Association Between Diarrhea Duration and Severity and Probiotic Efficacy in Children With Acute Gastroenteritis

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INTRODUCTION: **It is unclear whether the alleged efficacy of probiotics in childhood acute gastroenteritis depends on the duration and severity of symptoms before treatment.**

METHODS: **Preplanned secondary analysis of 2 randomized placebo-controlled trials in children 3–48 months of age was conducted in 16 emergency departments in North America evaluating the efficacy of 2 probiotic products (*Lactobacillus rhamnosus* GG and a combination probiotic: *L. rhamnosus* and *L. helveticus*). Participants were categorized in severity groups according to the duration (<24, 24–<72, and ≥72 hours) and the frequency of diarrhea episodes in the 24 hours (≤3, 4–5, and ≥6) before presentation. We used regression models to assess the interaction between pretreatment diarrhea severity groups and treatment arm (probiotic or placebo) in the presence of moderate-to-severe gastroenteritis (Modified Vesikari Scale score ≥9). Secondary outcomes included diarrhea frequency and duration, unscheduled healthcare provider visits, and hospitalization.**

RESULTS: **A total of 1,770 children were included, and 882 (50%) received a probiotic. The development of moderate-to-severe gastroenteritis symptoms after the initiation of treatment did not differ between groups (probiotic—18.4% [162/882] vs placebo—18.3% [162/888]; risk ratio 1.00; 95% confidence interval 0.87, 1.16; $P = 0.95$). There was no evidence of interaction between baseline severity and treatment ($P = 0.61$) for the primary or any of the secondary outcomes: diarrhea duration ($P = 0.88$), maximum diarrheal episodes in a 24-hour period ($P = 0.87$), unscheduled healthcare visits ($P = 0.21$), and hospitalization ($P = 0.87$).**

DISCUSSION: **In children 3–48 months with acute gastroenteritis, the lack of effect of probiotics is not explained by the duration of symptoms or frequency of diarrheal episodes before presentation.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C5

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INTRODUCTION

Acute gastroenteritis (AGE) is an exceedingly common and burdensome pediatric illness that continues to account for over 500,000 deaths in children <5 years of age worldwide each year (1,2). Treatment strategies are limited to supportive care directed at averting dehydration, provision of fluid replacement therapy, and minimizing the impact of vomiting (3). Despite weak evidence, some guidelines (4,5) recommend probiotic use, and consequently, probiotics are commonly used to treat AGE in children in high-income countries (6–9). However, evidence for support of probiotic use has been more closely scrutinized (10) in light of 2 recent large, multicenter, randomized controlled trials (RCTs) that failed to find any benefit associated with 2 probiotic formulations in children with AGE (11,12). Hence, the latest Cochrane review on the subject and leading associations such as the American Gastroenterology Association are now reconsidering and revising their support of probiotic use in children with acute infectious gastroenteritis (13,14).

These results conflict with earlier studies (10,15–17) and have led to questions regarding whether study population characteristics may explain the opposing conclusions. Specifically, it has been proposed that the timing of probiotic initiation in the course of illness and a prolonged interval from symptom onset to the initiation of probiotics may explain the identified lack of benefit (18–23). Questions have also been raised about the role of severity of illness (i.e., diarrhea frequency) on the lack of probiotic treatment effect (21,22).

Addressing the association between AGE characteristics and probiotic therapy efficacy is crucial to assess the generalizability of the findings from recent RCTs (11,12). Therefore, we conducted a secondary, *a priori* planned analysis using combined patient-level data from the 2 large RCTs (11,12) to determine whether probiotic efficacy varies based on duration of symptoms and frequency of diarrhea at the time of treatment initiation.

METHODS

We conducted an *a priori* planned secondary analysis of the Pediatric Emergency Care Applied Research Network (PECARN) Probiotic and the Pediatric Emergency Research Canada (PERC)—Probiotic Regimen for Outpatient Gastroenteritis Utility of Treatment studies (24,25). Briefly, these were prospective, randomized, parallel-group, double-blind trials of children 3–48 months of age with AGE who presented to 10 US and 6 Canadian pediatric emergency departments (EDs). The studies were approved by all local Institutional Review Boards. Written informed consent was obtained from the legal guardians of all participants. All authors had access to the study data and reviewed and approved the final article.

Population

Eligible participants experienced 3 or more watery stools per day, with or without vomiting, and were diagnosed by the ED physician as having AGE. The maximum symptom duration permitted at time of recruitment was ≤72 hours and ≤7 days in the PERC and PECARN studies, respectively. Children were excluded if they or their household members had risk factors for bacteremia (i.e., immunocompromised status, treatment with immunosuppressive therapy, and presence of an indwelling intravascular catheter). Additional exclusion criteria were known presence of structural heart disease, chronic gastrointestinal disorder (e.g., inflammatory bowel disease), pancreatic dysfunction, bilious emesis, hematochezia, use of probiotics during the preceding 14 days, allergy to the products used in the trials, and/or inability to complete follow-up. For this substudy, only children who completed follow-up were included.

Randomization and blinding

Both studies used random-number generating software, accessed through a Web-based randomization system (www.randomize.net), which used permuted blocks of random block sizes and 1:1 trial-group assignment ratios stratified according to site to sequentially assign children to probiotics or placebo. In the PECARN study, randomization was also stratified according to symptom duration (<48 hours vs ≥48 hours). Participants and their parents or guardians, trial and clinical staff, and data analysts were unaware of the trial-group assignments.

Intervention

Consented participants received an oral 5-day course of a probiotic or a placebo that was identical in appearance, smell, taste, and weight. In the PECARN study, the probiotic product was *Lactobacillus rhamnosus* GG (LGG; Culturelle; I-Health), 1×10^{10} colony forming units twice daily. In the PERC trial, participants received a combination probiotic containing 4.0×10^{9} colony forming units of 2 bacterial strains—*L. rhamnosus* R0011 and *L. helveticus* R0052 (Lacidofil; Lallemand Health Solutions)—in a 95:5 ratio, twice daily. In both studies, follow-up data were collected through e-mail or telephone daily for 5 days or until symptoms resolved (if greater than 5 days) and again 14 days after enrollment.

Outcomes

The primary outcome was the presence of moderate-severe gastroenteritis, defined by a total postenrollment Modified Vesikari Scale (MVS) score ≥9 during the 14-day follow-up interval (see Supplementary Table S1, Supplementary Digital Content 1, http://links.lww.com/AJG/C5). The MVS score quantifies severity over a broad range of symptoms and interventions (26), is designed for outpatient use, and has been validated for use in most of the participating hospitals (27,28). This score is a composite measure that incorporates individual symptoms and outcomes that occur during the follow-up period (i.e., the interval where an intervention such as probiotics may provide benefit) including diarrhea frequency and duration, vomiting frequency and duration, maximum temperature, healthcare resource use, and treatments received. Scores range from 0 to 20; higher scores indicate greater severity (27,28). In the 2-study RCTs, the MVS score was calculated based on events occurring between randomization and the final day 14 follow-up data collection point (i.e., symptoms occurring before the visit to the ED were not included in the outcome measure). Events occurring after symptoms had resolved for 24 hours (i.e., absence of vomiting, diarrhea, and fever for 24 hours) are not included in the final score.

Secondary outcomes included diarrhea severity quantified by the maximal number of diarrhea episodes in a 24-hour period, diarrhea duration, unscheduled healthcare provider visits for AGE symptoms, and hospitalization for 48 hours or more. All outcomes refer to events occurring during the 14-day study period after randomization.

Definitions

The severity of diarrhea at enrollment was classified based on the number of episodes in the 24 hours before enrollment as mild (≤3 episodes), moderate (4–5 episodes), or severe (≥6 episodes). Symptom duration at the time of enrollment was categorized as <24, 24–<72, and ≥72 hours. We categorized dehydration as none, mild-to-moderate, and severe based on the Clinical Dehydration Scale score (29,30).

Statistical analyses

All analyses were specified *a priori*. In cases in which information needed to derive the primary outcome was incomplete, we applied multiple imputation methods in each primary study using a sequence of regression models to assign values from corresponding predictive distributions, using the assumption that data were missing at random (31). The results from multiple imputations were combined using standard methods (32).

We described demographic and clinical characteristics and study outcomes by treatment allocation, the frequency of diarrhea episodes in the 24 hours preceding randomization, and diarrhea duration, using the aforementioned variable severity groupings. We combined diarrhea frequency and diarrhea duration into an 8-level measure of baseline diarrhea severity for use in regression models: mild episodes (1–3) for <24 hours, mild episodes (1–3) for 24 hours or more, moderate episodes (4–5) for <24 hours, moderate episodes (4–5) for 24 to <72 hours, moderate episodes (4–5) for 72 hours or more, severe episodes (≥6) for <24 hours, severe episodes (≥6) for 24 to <72 hours, and severe episodes (≥6) for 72 hours or more (Table 1). The adjusted conditional effect of treatment (probiotic vs placebo) on the primary outcome was estimated for each level of baseline severity.

Unadjusted and adjusted conditional effects were estimated as relative risks of experiencing the primary outcome of moderate-to-severe AGE during follow-up, defined by an MVS ≥9. Relative risks were estimated using the modified Poisson regression models fit using generalized estimating equation methods accounting for correlation within the enrolling site (33). A covariate-adjusted model included baseline Clinical Dehydration Severity score, vomiting frequency in the 24-hours preceding randomization, and the study into which the patient was enrolled (i.e., country). We tested for interactions between diarrhea severity (i.e., the combined frequency and duration categorical variable) and treatment using an *F*-test. We estimated conditional relative risks of experiencing an MVS ≥9 for probiotic vs placebo for the 8 levels of baseline diarrhea severity, along with 95% Bonferroni confidence intervals (CIs), resulting in 8 separate 99.375% CIs to adjust for 8 comparisons.

We used the same regression model structure, including estimating unadjusted and adjusted relative risks, testing for interactions, and estimating 95% Bonferroni CIs for conditional effects of treatment on the secondary outcomes: unscheduled healthcare visits for AGE symptoms within 14 days of the index visit and hospitalization after discharge or from the index ED visit lasting >48 hours. We were not able to estimate conditional effects of hospitalization for the 8 levels of baseline diarrhea severity because the outcome was rare and the statistical model did not converge. Instead, we estimated the conditional effect of treatment for 3 levels of frequency of diarrheal episodes in the 24-hours preceding randomization. We tested for an interaction using an *F*-test and estimated 95% Bonferroni CIs adjusted for 3 levels of diarrhea frequency resulting in 3 separate 98.33% CIs to adjust for 3 comparisons.

We fit negative binomial regression models using generalized estimating equation methods to estimate conditional effects of treatment by baseline diarrhea severity for the secondary outcomes of diarrhea frequency and duration. These models estimated incidence rate ratios adjusted for enrolling hospital, baseline Clinical Dehydration Scale score, vomiting frequency in 24-hour period preceding enrollment, and country in which the trial took place. 95% CIs were again adjusted using the Bonferroni method.

Interactions were evaluated using F-tests and were not adjusted for multiple comparisons. Analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

The 2 studies enrolled a total of 1,857 patients (Figure 1); 87 (5%) were lost to follow-up and were excluded, leaving 1,770 patients (943 and 827 from the PECARN and PERC studies, respectively) for inclusion in the analysis. The PERC and PECARN studies recruited between November 2013 and April 2017, and July 2014 and June 2017, respectively. Fifty percent (882/1,770) of study participants were allocated to receive a probiotic. The participant median age was 16 months (interquartile range 10–26), and 55.1% (976/1,770) were male. The median number of diarrheal episodes in the 24 hours preceding enrollment was 5 (interquartile range 4–8), and 76.4% (1,352/1,770) of participants vomited in the preceding 24 hours. Participant groups were well matched for baseline characteristics (Table 1). Most participants (58.7%; 1,039/1,770) had severe diarrhea (≥6 episodes in the preceding 24 hours) and diarrhea duration 24–72 hours before presentation (59.7%; 1,056/1,770; Table 2).

Primary outcome

The proportion of participants who had an MVS score ≥9 after enrollment was similar in the 2 groups (18.4% in the probiotic group [162/882] vs 18.3% in the placebo group [162/888]) with unadjusted relative risk 1.00 (95% CI 0.87–1.16; $P = 0.95$). When analyzed based on the severity group, there was no evidence of interaction across the 8 groups included in the model (interaction $P = 0.61$). Particularly, probiotics conferred no benefit for the subgroup which would theoretically benefit the most from probiotic administration (those with severe diarrhea [≥6 diarrheal episodes in the preceding 24 hours] but short duration [<24 hours]). In that subgroup, the relative risk of experiencing moderate-to-severe disease when taking a probiotic vs placebo was 0.94 (95% CI 0.49–1.79) (Figure 2).

Secondary outcomes

The proportion of participants who visited a healthcare provider after enrollment did not differ between the 2 groups (14.4% in the probiotic group [127/882] vs 14.4% in the placebo group [128/888]) with unadjusted relative risk 1.00 (95% CI 0.83–1.20; $P = 0.96$) (Table 3). There was no evidence of interaction across the 8 diarrhea severity groups for any of the secondary outcomes (Figures 2 and 3). The relative risk of a repeat visit among those with diarrhea of severe frequency but of short duration was 0.73 (95% CI 0.22–2.46) (Figure 2). Because only 57 participants were hospitalized for 48 hours or more, we only analyzed that outcome based on the frequency of diarrhea in the preceding 24 hours and found no evidence of differential effect ($P = 0.87$; Figure 2).

Table 1. Demographics and clinical characteristics by the treatment group

	Placebo (N = 888)	Probiotic (N = 882)	Overall (N = 1,770)
Age in months	16.0 (10.0, 25.9)	16.0 (10.3, 27.0)	16.0 (10.0, 26.0)
Male sex	499 (56.2)	477 (54.1)	976 (55.1)
Country/study			
Canada PROGUT study	413 (46.5)	414 (46.9)	827 (46.7)
US PECARN study	475 (53.5)	468 (53.1)	943 (53.3)
Weight-for-age *Z*-score[a]	0.3 (−0.4, 1.1)	0.3 (−0.5, 1.0)	0.3 (−0.5, 1.0)
Received antibiotics in the past 14 d	95 (10.7)	89 (10.1)	184 (10.4)
Received a vaccine against rotavirus[c]	498 (56.1)	496 (56.2)	994 (56.1)
Symptom duration before randomization (d)	2.1 (1.2, 2.9)	2.1 (1.2, 3.0)	2.1 (1.2, 2.9)
Clinical dehydration scale score (30)			
None (0)	551 (62.0)	519 (58.8)	1,070 (60.4)
Mild to moderate (1–4)	320 (36.0)	341 (38.7)	661 (37.3)
Severe (5–8)	18 (2.0)	22 (2.5)	40 (2.2)
Baseline MVS score	11.0 (9.0, 13.0)	12.0 (10.0, 13.0)	11.0 (9.0, 13.0)
Presence of vomiting at presentation	675 (76.0)	677 (76.8)	1,352 (76.4)
No. of vomiting episodes in the 24 hr before randomization	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)
No. of diarrheal episodes in the 24 hr before randomization	5.0 (4.0, 8.0)	5.0 (4.0, 8.0)	5.0 (4.0, 8.0)
Fever	459 (51.7)	479 (54.3)	938 (53.0)
IV fluids administered during ED visit	116 (13.1)	117 (13.3)	233 (13.2)
Admitted to the hospital from the ED	30 (3.4)	33 (3.7)	63 (3.6)
Infectious agent			
None	338 (38.1)	299 (33.9)	637 (36.0)
Adenovirus	78 (8.8)	61 (6.9)	139 (7.9)
Aeromonas spp.	2 (0.2)	0 (0.0)	2 (0.1)
Campylobacter spp.	6 (0.7)	8 (0.9)	14 (0.8)
Clostridioides difficile (if 2 yr or older)[b]	5 (0.6)	0 (0.0)	5 (0.3)
Cryptosporidium	3 (0.3)	5 (0.6)	8 (0.5)
Enterotoxigenic *Escherichia coli*	5 (0.6)	1 (0.1)	6 (0.3)
Entamoeba	1 (0.1)	1 (0.1)	2 (0.1)
Giardia	1 (0.1)	1 (0.1)	2 (0.1)
Norovirus	166 (18.7)	156 (17.7)	322 (18.2)
Rotavirus	122 (13.7)	166 (18.8)	288 (16.3)
Shiga-toxin producing *Escherichia coli*	3 (0.3)	2 (0.2)	5 (0.3)
Salmonella spp.	11 (1.2)	14 (1.6)	25 (1.4)
Shigella spp.	13 (1.5)	22 (2.5)	35 (2.0)
Other coinfection	4 (0.5)	3 (0.3)	7 (0.4)
Not tested	101 (11.4)	104 (11.8)	205 (11.6)
Preenrollment diarrhea severity			
Mild frequency (1–3 episodes), short (<24 hr) duration	34 (3.9)	39 (4.4)	73 (4.1)
Mild frequency (1–3 episodes), 24 hr or more[a]	81 (9.1)	87 (9.9)	168 (9.5)

Table 1. (*continued*)

	Placebo (N = 888)	Probiotic (N = 882)	Overall (N = 1,770)
Moderate frequency (4–5 episodes), short (<24 hr) duration	48 (5.4)	45 (5.1)	93 (5.3)
Moderate frequency (4–5 episodes), medium (24–<72 hr) duration	155 (17.4)	135 (15.3)	290 (16.4)
Moderate frequency (4–5 episodes), long (≥72 hr) duration	56 (6.3)	52 (5.9)	108 (6.1)
Severe frequency (≥6 episodes), short (<24 hr) duration	67 (7.6)	72 (8.2)	140 (7.9)
Severe frequency (≥6 episodes), medium (24–<72 hr) duration	319 (35.9)	305 (34.6)	624 (35.2)
Severe frequency (≥6 episodes), long (≥72 hr) duration	129 (14.5)	147 (16.6)	275 (15.5)

Number (%) or median (Q1, Q3) shown.
ED, emergency department; IV, intravenous; MVS, Modified Vesikari Scale; PECARN, Pediatric Emergency Care Applied Research Network; PROGUT, Probiotic Regimen for Outpatient Gastroenteritis Utility of Treatment.
[a]Implausible or missing weight *Z*-scores for 10 patients (3 placebo, 7 probiotic) were not included in the summary.
[b]Children <2 years with PCR positive *Clostridioides difficile* were assumed to be colonized.
[c]Rotavirus vaccine information was unknown for 104 (11.7%) placebo and 99 (11.2%) probiotic patients.

Finally, there were no differences between the probiotic and placebo groups in diarrhea duration and maximum diarrheal episodes across the 8 severity groups ($P = 0.88$ and 0.87, respectively; Figure 3).

DISCUSSION

In this patient-level analysis of combined data from 2 large RCTs of 2 different probiotic formulations conducted in 2 countries evaluating outcomes in children with AGE, we explored the effect of both duration and frequency of diarrhea before enrollment on outcomes. In this analysis, we identified no evidence that either of these features influenced the findings of the original trials. Despite concerns (19–23) that these RCTs overlooked the benefits of probiotics because they were administered too late in the illness or that benefits accruing to children with severe diarrhea were diluted by those with less severe illnesses, our findings refute such assertions. Notably, we evaluated 8 different combinations of diarrhea duration and severity and identified no benefit of probiotic treatment on any outcome explored including overall illness severity, healthcare resource utilization, and ongoing diarrheal symptoms. These results clarify that diarrhea duration and frequency before initiating probiotic therapy are not associated with the presence or absence of beneficial effects in the study population.

To address the sentiment that probiotics effectiveness is more pronounced when initiated early in the course of illness and when provided to children with more severe disease (18,20–22), we analyzed our data in subgroups using the combination of these 2 features. Nonetheless, even among children with severe diarrhea of short duration, we identified no differences in the number of children experiencing moderate-to-severe AGE, or any of our secondary outcomes, between treatment groups. Because most previous probiotic studies focused on the isolated outcomes of diarrhea frequency and duration, we specifically analyzed these outcomes, yet found no benefits that could be attributed to probiotic treatment.

Evidence that probiotic efficacy is greater when initiated early in illness is limited and inconsistent. In a meta-analysis of 8 studies (total n = 966) (34), probiotics were most effective when initiated between 49 and 72 hours (mean decrease in diarrhea duration of 16 hours [95% CI 11–21]). When initiated within 24–48 hours of symptom onset, the mean decrease in diarrhea duration was only 2 hours (95% CI 0.1–3). A separate meta-analysis (35) reported that in studies where enrollment was limited to patients with ≤5 days of diarrhea (total n = 923), the mean duration of diarrhea symptoms in patients given a probiotic vs placebo was decreased by 1.4 days (95% CI 0.5–2.3) compared with no decrease in diarrhea duration (0.4 days; 95% CI: −0.1 to 1) in studies where patients with <7 days of symptoms were enrolled (total n = 1,258). Finally, a US, ED-based study not included in these meta-analyses reported a trend toward benefit in patients with symptoms lasting >48 hours (36).

Although it has been postulated that probiotic AGE trials with negative results may reflect the recruitment of disproportionate numbers of children with mild disease (21,22), the literature points in the opposite direction. Using inpatient status as a proxy for increased disease severity, a 2010 Cochrane review found diarrhea duration was decreased by 42 hours (95% CI 31–55) in outpatients as compared with a 21-hour reduction (95% CI 10–31) among hospitalized children, reflecting a greater postulated benefit among those with milder disease (37). In an updated 2019 meta-analysis (35), the duration of diarrhea was decreased by 0.95 days (95% CI 0.56–1.91) in outpatients as compared with 0.66 days (95% CI 0.05–1.27) among inpatients. To directly address this issue, we conducted an analysis evaluating the relationship between diarrhea severity and outcomes and identified no benefits associated with probiotic use among children with severe diarrhea, even when restricted to children with <48 hours of symptoms.

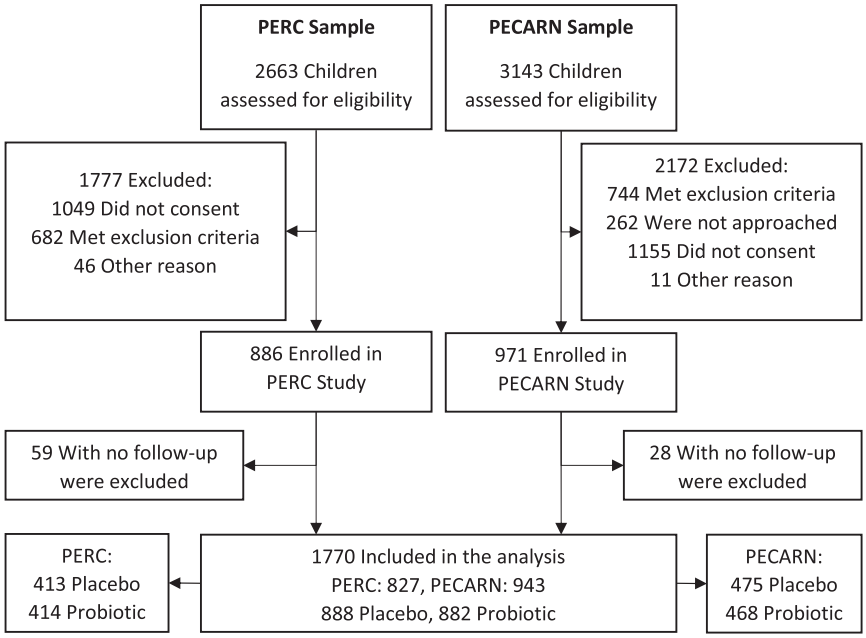

Figure 1. Study flow. PECARN, Pediatric Emergency Care Applied Research Network; PERC, Pediatric Emergency Research Canada.

This study uniquely amalgamates 2 data sets that used similar data fields and definitions thereby permitting their integration to conduct this subanalysis that addresses important questions in the probiotic field. Because we included studies that were conducted in 2 countries and 16 institutions and used 2 different probiotic formulations, our findings have wide applicability.

Table 2. Demographics and clinical characteristics by diarrhea severity and duration

	Baseline no. of diarrhea episodes/24 hr			Baseline duration of diarrhea		
	Mild (1–3) (N = 241)	Moderate (4–5) (N = 490)	Severe (6+) (N = 1,039)	<24 hr (N = 306)	24–<72 hr (N = 1,056)	72 hr or more (N = 408)
Male sex	132 (54.8)	277 (56.6)	567 (54.5)	175 (57.1)	568 (53.8)	234 (57.2)
Age in months	18.0 (11.0, 26.4)	16.0 (10.1, 26.9)	16.0 (9.7, 25.8)	19.6 (11.0, 29.8)	15.4 (10.0, 25.7)	15.9 (9.8, 25.3)
Country/study						
Canada PROGUT study	143 (59.3)	253 (51.6)	431 (41.5)	155 (50.7)	624 (59.1)	48 (11.7)
US PECARN study	98 (40.7)	237 (48.4)	608 (58.5)	151 (49.3)	432 (40.9)	361 (88.3)
Treatment received						
Placebo	115 (47.8)	258 (52.7)	515 (49.5)	149 (48.8)	545 (51.7)	193 (47.3)
Probiotic	126 (52.2)	232 (47.3)	524 (50.5)	157 (51.2)	510 (48.3)	215 (52.7)
Clinical dehydration score (30)						
None (0)	155 (64.2)	312 (63.6)	603 (58.0)	195 (63.6)	602 (57.1)	273 (66.8)
Mild to moderate (1–4)	83 (34.5)	173 (35.3)	404 (38.9)	106 (34.8)	423 (40.1)	131 (32.1)
Severe (5–8)	3 (1.3)	5 (1.1)	31 (3.0)	5 (1.6)	30 (2.8)	5 (1.1)
No. of vomit episodes in the 24 hr preceding enrollment						
None	46 (19.1)	135 (27.6)	237 (22.8)	69 (22.5)	248 (23.5)	101 (24.7)
1	23 (9.5)	47 (9.6)	74 (7.1)	31 (10.2)	74 (7.0)	38 (9.4)
2–4	85 (35.3)	140 (28.6)	281 (27.1)	76 (24.9)	284 (26.9)	146 (35.8)
5 or more	87 (36.1)	168 (34.3)	447 (43.0)	130 (42.4)	449 (42.5)	123 (30.1)

Number (%) or median (Q1, Q3) shown.
MVS, Modified Vesikari Scale; PECARN, Pediatric Emergency Care Applied Research Network; PROGUT, Probiotic Regimen for Outpatient Gastroenteritis Utility of Treatment.

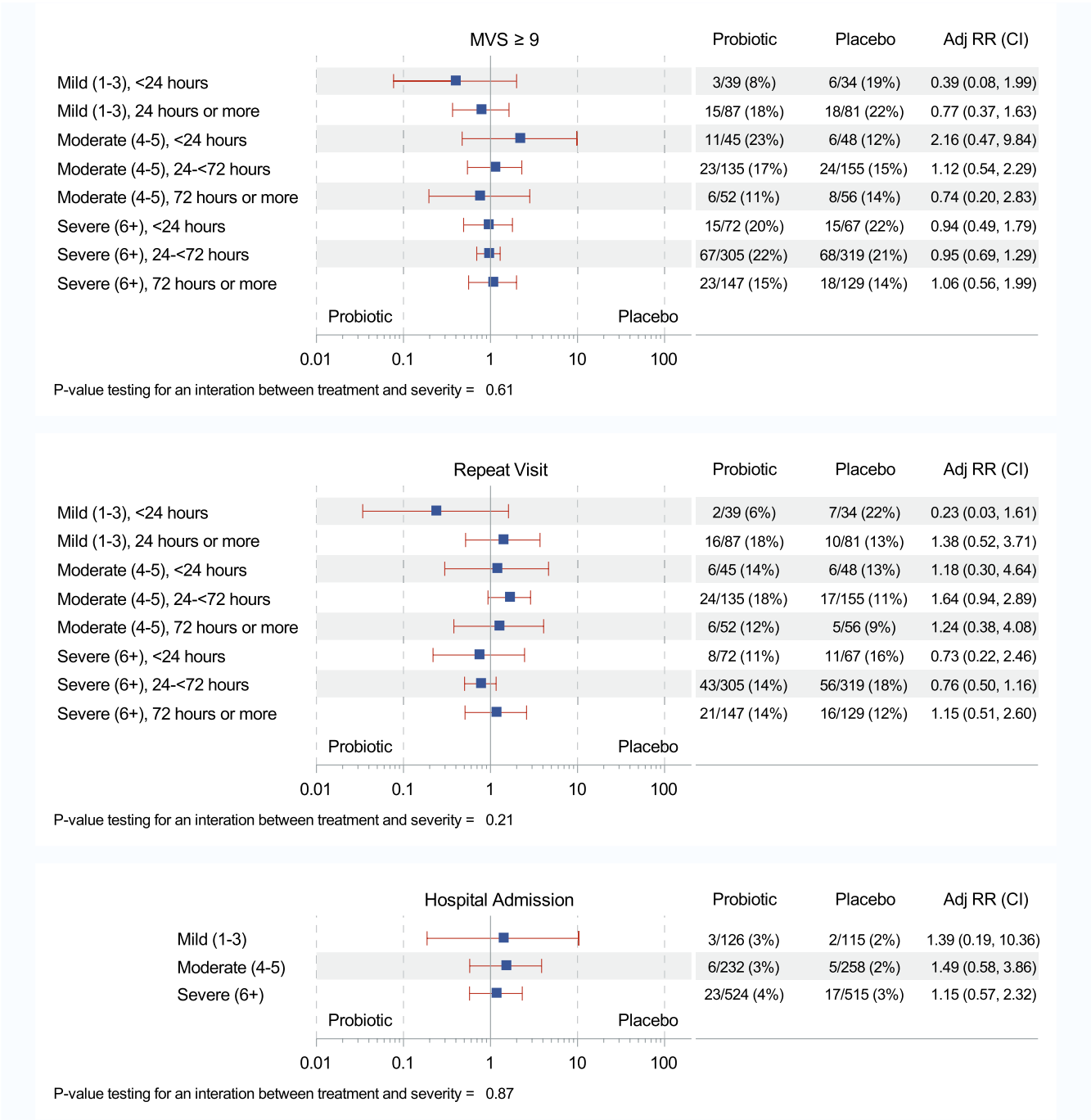

Figure 2. Conditional effect of the probiotic treatment within severity subgroups on outcomes: moderate-severe gastroenteritis (Modified Vesikari Scale [MVS] ≥9), repeat healthcare visit after discharge and before symptom resolution, and hospital admission resulting from index visit lasting ≥48 hours or postdischarge and before symptom resolution. The number (%) with each outcome and the adjusted relative risk (RR) and 95% Bonferroni confidence interval (CI) are shown. Global *P* value testing for any interaction between treatment effect and baseline diarrhea severity is shown.

Moreover, after adjusting for country and institution, our models accounted for other markers of disease severity such as degree of dehydration and frequency of vomiting at presentation. Finally, our results were consistent across the primary and secondary outcomes, thereby solidifying our confidence in result interpretation.

We do acknowledge several potential limitations. Although combining studies which used 2 different probiotics is not ideal, as that might diminish the detection of strain-specific effects (38), the individual studies were both negative for the outcomes evaluated, and we therefore hypothesized that increasing the power might enable the detection of more subtle beneficial effects. It should be noted that our findings are specific to the probiotics that we studied and to our population which included children under 4 years of age who sought ED care in the United States and Canada.

Table 3. Primary and secondary outcomes by diarrhea severity

Primary and secondary outcomes measured after study enrollment	Baseline no. of diarrhea episodes			Baseline duration of diarrhea			Overall (N = 1,770)
	Mild (1–3) (N = 241)	Moderate (4–5) (N = 490)	Severe (6+) (N = 1,039)	<24 hr (N = 306)	24–<72 hr (N = 1,056)	72 hr or more (N = 408)	
Moderate-severe acute gastroenteritis (MVS ≥9)	43 (17.9)	76 (15.6)	205 (19.7)	56 (18.2)	211 (19.9)	58 (14.3)	325 (18.3)
Maximum no. of diarrhea episodes/24 hr	6.9 (9.44)	7.7 (10.59)	12.8 (15.75)	10.3 (12.34)	10.6 (13.69)	10.9 (15.67)	10.6 (14.09)
Days of diarrhea	2.4 (2.45)	2.3 (2.13)	3.0 (2.82)	2.5 (2.22)	2.8 (2.65)	2.8 (2.80)	2.8 (2.62)
Healthcare visit	36 (14.8)	65 (13.2)	155 (14.9)	41 (13.3)	165 (15.6)	49 (12.1)	255 (14.4)
Hospital admission	6 (2.4)	11 (2.3)	40 (3.8)	8 (2.5)	36 (3.4)	14 (3.3)	57 (3.2)

Number (%) or mean (SD) shown.
MVS, Modified Vesikari Scale.

In conclusion, our study demonstrates that in children who presented to the ED with AGE, probiotic administration does not prevent the development of moderate-to-severe gastroenteritis within 14 days after enrollment, irrespective of the duration or frequency of diarrhea before presentation.

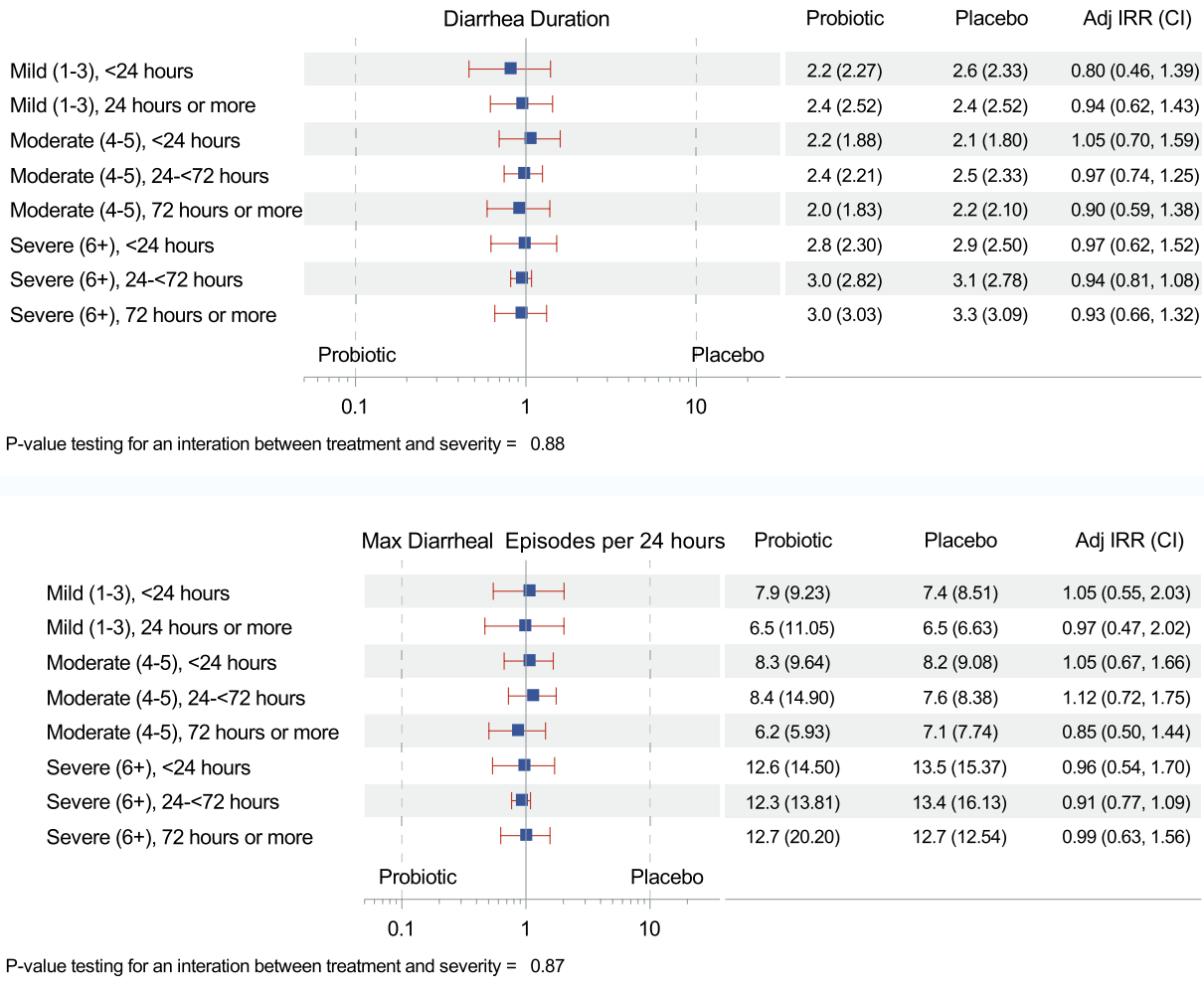

Figure 3. Conditional effect of the probiotic treatment within severity subgroups on outcomes of diarrhea duration (days) and the maximal number of diarrheal episodes per 24-hour period. The mean (standard deviation) of each outcome along with the adjusted incidence rate ratio (IRR) and 95% Bonferroni confidence interval (CI) are shown. Global *P* value testing for any interaction between treatment effect and baseline diarrhea severity is shown.

CONFLICTS OF INTEREST

Guarantor of the article: David Schnadower, MD, MPH.

Specific author contributions: D.S., S.B.F., and P.I.T.: conceptualized and designed the study, drafted, reviewed, and revised the article. J.M.V. and C.S.O.: performed all statistical analyses. K.J.O., C.V., S.S., K.H., A.J.R., N.P., C.G.R., S.R.B., S.G., P.M., E.C.P., K.F., R.E.S., and T.H.C.: collected data and reviewed the article for important intellectual content. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

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Potential competing interests: D.S. received in-kind study drug and placebo from iHeath; however, the company did not contribute financially to the study or to the investigators, and their employees do not have access study data. I-Health personnel had no role in study design, collection management, analysis and interpretation of data, nor did they have any role or authority in writing the report nor the decision to submit the trial for publication. S.B.F. has received in-kind (study drug and placebo) from Lallemand Health Solutions. He provides consulting services to Takeda Pharmaceutical Company, RedHill Biopharma and Eligo Bioscience S.A.S. on childhood intestinal disorders and was supported by the Alberta Children's Hospital Foundation Professorship in Child Health and Wellness. All other authors report no relevant conflicts.

Clinical trial registration: ClinicalTrials.gov # NCT01773967 and NCT01853124.

Study Highlights

WHAT IS KNOWN

- ✓ Probiotics are commonly used to treat pediatric acute gastroenteritis.
- ✓ They are believed to be most effective if started early and in more severe cases of acute gastroenteritis.

WHAT IS NEW HERE

- ✓ Probiotics offer no benefits in children with gastroenteritis, regardless of the timing or severity of symptoms.

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