Pathogens associated with linear growth faltering in children with diarrhea and impact of antibiotic treatment: The Global Enteric Multicenter Study

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Abstract

Background The association between childhood diarrheal disease and linear growth faltering in developing countries is well-described. However, the impact attributed to specific pathogens has not been elucidated, nor has the impact of recommended antibiotic treatment.

Methods The Global Enteric Multicenter Study (GEMS) enrolled children seeking healthcare with moderate-to-severe diarrhea (MSD) at seven sites in sub-Saharan Africa and South Asia. At enrollment, we collected stool samples to identify enteropathogens. Length/height was measured at enrollment and follow-up, ~60 days later, to calculate change in length/height for age Z scores (ΔHAZ). The association of pathogens with ΔHAZ was tested by linear mixed effects regression models.

Results Among 8,077 MSD cases analyzed, the proportion with stunting (HAZ<-1) increased from 59% at enrollment to 65% at follow-up (p<.0001). Pathogens significantly associated with linear growth decline were *Cryptosporidium* (p<0.001), typical enteropathogenic *Escherichia coli* (p=0.013), and untreated *Shigella* (p=0.009) among infants (0-11 months), and enterotoxigenic *E. coli* encoding heat stable toxin (p<0.001) and *Cryptosporidium* (p=0.03) among toddlers (12-23 months). *Shigella*-infected toddlers given antibiotics had improved linear growth (p=0.02).

Conclusion Linear growth faltering among children aged 0-23 months with MSD is associated with specific pathogens and can be mitigated with targeted treatment strategies, as demonstrated for *Shigella*.

Keywords: Diarrhea, pathogens, growth faltering, stunting, children, antibiotics

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BACKGROUND

Diarrheal disease is associated with linear growth faltering among young children [1]. Community-based studies in low-resource settings demonstrate an increasing risk of stunting at age 24 months with each diarrheal episode and each day of diarrhea before that age [2]. In turn, stunting is a risk factor for poor health and development [3]. Even mild stunting predicts an increased risk of death during the first two years of life [4].

Although most acute diarrhea is caused by infection, few studies have elucidated the impact of specific pathogens on growth, and a limited array of pathogens has been examined [5-8]. Moreover, trials designed to evaluate the efficacy of pathogen-specific treatment have used short-term clinical and bacteriologic cure as endpoints [9, 10], while the impact on growth has not been characterized.

The Global Enteric Multicenter Study (GEMS) is a prospective, matched case-control study of the burden, etiology, and adverse clinical outcomes of moderate-to-severe diarrhea (MSD) in children aged 0-59 months in sub-Saharan Africa and South Asia. GEMS found an association between MSD and linear growth faltering [11, 12]. In this paper, we assessed pathogen-specific associations and whether antibiotic treatment of *Shigella* dysentery, according to World Health Organization (WHO) recommendations, improved growth outcomes.

MATERIALS AND METHODS

Study design and participants

For 36 months at each site, children aged 0-59 months were enrolled into GEMS at sites in Basse (The Gambia), Bamako (Mali), Manhiça (Mozambique), Siaya County (Kenya), Kolkata (India), Mirzapur (Bangladesh), and Karachi, Bin Qasim town (Pakistan) according to published methods [13-15]. To be eligible for enrollment, a child had to reside in the site's demographic surveillance area, seek care at a study health center with diarrhea ($\geq$ 3 abnormally loose stools in the previous 24

hours) that began in the previous 7 days, and meet at least one of the following criteria for MSD: sunken eyes, decreased skin turgor, visible blood in stool, or a clinician recommendation for intravenous rehydration or hospitalization. We aimed to enroll ~220 eligible children per site per year into each of three age groups: infants 0-11 months, toddlers 12-23 months, and young children 24-59 months. Cases were eligible for re-enrollment if they developed a new episode of MSD after their 60-day follow-up visit [13]. For this paper, only children with MSD were included.

Data collection

During the enrollment visit at the health center, all children underwent a standardized clinical assessment, anthropometric measurements, and provided a stool sample to identify enteropathogens [13, 15]. Stool collection, transport, and pathogen identification methods have been described [16]. Management of diarrhea at the health center, including antibiotic use, was documented. Approximately 60 days after enrollment (49-91 days), participants were visited at home to assess vital status and repeat anthropometric measurements.

Anthropometric measurements

We measured standing height for children ≥2 years old, and recumbent length for younger children and those unable to stand unassisted, thrice to the nearest 0.1 cm using a "Shorr board," following a two-person standardized measurement procedure [17]. The median of the three measurements was used to calculate the length/height-for-age Z score (HAZ) [18, 19].

Before study initiation, staff at each site underwent anthropometry training followed by a standardization exercise to calculate intra-rater and inter-rater (trainee versus instructor) variability [13]. Trainees who exceeded the acceptable measurement error (0.5 cm) at least half the time did not undertake field activities until retrained and deemed competent. A proficient member of each local team provided training and standardization exercises for newly hired staff and refresher

training for existing staff every 4-6 months. The core team visited each site approximately twice annually to train, observe field activities, and review standardization results.

The study was approved by ethics committees at the University of Maryland, Baltimore, and each field site. Informed consent was obtained from the parent or guardian of each child prior to performing study procedures.

Statistical methods

Variable definitions

Age was measured on a continuous scale and analysis were stratified by age group. The HAZ was calculated at enrollment and follow-up using the median of the three length/height measurements and age, according to WHO standards [19]. We defined stunting as HAZ < -1 and degree of stunting, as mild (-2 $\leq$HAZ < -1), moderate (-3 $\leq$ HAZ < -2), or severe (HAZ < -3), at enrollment and follow-up.

Data analysis

This analysis included MSD cases with both enrollment and follow-up measurements; implausible or inconsistent measurements between enrollment and follow-up were excluded (**Supplemental Figure S1**).

The primary outcome is change in linear growth (ΔHAZ), which was calculated for each child as the difference in HAZ from enrollment to follow-up. A negative change in linear growth is deemed growth faltering. We initially compared enrollment and follow-up HAZ within each age group (and study site) using a one sample t-test for ΔHAZ and adjusted for individuals with multiple episodes of MSD during the study period (SAS proc surveymeans t with CLUSTER statement). We compared presence of stunting and degree of stunting at enrollment and follow-up using a Wilcoxon signed-rank test.

Pathogens were tested for association with change in linear growth within each age group. We limited the analysis to pathogens that were 1) significantly associated with MSD in at least four sites [12] and/or 2) associated with increased risk of dying in a pooled analysis of cases at all sites [12]. For the first criterion, we included rotavirus, *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli* encoding heat stable toxin with or without targets for heat labile enterotoxin (ST-ETEC) for all age groups, and adenovirus serotypes 40 and 41 for the two youngest groups. For the second criterion, we additionally included typical enteropathogenic *E. coli* (tEPEC) in the analyses involving infants [12]. We used a linear mixed effects regression model to examine the association of each of the above-named pathogens individually with change in linear growth among MSD cases by age group. In addition to the pathogen, the model also included HAZ at enrollment, age at enrollment in months, duration to follow-up in days, and study site. Treatment of *Shigella* with a WHO-recommended antibiotic (ciprofloxacin, third-generation cephalosporins, azithromycin, pivmecillinam) [20] could modify any potential association of *Shigella* with linear growth. We therefore examined the need for an interaction term between the presence and absence of *Shigella* with or without antibiotic treatment. The interaction term was retained if the associated p-value was < 0.10. Pathogens associated (p-value < 0.10) with ΔHAZ in the individual models were combined into a single age stratified model, which included the same confounding variables described previously for the individual models. Unless otherwise stated, a p-value < 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Cary, NC) was used for all summary statistics and associated tests, STATA/SE version 17 was used to fit the LMMs.

RESULTS

Subjects

Between December 1, 2007 and March 3, 2011, 8,077 MSD episodes occurring among 7,545 children were analyzed: 3,408 were ages 0-11 months, 2,741 were12-23 months, and 1,928 were 24-59 months. There were 1,362 episodes excluded from analysis due to missing measurements (63.2%), implausible values (17.8%), death before follow-up (14.0%), and follow-up visit outside the acceptable time window (5.0%) (**Supplemental Figure S1**). Children with excluded and included episodes had similar demographic features (**Supplemental Table S1**), except those excluded because of death had significantly lower enrollment HAZ scores compared to included children in 14 of 21 comparisons (3 age groups at 7 sites).

Mean enrollment HAZ in each age group, at every site, was below zero and became more negative with increasing age (**Supplemental Table S2**), as did the proportion with stunting at enrollment (**Table 1**). A total of 58.7% of cases were stunted at enrollment (32.2% mild, 18.0% moderate, 8.5% severe).

The proportion of cases with stunting was significantly higher at follow-up than enrollment in every age group (**Table 1, Supplemental Table S2**), with a difference of 9.2% in infants, 5.8% in toddlers, 1.5% in young children. A total of 64.9% of cases were stunted at follow-up (33.3% mild, 20.6% moderate, 11.0% severe).

Pathogens associated with linear growth faltering

In the individual pathogen analyses for infants, the presence of *Cryptosporidium* or tEPEC was significantly associated with a greater decline in linear growth compared to those without either pathogen (difference in ΔHAZ for *Cryptosporidium* -0.09, 95% CI -0.14 and -0.04, p<0.001; and for tEPEC -0.08, 95% CI -0.15 and -0.02, p=0.012, **Table 2**). In addition, the interaction between *Shigella*

and WHO-prescribed antibiotics was statistically significant (p = 0.012). *Shigella* episodes not treated with antibiotics resulted in a greater decline in linear growth compared to treated episodes (difference in ΔHAZ -0.16, 95% CI -0.29, -0.03, p=0.017) while *Shigella* episodes treated with antibiotics were not associated with positive or negative linear growth. These three pathogens, including the interaction term, were included in a final fully adjusted model. Rotavirus and ST-ETEC were not associated with linear growth faltering among infants.

Amongst toddlers, *Cryptosporidium* was associated with a greater decline in linear growth compared to those without *Cryptosporidium* (difference in ΔHAZ -0.05, 95% CI -0.09, -0.003, p=0.038, **Table 2**), with the difference in ΔHAZ very similar to infants. The presence of rotavirus or ST-ETEC also resulted in a greater decline in linear growth (difference in ΔHAZ for rotavirus -0.04, 95% CI -0.07, -0.002, p=0.063 and for ST-ETEC -0.12, 95% CI -0.17, -0.06, p <0.001, respectively). The result for rotavirus was not statistically significant but met our criteria for inclusion in the final adjusted model. The interaction term between *Shigella* and antibiotic treatment was significant (p-value 0.003), and antibiotic treatment improved linear growth in toddlers with shigella (difference in ΔHAZ 0.07, 95% CI 0.01, 0.13, p=0.019). *Shigella* not treated with antibiotics resulted in further declines in linear growth (difference in ΔHAZ -0.06, 95% CI -0.12, 0.006, p=0.08). Adenovirus 40/41 was not associated with linear growth among MSD cases aged 12-23 months. Each of *Cryptosporidium*, rotavirus, ST-ETEC, and the interaction between *Shigella* and antibiotic treatment were included in a final model; however, rotavirus was subsequently excluded from the final model as the p-value was not statistically significant. For those pathogens remaining in the final model, the results of this pathogen adjusted analysis were very similar to those of the individual pathogen analyses (**Table 2**).

None of the individual pathogens were associated with linear growth faltering in the oldest age group, 24-59 months.

Antibiotic prescribing practices and susceptibility patterns

In an *ad hoc* analysis, we further explored the observed association between linear growth faltering and failure to treat *Shigella* with antibiotics recommended by WHO for dysentery. For context, we first examined antibiotic prescribing practices for *Shigella* dysentery (**Figure 1 and Supplemental Table S3**) and the susceptibility patterns of offending strains.

A total of 2,026 of all MSD episodes (25.1%) had dysentery; 1,894 (93.5%, range 79.9% [Pakistan] to 99.6% [Bangladesh]) were prescribed antibiotics. The most common antibiotics were ciprofloxacin, trimethoprim/sulfamethoxazole, and metronidazole (59.9%, 22.6%, and 11.6%, respectively). A WHO-recommended antibiotic was prescribed for 1,272 dysentery episodes (62.8%) and for 583 *shigella*-positive dysentery episodes (79.8%) (**Figure 1, Supplemental Table S3**).

There was considerable regional diversity in antibiotic prescribing practices. A WHO-recommended antibiotic was prescribed for 614 of the 621 *Shigella* dysentery episodes in Asia (98.9%), but for only 20 of the 110 episodes at the four African sites (18.1%). Ciprofloxacin was the most prescribed antibiotic at the Asian sites, including India (77.8%), Bangladesh (86.5%), and Pakistan (78.9%), but was a rare choice in Africa. At the African sites, the most commonly prescribed antibiotic was trimethoprim-sulfamethoxazole in The Gambia (60.0%), Mali (60.0%), and Kenya (40.5%), and nalidixic acid in Mozambique (87.5%).

Virtually all (≥99%) *Shigella* strains were susceptible to ciprofloxacin in The Gambia, Mali, Mozambique, Kenya, and Pakistan, compared to 87.0% in Bangladesh and only 35.4% in India. At the African sites, >80% of *Shigella* isolates were resistant to trimethoprim/sulfamethoxazole, while 85% were susceptible to nalidixic acid in Mozambique.

Impact of antibacterial treatment of shigellosis on linear growth

Shigella was cultured in 731 of the dysentery episodes (36.1%) and 270 watery diarrhea episodes (4.5%) (Figure 1). A WHO-recommended antibiotic was prescribed for 583 shigella-positive dysentery episodes (79.8%) compared to 71.(26.3%) shigella-positive watery diarrhea episodes (**Figure 1).** Analysis of the impact of antibiotic treatment of shigellosis on linear growth was performed separately for *shigella*-positive watery diarrhea and dysentery (**Table 3**).

In toddlers, whose incidence of Shigella-positive MSD was almost double that of the other two age groups [12], a ~4-fold reduction in linear growth faltering was observed among *Shigella*-positive dysentery cases treated with WHO-recommended antibiotics compared to untreated children (ΔHAZ -0.10, 95% CI -0.18, 0.03 versus ΔHAZ -0.37, 95% CI -0.48, -0.26, p=0.03). A similar trend was observed among infants with *Shigella*-positive dysentery and toddlers with *Shigella*-positive watery diarrhea, but the differences did not reach statistical significance with the small sample sizes (**Table 3**).

To address whether antibiotics exert a nonspecific growth-promoting effect on children with diarrhea, we compared ΔHAZ among MSD cases with rotavirus (n=1,493) or *Cryptosporidium* (n=945) who were offered either ciprofloxacin, third-generation cephalosporins, azithromycin, or pivmecillinam with those not offered these antibiotics. Overall, 33.0% of rotavirus-positive cases and 32.0% of *Cryptosporidium*-positive cases received one of these antibiotics, but no significant associations were observed.

DISCUSSION

We previously demonstrated that among children 0-59 months of age living in low-resource settings in South Asia and sub-Saharan Africa, an episode of MSD was associated with an increased risk of stunting over the ensuing 2-3 months. Now we present findings involving a broad array of pathogens indicating that four pathogens (*Cryptosporidium*, tEPEC, *Shigella*, and ST-ETEC) exert the largest negative effect on linear growth among infants and toddlers. We found that the risk associated with *Shigella* was largely limited to episodes not treated with WHO-recommended antibiotics.

To our knowledge, this is the first study to demonstrate that antibiotic treatment of dysentery according to WHO guidelines significantly ameliorates the linear growth impairment associated with *Shigella* infection, and in toddlers also augments growth. Previous clinical trials of children with shigellosis examined the short-term benefits of antibiotics (resolution of diarrheal disease symptoms and fecal shedding) but did not evaluate the impact on linear growth faltering, widely believed to be a proxy for mortality and poor health outcomes in the longer term. We observed a statistically significant improvement in linear growth among children with *Shigella*-positive dysentery in the 12-23 month age group, and a similar trend among infants with *Shigella*-positive dysentery and toddlers with *Shigella*-positive watery diarrhea that did not reach statistical significance. Regional differences in executing WHO guidelines were apparent. Although most Asian sites administered the recommended first line therapy with ciprofloxacin, 20% of episodes were missed and escalating prevalence of ciprofloxacin resistance threatens the efficacy of recommended treatment, particularly in India. The African sites provided treatment to only 20% of *Shigella*-positive dysentery episodes but in most cases *Shigella* was resistant to the antibiotic chosen (trimethoprim/sulfamethoxazole). The prevalence of resistance to trimethoprim/sulfamethoxazole precludes its routine use unless supported by local susceptibility patterns.

Our findings corroborate and expand results of studies in Peru [6] and Guinea Bissau [7], which suggested *Cryptosporidium* infection in infancy imparted a lasting adverse effect on linear growth.

We previously reported this risk period extends to include the second year of life, when *Cryptosporidium* was strongly associated with MSD at all GEMS sites, regardless of HIV prevalence [12] and was associated with death during the ~60 days following an MSD episode in toddlers. Our current findings suggest the impact of *Cryptosporidium* on mortality may be linked to its considerable nutritional insult, as measured by a negative ΔHAZ. Strategies for point-of-care diagnosis and identification of appropriate therapeutic agents for case management of cryptosporidiosis in low-resource settings are needed and should be evaluated for their impact on growth, and if possible, survival.

Our findings also demonstrate an association between ST-ETEC diarrhea and linear growth faltering during the second year of life. Previous studies of the relationship between ST-ETEC and stunting have conflicting results. One study of children aged 3-48 months in rural Bangladesh demonstrated a significant association between the percentage of days with ETEC diarrhea during 60-day intervals and failure to gain weight but not with impeded linear growth [5]. Another study involving a birth cohort followed for two years in urban Bangladesh found that stunted or undernourished children aged 12-24 months were significantly more likely to have experienced ETEC diarrhea than those who were not stunted [21]. Our analysis differs from previous studies in that it distinguishes ST-ETEC from the less virulent ETEC pathotype encoding only LT, and we limited enrollment to clinically more severe forms of diarrheal illness. In addition, we examined linear growth over a relevant time frame (2-3 months after MSD onset) and demonstrated ST-ETEC's impact relative to other pathogens that were significantly associated with MSD. Nonetheless, the observed effect of infection on linear growth was somewhat unexpected since ETEC is often considered a self-limited secretory diarrhea that in animal models [22] and human challenge studies caused little or no inflammation or alteration of intestinal integrity that might interfere with growth [23, 24]. Other data, however, suggest ST-ETEC can elicit an inflammatory response involving IL-8 expression [25, 26]. Peruvian children aged younger than two years with ETEC infection had fecal leukocytes in their diarrheal stools [27].

Several limitations of this study could not be addressed in the case-control analysis. First, unmeasured events between enrollment and follow-up may have influenced growth, so it is notable that MSD cases grew significantly less during follow-up than their matched controls, despite having comparable HAZ at enrollment [12]. Second is that the detrimental effects of growth faltering following MSD can be overcome by catch-up growth. Even if that were the case, the 2-3 months after MSD onset were a particularly vulnerable period when mortality rates among cases were 8.5-fold higher than among matched controls [12]. We recognize that observational studies are suboptimal for evaluating the impact of antibiotics against *Shigella*-associated linear growth faltering; however, the inclusion of objective endpoints (height/length, pre-defined diarrhea and dysentery, and fecal microbiology) mitigate these concerns. Finally, we used directly observed inpatient administration of antibiotics and/or prescription of antibiotics as a proxy for antibiotic use and were unable to measure compliance.

In conclusion, our findings suggest prevention or treatment of infection with four pathogens (*Cryptosporidium*, ST-ETEC, tEPEC, and *Shigella*) may reduce the burden of linear growth faltering in children. The adverse effects of *Shigella* were mitigated by administration of WHO-recommended antibiotics; however, these antibiotics were prescribed in only 63% of dysentery episodes and in several sites antibiotic practices did not match local susceptibility patterns. Increasing resistance of *Shigella* to antibiotics globally could leave few options for effective therapy[28]. Accordingly, WHO has declared antibiotic-resistant *Shigella* to be a serious threat[29]. It seems prudent that for benefit to exceed risk, treatment of shigellosis should be judicious, guided by susceptibility data when possible, and directed toward individuals at risk for severe disease or complications. Because stunting is prevalent worldwide and directly associated with poor outcomes, interventions with a relatively small but significant effect have the potential to benefit many children's lives.

Contributors

MML conceived the project and acquired the grant funds. MML, KLK, and JPN designed the protocol. DN did the statistical analysis with WCB, KLK, YL, YW, HP, AR, UR and HS. KLK, JPN, DN, THF, SP, DSu, MJH, SOS, RFB, RAA, DSah, ASGF, AKMZ, EDM, and CEOR planned and supervised the study. DSan, SK, RO, SKD, FQ, TN, SA, and QB coordinated clinical data collection; BT, TR, JBO, JOO, AH, SQ, MA, and IM did the laboratory assays; and UO, BM, MJH, and KB participated in data management. DN, KLK, WCB, THF, YW, JPN, and MML had full access to all the data in the study and did data analysis; KLK, and DN wrote the report with input from all authors and had final responsibility for the decision to submit for publication. All authors reviewed the draft and approved the decision to submit for publication.

Conflicts of interest

We declare that we have no conflicts of interest.

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TABLES FOR MAIN BODY OF PAPER

Table 1. Degree of stunting in cases with moderate-to-severe diarrhea at enrollment and at ~60-day follow-up visit, by age group

Degree of stunting at enrollment, by age (No. (%))	Degree of stunting at follow-up, by age (No. (%))			
	None	Mild	Moderate	Severe
0-11 months (n=3,408)	1,414 (41.5)	1,093 (32.1)	616 (18.1)	285 (8.3)
None 1,727 (50.7)	1302 (75.4)	391 (22.6)	32 (1.9)	2 (0.1)
Mild 1,049 (30.8)	104 (9.9)	640 (61.0)	291 (27.7)	14 (1.3)
Moderate 435 (12.7)	8 (1.8)	57 (13.1)	257 (59.1)	113 (26.0)
Severe 197 (5.8)	0 (0)	5 (2.5)	36 (18.3)	156 (79.2)
12-23 months (n=2,741)	838 (30.6)	951 (34.7)	591 (21.6)	361 (13.2)
None 998 (36.4)	774 (77.6)	222 (22.2)	2 (0.2)	0
Mild	63 (6.9)	654 (71.8)	191 (21.0)	3 (0.3)

911 (33.2)				
Moderate 556 (20.3)	1 (0.2)	74 (13.3)	374 (67.3)	107 (19.2)
Severe 276 (10.1)	0	1 (0.4)	24 (8.7)	251 (90.9)
24-59 months (n-1,928)	582 (30.2)	647 (33.6)	457 (23.7)	242 (12.6)
None 612 (31.7)	528 (86.3)	84 (13.7)	0	0
Mild 642 (33.3)	54 (8.4)	509 (79.3)	79 (12.3)	0
Moderate 462 (24.0)	0	54 (11.7)	358 (77.5)	50 (10.8)
Severe 212 (11.0)	0	0	20 (9.4)	192 (90.6)

Degree of stunting was significantly higher at follow-up in each age group: p<0.0001 for the 0-11 and 12-23 month groups and p=0.0001 for the 24-59 month group, by Wilcoxon signed-rank test on the difference (follow-up minus enrollment) in stunting score: 0=none (HAZ ≥-1), 1=mild (<-1 HAZ ≥-2), 2=moderate (HAZ<-2 to ≥-3), 3=severe (HAZ<-3); HAZ denotes height-for-age z score.

Table 2: Change in linear growth (ΔHAZ) between enrollment and follow-up from individual and multiple pathogen models among children from seven GEMS sites, by age group.

	No. (%) of episodes with pathogen	Individual pathogen model*		Multiple pathogen model□	
		Difference in ΔHAZ (95% CI)	p-value	Difference in ΔHAZ (95% CI)	p-value
0-11 months (n=3,408)					
Cryptosporidium	525 (15.4)	-0.09 (-0.14, -0.04)	<0.001	-0.09 (-0.14, -0.04)	<0.001
***Shigella,* not treated with antibiotic**	72 (2.1)	-0.16 (-0.29, -0.03)	0.017	-0.17 (-0.31, -0.04)	0.009
***Shigella,* treated with antibiotic**	93 (2.7)	0.05 (-0.07, 0.17)	0.38	0.05 (-0.07, 0.17)	0.41
Typical EPEC	304 (8.9)	-0.08 (-0.15, -0.02)	0.012	-0.08 (-0.15, -0.02)	0.013
Rotavirus	859 (25.2)	0.02 (-0.02, 0.06)	0.40		

ST-ETEC	203 (6.0)	0.006 (-0.07, 0.08)	0.89		
Adenovirus 40/41	104 (3.0)	-0.06 (-0.17, 0.05)	0.27		
12-23 months (n=2,741)					
Cryptosporidium	312 (11.4)	-0.05 (-0.09, -0.003)	0.038	-0.05 (-0.09, -0.005)	0.029
***Shigella*, not treated with antibiotic**	159 (5.8)	-0.06 (-0.12, 0.006)	0.08	-0.06 (-0.12, 0.001)	0.054
***Shigella*, treated with antibiotic**	282 (10.3)	0.07 (0.01, 0.13)	0.019	0.06 (0.009, 0.13)	0.024
Rotavirus	492 (18.0)	-0.04 (-0.07, 0.002)	0.063		
ST- ETEC	199 (7.3)	-0.12 (-0.17, -0.06)	<0.001	-0.12 (-0.17, -0.06)	<0.001
Adenovirus 40/41	76 (2.8)	0.008 (-0.08, 0.09)	0.86		

Table 3. Linear growth following an episode of *Shigella*-positive dysentery and watery diarrhea, according to whether WHO-recommended treatment was prescribed*, by age group

Age group	0-11 months		12-23 months		24-59 months	
WHO-recommended antibiotics prescribed‡	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Shigella-positive watery diarrhea ΔHAZ	N=11 -0.40	N=45 -0.44	N=29 -0.16	N=92 -0.25	N=31 -0.15	N=62 -0.13
(95% CI)	(-0.63, -0.17)	(-0.57, -0.31)	(-0.36, 0.04)	(-0.34, -0.16)	(-0.27, -0.02)	(-0.21, -0.05)
Shigella-positive	N=82	N=26	N=253	N=67	N=248	N=55

dysentery	-0.21	-0.47	-0.10	-0.37	-0.12	-0.14
ΔHAZ (95% CI)	(-0.28, -0.13)	(-0.72, -0.23)	(-0.18, 0.03)	(-0.48, -0.26)†	(-0.15, -0.08)	(-0.28, -0.009)

Assessed using linear regression, controlling for age, site, enrollment HAZ, and days until follow-up visit.

* Prescription of a WHO-recommended antibiotic for dysentery (either ciprofloxacin, third generation cephalosporin, azithromycin, or pivmecillinam).

† p =0.03.

Figure Legends

Figure 1. Distribution of diarrhea episodes included in the analysis according to the presence of dysentery, *Shigella* isolation, and antibiotic treatment.

Figure 1