome: duration of diarrhoea

The mean duration of diarrhoea from randomization to resolution was significantly shorter in the probiotic arm than in the placebo arm (54.6 ± 16.8 vs 78.4 ± 22.4 hours; mean difference 23.8 hours, 95% CI 17.2–30.4; $p < 0.001$). The median duration was 52 hours (IQR 42–66) in the probiotic group and 78 hours (IQR 60–94) in the placebo group ($p < 0.001$). Kaplan–Meier analysis demonstrated a significantly faster resolution in the probiotic arm (log-rank $p < 0.001$) (Table 2).

Table 2: Primary outcome and key efficacy measures

Outcome	Probiotic (n=75)	Placebo (n=75)	p-value
Duration of diarrhoea (h), mean ± SD	54.6 ± 16.8	78.4 ± 22.4	<0.001
Duration of diarrhoea (h), median (IQR)	52 (42–66)	78 (60–94)	<0.001
Mean difference (h), 95% CI	–23.8 (–30.4 to –17.2)	—	—
Resolution by day 2, n (%)	22 (29.3)	8 (10.7)	0.005
Resolution by day 3, n (%)	45 (60.0)	21 (28.0)	<0.001
Resolution by day 5, n (%)	72 (96.0)	64 (85.3)	0.025
Diarrhoea persisting beyond 7 days, n (%)	1 (1.3)	5 (6.7)	0.097

Secondary outcomes: stool frequency, vomiting and rehydration

Mean stool frequency was significantly lower in the probiotic group on day 1 (5.8 ± 1.8 vs 6.6 ± 2.0 per 24 hours; $p = 0.011$), day 2 (3.8 ± 1.4 vs 5.6 ± 1.8; $p < 0.001$) and day 3 (2.0 ± 1.2 vs 3.6 ± 1.6; $p < 0.001$). Mean number of vomiting episodes during the study period was lower in the probiotic group (1.2 ± 1.0 vs 1.9 ± 1.4; $p = 0.001$). Intravenous rehydration was required in 9 children (12.0%) in the probiotic group versus 20 children (26.7%) in the placebo group ($p = 0.024$) (Table 3).

Table 3: Stool frequency, vomiting and rehydration requirements

Parameter	Probiotic (n=75)	Placebo (n=75)	p-value
Stool frequency day 1 (per 24 h)	5.8 ± 1.8	6.6 ± 2.0	0.011
Stool frequency day 2 (per 24 h)	3.8 ± 1.4	5.6 ± 1.8	<0.001
Stool frequency day 3 (per 24 h)	2.0 ± 1.2	3.6 ± 1.6	<0.001
Vomiting episodes (total, mean ± SD)	1.2 ± 1.0	1.9 ± 1.4	0.001
ORS volume (mL/kg, mean ± SD)	168 ± 42	212 ± 58	<0.001
IV rehydration required, n (%)	9 (12.0)	20 (26.7)	0.024
Antibiotic use, n (%)	6 (8.0)	9 (12.0)	0.413

Hospital stay and treatment failure

The mean length of hospital stay was significantly shorter in the probiotic arm (3.2 ± 1.1 vs 4.4 ± 1.3 days; $p < 0.001$). Treatment failure occurred in 1 child (1.3%) in the probiotic group and 5 children (6.7%) in the placebo group ($p = 0.097$). No child died during the study period. Late recurrence of diarrhoea within 14 days of resolution was infrequent and comparable between groups (Table 4).

Table 4: Hospital stay, treatment failure and recurrence

Outcome	Probiotic (n=75)	Placebo (n=75)	p-value
Hospital length of stay (days), mean ± SD	3.2 ± 1.1	4.4 ± 1.3	<0.001
Hospital LOS (days), median (IQR)	3 (2–4)	4 (3–5)	<0.001
Treatment failure, n (%)	1 (1.3)	5 (6.7)	0.097

Persistence of diarrhoea >7 days, n (%)	1 (1.3)	5 (6.7)	0.097
Recurrence within 14 days, n (%)	3 (4.0)	4 (5.3)	0.699
Mortality, n (%)	0 (0.0)	0 (0.0)	—

Subgroup analysis by aetiology and age

The benefit of probiotic supplementation was observed in both rotavirus-positive and rotavirus-negative subgroups, with a numerically larger absolute reduction in rotavirus-positive cases (mean difference 26.4 hours vs 20.8 hours), although the test for subgroup interaction was non-significant (p for interaction = 0.176). Age-stratified analysis showed consistent benefit across age groups (Table 5).

Table 5: Subgroup analysis of the primary outcome

Subgroup	Probiotic (h)	Placebo (h)	Difference (h)	p-value
Rotavirus positive (n=84)	53.2 ± 16.4	79.6 ± 22.8	–26.4	<0.001
Rotavirus negative (n=66)	56.4 ± 17.2	77.2 ± 22.0	–20.8	<0.001
Age 6–24 months (n=98)	55.4 ± 17.0	79.2 ± 22.6	–23.8	<0.001
Age 25–60 months (n=52)	53.4 ± 16.4	77.2 ± 22.0	–23.8	<0.001
With vomiting at baseline (n=90)	56.8 ± 17.4	80.6 ± 23.0	–23.8	<0.001

Safety and tolerability

The intervention was well tolerated. Any adverse event during the study period was reported in 8 children (10.7%) in the probiotic arm and 9 children (12.0%) in the placebo arm (p = 0.797). The commonest events were mild bloating (6.7% vs 5.3%) and transient mild flatulence (4.0% vs 5.3%). No bacteraemia or systemic infection attributable to the probiotic product was recorded. No serious adverse events occurred in either arm (Table 6).

Table 6: Adverse events and tolerability

Adverse event	Probiotic, n (%)	Placebo, n (%)	p-value
Any adverse event	8 (10.7)	9 (12.0)	0.797
Mild bloating	5 (6.7)	4 (5.3)	0.731
Flatulence	3 (4.0)	4 (5.3)	0.699
Rash	1 (1.3)	1 (1.3)	1.000
Worsening of vomiting	2 (2.7)	3 (4.0)	0.649
Probiotic bacteraemia / fungaemia	0 (0.0)	0 (0.0)	—
Serious adverse events	0 (0.0)	0 (0.0)	—
Discontinuation due to AE	1 (1.3)	2 (2.7)	0.560

DISCUSSION

In this single-centre, double-blind, placebo-controlled randomized trial of 150 Indonesian children aged 6 to 60 months with acute watery diarrhoea, adjunctive Lactobacillus rhamnosus GG 10^{10} CFU twice daily produced a clinically and statistically significant reduction in the duration of diarrhoea (mean reduction 23.8 hours), accompanied by lower stool frequency, fewer vomiting episodes, a lower need for intravenous rehydration, and shorter hospital stay. The intervention was well tolerated and no serious adverse events were observed.

These findings are consistent with the prevailing meta-analytic evidence base. Szajewska and colleagues, in successive systematic reviews and meta-analyses, have repeatedly demonstrated that LGG shortens the duration of acute diarrhoea by approximately 24 to 26 hours and reduces the risk of diarrhoea lasting ≥4 days [11]. The Cochrane review by Allen *et al*., updated over multiple iterations, similarly concluded that probiotics shortened diarrhoea duration by approximately 25 hours and reduced stool frequency on day 2, with LGG and S. boulardii providing the strongest evidence [6]. The 2014 ESPGHAN guidelines provided a strong positive recommendation for these two strains, with low to moderate quality of evidence [5].

The present findings also align with regional Asian data. Misra *et al*., reported in an Indian randomized trial that LGG reduced diarrhoea duration by approximately 18 hours, with significant reductions in stool frequency and need for intravenous rehydration [12]. Subsequent paediatric trials from Southeast Asia, including small studies in Indonesian children with rotavirus diarrhoea, have likewise reported clinically meaningful reductions in diarrhoea duration with both LGG and S. boulardii [10, 13]. The subgroup observation in the present cohort of larger benefit in rotavirus-positive cases mirrors prior reports suggesting greater efficacy of LGG in viral diarrhoea, although the interaction term did not reach statistical significance and this observation should be considered hypothesis-generating [11, 14].

Importantly, the present results contrast with two large North American emergency-department-

based trials that found no significant clinical benefit of probiotics in children with acute gastroenteritis. The PERC LGG trial by Schnadower *et al*., randomized 943 children to LGG or placebo and found no significant difference in moderate-to-severe gastroenteritis at 14 days [7]. The Canadian PROGUT trial by Freedman *et al*., using a different probiotic product, also reported no significant benefit [8]. Several explanations have been proposed for this divergence, including differences in pathogen distribution (viral predominance in North American trials but a different mix of pathogens elsewhere), baseline severity (often milder in outpatient North American cohorts, reducing the absolute benefit observable), timing of probiotic initiation, dose and strain specificity, and the higher baseline standard of care in high-income settings, which may leave less room for incremental benefit [7-9]. The greater absolute benefit observed in the present cohort, consistent with most prior trials in LMIC settings, may reflect a higher baseline burden of disease, an LGG-rich intervention initiated early in the course, and a population with greater room for therapeutic gain.

Mechanistically, the benefit observed here is biologically plausible. LGG produces antimicrobial peptides, competitively inhibits the binding of enteropathogens to intestinal epithelial cells, enhances intestinal mucin secretion, modulates tight-junction integrity to reduce mucosal permeability, and stimulates production of secretory IgA and IL-10—a profile particularly relevant in rotavirus and other viral enteritis [4, 15]. The complementary action of zinc supplementation, which all children in both arms received, may explain why even the placebo arm achieved a relatively short median duration of diarrhoea by international standards.

Limitations of the present trial include its single-centre design, which limits external generalizability, the absence of comprehensive multiplex molecular pathogen testing beyond rotavirus and standard bacterial culture, and the relatively short follow-up (14 days), which precludes assessment of post-infectious gut function or longer-term microbiota effects. The cost-effectiveness of routine LGG supplementation was not formally evaluated. Notwithstanding these limitations, the trial provides contemporary, locally relevant evidence supporting the role of LGG as an adjunct to WHO-recommended care in Indonesian children with acute watery diarrhoea.

CONCLUSION

Adjunctive Lactobacillus rhamnosus GG supplementation, given at 10^{10} CFU twice daily for up to 5 days in addition to standard WHO-recommended care, significantly reduced the duration of acute watery diarrhoea by approximately 24 hours in Indonesian children aged 6 to 60 months. Reductions in stool frequency, vomiting episodes, need for intravenous rehydration and length of hospital stay were also observed, with a favourable safety profile and no serious adverse events. These findings support the consideration of LGG as an adjunct to oral rehydration solution and zinc supplementation in the management of acute watery diarrhoea in Indonesian paediatric practice. Larger multicentre studies and formal cost-effectiveness analyses are warranted to confirm and extend these observations across diverse Indonesian healthcare settings.

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