# Small Intestine Bacterial Overgrowth and Environmental Enteropathy in Bangladeshi Children

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**ABSTRACT**   Recent studies suggest small intestine bacterial overgrowth (SIBO) is common among developing world children. SIBO's pathogenesis and effect in the developing world are unclear. Our objective was to determine the prevalence of SIBO in Bangladeshi children and its association with malnutrition. Secondary objectives included determination of SIBO's association with sanitation, diarrheal disease, and environmental enteropathy. We performed a cross-sectional analysis of 90 Bangladeshi 2-year-olds monitored since birth from an impoverished neighborhood. SIBO was diagnosed via glucose hydrogen breath testing, with a cutoff of a 12-ppm increase over baseline used for SIBO positivity. Multivariable logistic regression was performed to investigate SIBO predictors. Differences in concomitant inflammation and permeability between SIBO-positive and -negative children were compared with multiple comparison adjustment. A total of 16.7% (15/90) of the children had SIBO. The strongest predictors of SIBO were decreased length-for-age $Z$ score since birth (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.03 to 0.60) and an open sewer outside the home (OR, 4.78; 95% CI, 1.06 to 21.62). Recent or frequent diarrheal disease did not predict SIBO. The markers of intestinal inflammation fecal Reg 1$\beta$ (116.8 versus 65.6 $\mu$g/ml; $P = 0.02$) and fecal calprotectin (1,834.6 versus 766.7 $\mu$g/g; $P = 0.004$) were elevated in SIBO-positive children. Measures of intestinal permeability and systemic inflammation did not differ between the groups. These findings suggest linear growth faltering and poor sanitation are associated with SIBO independently of recent or frequent diarrheal disease. SIBO is associated with intestinal inflammation but not increased permeability or systemic inflammation.

**IMPORTANCE**   A total of 165 million children worldwide are considered stunted, which is associated with increased risk of death prior to age 5 years and cognitive disability. Stunting has, in part, been attributed to the presence of environmental enteropathy. Environmental enteropathy is a poorly understood condition leading to chronic intestinal inflammation. It has been postulated that small intestine bacterial overgrowth contributes to the pathogenesis of environmental enteropathy as overgrowth has been associated with intestinal inflammation and micronutrient malabsorption when it develops in other clinical contexts. This study confirms the finding that overgrowth occurs at high rates in the developing world. This is the first study to show that overgrowth is associated with intestinal inflammation and linear growth delay in this setting and is the first to examine why children with no known gastrointestinal dysfunction develop overgrowth from the developing world environment.

Small intestine bacterial overgrowth (SIBO) is defined as greater than $10^5$ CFU/ml upper intestinal aspirate as assessed by both anaerobic and aerobic cultures (1). SIBO can be measured by culture of endoscopically obtained upper gastrointestinal (GI) aspirates or noninvasively by hydrogen breath testing. Traditionally, SIBO has been considered a secondary condition that develops in the setting of altered intestinal anatomy, slowed intestinal motility, or aberrant gastrointestinal function. SIBO in this setting has been associated with poor nutritional outcomes, including steatorrhea with loss of fat-soluble vitamins (excluding vitamin K) (2–9), carbohydrate malabsorption (10–13), and a protein-losing enteropathy (14–18). Deficiencies in cobalamin (19–21), thiamine (22), riboflavin (18), pyridoxine (18), and nicotinamide (23) have been documented. SIBO has also been shown to lead to increased GI permeability (24, 25) and alteration of mucosal immunity, including an increase in IgA plasma cells and increased mucosal interleukin-6 (IL-6) (26, 27). SIBO has recently been recognized as an underdiagnosed condition in children in the developed world with gastrointestinal symptoms (28).

Recently, preliminary studies have suggested that children in

**TABLE 1** Enrollment characteristics of the study cohort stratified by SIBO positivity

| Parameter | Result for[a]: | | P value[b] |
|---|---|---|---|
| | SIBO negative (n = 75) | SIBO positive (n = 15) | |
| Female, no. (%) | 37 (49) | 9 (60) | 0.58* |
| Estimated gestational age, wk | 37.3 ± 1.3 | 37.5 ± 1.4 | 0.67** |
| Characteristic at enrollment | | | |
|   Age, days | 5.0 ± 1.8 | 4.7 ± 1.9 | 0.53** |
|   Length, cm | 48.7 ± 1.6 | 49.5 ± 1.9 | 0.11** |
|   Wt, kg | 2.8 ± 0.4 | 2.9 ± 0.4 | 0.73** |
|   Maternal age, yr | 24.4 ± 4.1 | 25.3 ± 4.1 | 0.40** |
| Mother as housewife, no. (%) | 67 (89) | 15 (100) | 0.34* |
| Income, taka | 13,283 ± 9,539 | 17,067 ± 12,759 | 0.94** |
| People/room living in home, no. | 3.9 ± 1.3 | 3.4 ± 0.9 | 0.24** |

[a] Data are expressed as the mean ± SD for continuous measures and count (percentage) for discrete measures.
[b] *, Exact Pearson chi-square test; **, Mann-Whitney U test.

the lower socioeconomic strata of developing world countries may develop SIBO at significantly higher rates than their more privileged counterparts, with a prevalence of up to 30% in slum-dwelling children (29–31). SIBO in children from low-income countries has been associated with poor carbohydrate absorption and underperformance of an oral cholera vaccine (32–34). The pathogenesis of SIBO in developing world children with no underlying intestinal pathology remains unclear. It is also unclear what role SIBO plays in environmental enteropathy (EE), an inflammatory intestinal disorder of the developing world that has been implicated in growth failure and poor neurocognitive outcomes (35–38).

In this study, we sought to test the prevalence of SIBO and its potential association with malnutrition, sanitation, and diarrheal disease. We also ought to determine SIBO's association with concomitant gut inflammation, intestinal permeability, and systemic inflammation. It was our primary hypothesis that development of SIBO in this setting would be associated with poor nutrition, poor sanitation, and recent or frequent diarrheal episodes. Our secondary hypothesis was that SIBO was associated with intestinal inflammation, increased intestinal permeability, and systemic inflammation.

## RESULTS

**Enrollment characteristics.** A total of 103 children were assessed for SIBO testing. Of note, none had known chronic gastrointestinal disease. Nine children were excluded for a weight-for-age Z (WAZ) score of ≤−3 standard deviations (SD) and were referred for nutritional therapy. One parent refused testing. Three children were unable to complete testing for the 3-h test period and were excluded from analysis. A total of 90 children successfully competed SIBO testing. The average age of children tested was 24.6 months (range, 24.3 to 25.1 months). Of the children tested, 46 (51%) were female. Birth demographics of the children showed an average estimated gestational age of 37.3 weeks with an average length and weight at enrollment of 48.9 cm and 2.8 kg, respectively. Mothers had an average age of 24.5 years, and 82 (91%) considered themselves housewives. The average monthly household income was 13,913 Bangladeshi taka (approximately $179 U.S. dollars). The average number of people living per room in homes was 3.8. There was no significant difference in the enrollment characteristics between SIBO-positive and SIBO-negative children (Table 1) or between these 90 children and the 700 chil-

dren in the full PROVIDE cohort (data not shown). Of note, data on estimated gestational age were not collected for the entire cohort of 700 children and thus were unavailable for comparison.

**SIBO was associated with growth faltering and lack of sanitation.** The prevalence of SIBO in our cohort was 16.7% (15/90). Figure 1 shows the glucose hydrogen breath test results from both SIBO-positive and SIBO-negative children. Children with SIBO had significantly worse linear growth (stunting) from enrollment to age 2 years compared to children without SIBO. A 1-U drop in length-for-age Z (LAZ) score from enrollment to 2 years conferred an odds ratio (OR) of 7.69 (95% confidence interval [CI], 1.67 to 33.33) for the development of SIBO.

The odds of developing SIBO were increased by the presence of an open drain/sewer outside the home (OR, 4.78; 95% CI, 1.06 to 21.62). Odds of developing SIBO were also increased by the household's drinking water being obtained from a source other than the municipal water supply and by the mother cutting her fingernails less than once a month. Because of the low number of households with a water source other than the municipal supply and the low number of mothers who did not cut their nails at least once a month (1 per group and 2 per group, respectively), the 95% CI for these OR was extremely large, making estimation of odds unreliable despite their significance.

Weight faltering (negative change in WAZ score from enrollment to 2 years), socioeconomic status (income), and diarrheal disease (number of diarrheal episodes in the child's life or presence of a diarrheal episode in the 30 days prior to SIBO testing) were not significant predictors of SIBO (Table 2).

**SIBO was associated with concomitant intestinal inflammation but not increased intestinal permeability or systemic inflammation.** Mean fecal Reg 1β was 116.8 μg/ml in the SIBO-positive group compared to 65.6 μg/ml in SIBO-negative children (P = 0.02). Fecal calprotectin was also significantly increased in SIBO-positive children compared to the SIBO-negative group (mean of 1,834.6 versus 766.7 μg/g, respectively; P = 0.004) (Fig. 2).

While SIBO-positive children had significantly increased markers of intestinal inflammation, there was no difference in lactose/mannitol (L/M) ratios between SIBO-positive and SIBO-negative children. Likewise, there was no difference in C-reactive protein or any of the 17 cytokines measured between the groups (data not shown). Anthropometry results at the time of SIBO
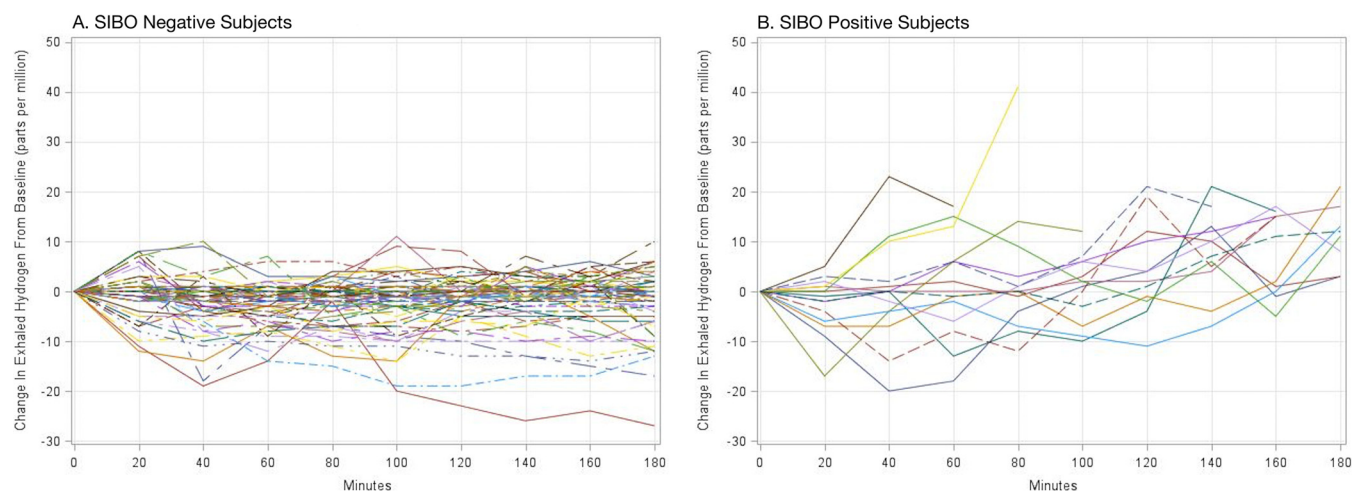
**FIG 1** Glucose-hydrogen breath testing results for 90 2-year-olds in Dhaka, Bangladesh, with the change in exhaled breath hydrogen from the patient's baseline shown on the *y* axis and time shown on the *x* axis. (A) Results for small intestine bacterial overgrowth (SIBO)-negative subjects demonstrate no increase in breath hydrogen greater than 12 ppm of exhaled hydrogen over the patient's own baseline. (B) Results for SIBO-positive subjects demonstrate a peak in exhaled breath hydrogen over the subject's baseline by ≥12 ppm.

testing were also not significantly different in SIBO-positive children compared to SIBO-negative children.

When the false discovery rate (FDR) correction was applied, fecal Reg 1β and fecal calprotectin remained significant, with FDR-adjusted values of 0.25 and 0.1, respectively.

## DISCUSSION

Our study demonstrates that SIBO in a developing world setting is associated with growth faltering, poor sanitation, and intestinal inflammation. Poor growth and intestinal inflammation are endemic in children from low-income countries, and the importance of this work derives from its identification of SIBO as a potentially treatable contributor to these problems of child morbidity. Of note, our findings are contradictory to other investigations which found an increase in intestinal permeability in adults with SIBO in the developed world (24, 25, 39). However, patients in previous studies had underlying gastrointestinal disease that may have predisposed them to increased intestinal permeability. The lack of increased L/M ratios in SIBO is also interesting because L/M ratios were increased in previous studies of EE (38, 40). This may indicate that SIBO and EE are separate but concomitant conditions or that EE is actually a syndrome encompassing a heterogeneous group of environmentally derived intestinal inflammatory conditions with variable manifestations but common outcomes. Furthermore, even SIBO-negative children in our cohort had fecal calprotectin levels that were elevated from those reported in asymptomatic children in the developed world, suggesting that the majority of children in our study population had some degree of EE (41).

This work is the first to investigate factors that may predispose developing world children with no known gastrointestinal pathology to SIBO. The significance of growth stunting in our model demonstrates an association between linear growth delay and overgrowth independent of diarrheal disease and sanitation. However, in the absence of longitudinal analysis, the details of this association remain unclear. Given the known nutritional consequences of SIBO in other settings, it is biologically plausible that SIBO plays a causative role in growth stunting. It is also possible that a variable we did not measure in our analysis leads to both SIBO and declining LAZ and thus is acting as a confounder in our model.

We designed our regression model to investigate two competing hypotheses on why children would develop SIBO from their environment. The first hypothesis was that children develop SIBO

**TABLE 2** Predictors of SIBO positivity at 2 years of age in Bangladeshi infants

| Parameter | Result for[a]: | | P value | OR (95% CI) |
|---|---|---|---|---|
| | SIBO negative (n = 75) | SIBO positive (n = 15) | | |
| Income, taka[b] | 13,394.6 ± 9,554.5 | 17,066.7 ± 14,758.6 | 0.15 | 1.00 (0.99, 1.01) |
| Diarrheal episodes in child's life, no. | 6.1 ± 5.0 | 4.9 ± 4.3 | 0.15 | 0.88 (0.74, 1.05) |
| At least 1 diarrheal episode in 30 days prior to SIBO testing, no. (%) | 12 (16) | 2 (13) | 0.97 | 0.97 (0.12, 7.83) |
| ΔWAZ score from enrollment to 2 yr of age | 0.03 ± 1.0 | −0.27 ± 0.9 | 0.19 | 1.99 (0.71, 5.56) |
| ΔLAZ score from enrollment to 2 yr of age | −0.36 ± 0.9 | −0.86 ± 0.7 | 0.01 | 0.13 (0.03, 0.60) |
| Presence of open drain/sewer outside home, no. (%) | 24 (32) | 8 (53) | 0.04 | 4.78 (1.06, 21.62) |
| Water source other than municipal supply, no. (%) | 1 (1) | 1 (6) | 0.01 | —[c] |
| Mother cuts her fingernails <1 time per mo, no. (%) | 2 (3) | 2 (13) | 0.03 | — |

[a] Data are expressed as the mean ± SD for continuous measures and count (percentage) for discrete measures. Homer-Lemeshow goodness of fit, $\chi^2 = 11.38$ and $P = 0.18$.
[b] One United States dollar = 77 to 82 Bangladeshi taka for the duration of this study.
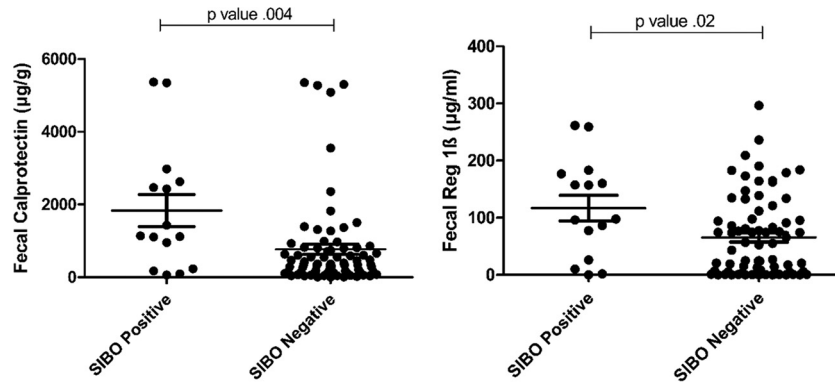[c] —, insufficient sample size to report a reliable OR.

**FIG 2** Inflammatory markers in small intestine bacterial overgrowth (SIBO)-positive and -negative subjects. (A) Calprotectin is a neutrophil-derived protein that, when elevated in the stool, indicates intestinal inflammation. The mean fecal calprotectin level in SIBO-positive subjects was 1,834.6 $\mu$g/g compared to 766.7 $\mu$g/g in SIBO-negative children ($P = 0.004$). (B) Reg 1$\beta$ is a proproliferative, antiapoptotic protein secreted by damaged epithelial cells. When elevated in the stool, it indicates damage to the intestinal epithelium. Children with SIBO had a mean Reg 1$\beta$ level of 116.8 $\mu$g/ml compared to 65.6 $\mu$g/ml in SIBO-negative children ($P = 0.02$).

due to lumenal stasis secondary to gastroparesis or ileus after recent or recurrent enteric infection. This is biologically plausible given that children in Bangladesh have a mean of 4.7 diarrheal episodes and a median of 3.3 enteric pathogens identified in nondiarrheal stools in the first year of life alone (42). The second hypothesis that has been suggested is that children develop a functional motility disorder with a hypoactive migrating motor complex and decreased intestinal contractility due to constant lipopolysaccharide exposure from an unsanitary environment (43). This phenomenon has been shown to occur in animal models and in women with late radiation enteropathy (44–46). Our analysis suggests that recent or frequent enteric infection does not predispose to SIBO, while measures of environmental contamination do. Although we did not test motility in this study, our results suggest this endeavor might be fruitful in future investigation.

To date, literature on environmentally derived SIBO in the developing world is sparse. It has been shown that SIBO occurs in the lower socioeconomic strata of developing world countries with increased prevalence compared to countries with greater financial means (29–31). SIBO in this setting has been shown to lead to poor carbohydrate absorption and oral vaccine underperformance (32–34). It has also been shown to have increased prevalence in severe malnutrition (47). Much of our understanding of the pathogenesis of SIBO comes from studies in the developed world in patients with underlying gastrointestinal pathology. While these studies are extremely informative, it is important to understand that the pathogenesis and pathophysiology of SIBO in developing world children with no underlying gastrointestinal disease may be different from those of patients in industrialized countries.

Our study has several important limitations. First, the natural history of overgrowth in the developing world setting is unknown. It may be present until treated as in underlying gastrointestinal disease or may have a waxing and waning course. Thus, a cross-sectional analysis that detects children with SIBO only at the time of testing may miss children who have had recent or prolonged SIBO in their lifetime. Second, we did not collect data on recent antibiotic use that may be a confounder in our analysis. Third, a cutoff of 12 ppm for the hydrogen breath test used to diagnose SIBO is based on adult studies in the developed world and may not

be optimal for our pediatric and developing world study environment. Currently, there is no evidence-based cutoff for SIBO diagnosis specific to developing world children. Fourth, our sample size was too low to obtain reliable odds ratios for several of the covariates tested, despite their significance. Finally, the inability to test children with a WAZ of $\leq -3$ SD may introduce selection bias into our study given that we did not evaluate children with the most severe outcomes.

Strengths of this study include duplicate measures intestinal and systemic inflammation. Use of the PROVIDE database for data on predictive variables also provided for duplicate measures of sanitation. This database allowed for accurate data on all diarrheal illnesses over the course of the children's lifetime.

**Conclusion.** SIBO was observed in 2-year-old Bangladeshi children living under unsanitary conditions and was associated with malnutrition, poor sanitation, and markers of intestinal inflammation. Future study is needed to prospectively determine whether SIBO itself has a detrimental impact on growth of developing world children. This should include longitudinal study of SIBO's natural history to better understand the burden of this disease and to identify the environmental exposures that cause SIBO. Based on this study, these efforts should focus on the role of environmental contamination's ability to cause a functional intestinal disorder that may predispose to SIBO and the development of EE.

## MATERIALS AND METHODS

**Data source and design.** We conducted a cross-sectional analysis of 90 2-year-old children from a cohort of 700 children followed since birth in Dhaka, Bangladesh. All children were previously enrolled in the PROVIDE study, which was a randomized clinical trial with two vaccine interventions designed to investigate causes of oral vaccine underperformance in the developing world. The materials and methods of the PROVIDE study have been described elsewhere (48). The children assessed for SIBO testing were the final 103 children enrolled in PROVIDE. This study was approved by the Research and Ethical Review Committees of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) as well as the Institutional Review Boards of the University of Vermont and the University of Virginia.

**Population and setting.** The study took place in the urban neighborhood of Mirpur in Dhaka, Bangladesh. Mirpur was settled primarily by

ethnic Bihari after Bangladesh obtained its independence in 1971. The neighborhood is densely populated, with an average of 5 people living in 1.5 rooms. The average monthly household income is 12,700 taka (approximately 163 U.S. dollars). Ninety-six percent of construction is tin or mud brick. Open sewers flow throughout the area and are directly adjacent to 59% of homes. Overall, our study participants tended to come from the lowest socioeconomic strata of the Mirpur community due to the area in which recruitment occurred and the location of our study clinic.

**Measures. (i) Primary outcome variable.** The primary dichotomous outcome was the presence or absence of SIBO at the 2-year-old study visit. SIBO was measured via glucose hydrogen breath testing using a QuinTron BreathTracker SC gas chromatograph (QuinTron Instrument Company, Inc., Milwaukee, WI). Patients fasted for 3 h prior to the onset of testing. Children with WAZ score of ≤−3 SD were not tested due to concern by the Research and Ethical Review Committees that fasting was unsafe in this vulnerable group. Children meeting this criteria were referred for nutritional therapy at the icddr,b nutritional rehabilitation unit. This was the only additional exclusion criteria added to those used in selection of the original PROVIDE cohort (48). Children with a WAZ score of > −3 SD were tested at baseline and then given a glucose solution of 100 g glucose in 500-ml sterile water administered at 5 ml/kg body weight. Breath was collected via the QuinTron infant bag collection system with an age-appropriate anesthesia mask attached at 20-min intervals for 3 h. $CO_2$ was measured to ensure sampling of alveolar gas. Children were allowed water during the fast and testing but not other food or drink. Presence of SIBO was defined as an increase of at least 12 ppm in breath hydrogen over baseline at any measurement within the 3-h test period, in accordance with expert consensus based on adult patients (49).

**(ii) Covariates in logistic regression to predict presence of SIBO at 2 years of age.** Covariates were selected to represent competing hypotheses on why children with no underlying gastrointestinal pathology would develop SIBO from environmental exposure. Income was included as a socioeconomic marker. The changes in LAZ and WAZ scores from enrollment to the time of SIBO testing at 2 years of age were included as markers of overall health and nutrition. The number of diarrheal episodes from birth to 2 years of age and presence of a diarrheal illness within the last 30 days were included as SIBO can develop under conditions of delayed intestinal motility, and postinfectious gastroparesis or ileus is common in children. Indicators of environmental fecal contamination included a primary drinking water source other than the municipal supply, the presence of an open drain/sewer directly outside the home, and a mother who trims her fingernails less than once a month (50). Data on covariates were collected from the PROVIDE database.

**(iii) Intestinal inflammation, intestinal permeability, and systemic inflammation.** To assess intestinal inflammation, both fecal Reg 1β and fecal calprotectin were measured on the same day as SIBO testing via enzyme-linked immunosorbent assay. Reg 1β is a proproliferative antiapoptotic protein secreted by damaged intestinal epithelial cells. It has been shown to be elevated in stool in the setting of environmental enteropathy and predictive of growth failure in developing world children (51). Fecal calprotectin is a neutrophil-derived protein also shown to be elevated in states of intestinal inflammation (52, 53). Intestinal permeability was measured via a L/M ratio as assessed via urinary analysis after ingestion of a lactose-mannitol solution. L/M ratio testing was not conducted on the same day as SIBO testing to prevent interference between separate carbohydrate substrates used for the two tests but was performed within 7 days of SIBO testing. To assess systemic inflammation, C-reactive protein and a 17-plex Luminex cytokine panel (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF], gamma interferon [IFN-γ], interleukin-1β [IL-1β], IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 [p70], IL-13, IL-17, monocyte chemoattractant protein 1 [MCP-1], macrophage inflammatory protein 1β [MIP-1β], and tumor necrosis factor alpha [TNF-α]) were conducted on plasma obtained on the day of SIBO testing. Cytokines were

dichotomized to ≤50th percentile (baseline) and >50th percentile of the tested cohort for this analysis.

**Statistical analysis.** The primary analysis to determine risk factors for SIBO development in the developing world was performed using multivariable logistic regression with the presence of SIBO at 2 years of age as the outcome measure. A Hosmer-Lemeshow statistic was produced for the regression model to ensure stability. A nonsignificant $\chi^2$ statistic was generated ($P > 0.05$), ensuring goodness of fit for our model. The secondary analysis of the difference between SIBO-positive and SIBO-negative children for the measures of inflammation and intestinal permeability was calculated via either Mann-Whitney $U$ test or Fisher's exact test, as appropriate. Correction for multiple comparisons was conducted via FDR calculation, with an FDR of 30% set for determination of importance. SPSS Statistics version 22 (IBM, Armonk, NY) and SAS version 9.4 (SAS Institute, Cary, NC) were used for all statistical analyses.

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