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The Association Between Antibiotic Treatment and Short-Term Diarrheal Outcomes in Children in Low-Resource Settings

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Master of Public Health

Epidemiology

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2021

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Abstract

The Association Between Antibiotic Treatment and Short-Term Diarrheal Outcomes in Children in Low-Resource Settings
By Karl Josef Protil III

Objective To study the association between antibiotic treatment and short-term growth, as well as the association between antibiotic treatment and diarrheal duration among children from birth to 2 years of age in low-resource settings.

Methods Data from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) birth cohort study were analyzed. Short-term growth was analyzed using linear regression and included 6,600 diarrhea episodes. Duration was analyzed using survival analysis and included 10,260 diarrhea episodes.

Findings Antibiotic treatment showed no consistent impact on short-term growth. While antibiotics improved growth for some antibiotic-pathogen pairings, it impaired growth for other antibiotic-pathogen pairings, including non-bacterial pathogens. Antibiotic treatment consistently reduced diarrheal duration, including for non-bacterial pathogens.

Conclusion The impact of antibiotics on outcomes for non-bacterial pathogens was unexpected, as antibiotics reduced duration for viral causes. Antibiotic treatment of some bacteria, such as *Shigella*, did not result in an impact on short-term growth, which was unexpected.

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Introduction

Childhood diarrhea is a pressing problem worldwide. The Global Burden of Disease Study estimates that, in 2016, there were 1,105,406,865 diarrhea episodes in children younger than 5 years old (Troeger 2018). These episodes resulted in an estimated 446,000 deaths, making diarrhea the fifth leading cause of death in this age group (Troeger 2018). These deaths are unevenly distributed, with Sub-Saharan Africa, the Indian subcontinent, and Southeast Asia having the highest mortality rate (Troeger 2018).

Diarrhea episodes can be caused by numerous different pathogens. An analysis of stool samples collected in the GEMS study found that, among children aged 0-11 months, Rotavirus, Adenovirus 40/41, *Cryptosporidium*, *C jejuni/C Coli*, and *Shigella* were the five most common causes of moderate to severe diarrhea (Liu 2016). The top five causes of diarrhea were the same for the 12-23 month age group, although in a different order (Liu 2016). Two out of five of these causes (*C jejuni/C Coli* and *Shigella*) are bacterial. The results were similar for the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) study: among children aged 0-11 months, rotavirus, adenovirus 40/41, sapovirus, norovirus, and ETEC were the five most common causes of diarrhea of any severity (Platts-Mills 2018). In the 12-24 month age group, *Shigella*, sapovirus, ETEC, rotavirus, and adenovirus 40/41 were the five most common causes of diarrhea of any severity (Platts-Mills 2018). In the 0-11 month age group, one out of five of the causes (ETEC) are bacterial. In the 12-24 month age group, two out of five of the causes (Shigella and ETEC) are bacterial. While the causes of diarrhea vary by age, site, and study, a substantial amount of the diarrhea burden is caused by bacterial infections that could benefit from antibiotics.

While death is a rare outcome of childhood diarrhea, non-fatal cases still cause long-lasting health effects such as linear growth stunting (Nasrin 2021). The Global Enteric Multicenter Study (GEMS) found that the proportion of children with stunted growth increased significantly between a diarrhea episode and follow-up, which took place approximately 60 days after a diarrhea episode (Nasrin 2021). The effects of growth faltering on a society and economy are wide-reaching and severe. In developing countries, growth faltering is estimated to cost each birth cohort 69.4 million years of educational attainment and $616.5 billion (purchasing power parity-adjusted) (Fink 2016). Different pathogens have different effects on growth. The GEMS study found that *Cryptosporidium* and tEPEC had a greater effect on linear growth stunting than other pathogens (Nasrin 2021). A previous paper using data from the MAL-ED study found that diarrhea caused by bacteria and parasites caused growth stunting at both 3 months and 2 years old, but that viruses did not cause growth stunting on this timeline (Rogawski 2018). These results further underscore the importance of treating diarrhea caused by bacteria.

Current WHO guidelines state that antibiotics should only be used in the case of bloody diarrhea (World Health Organization 2005). These guidelines are intended for use in low-resource settings, where point of care diagnostics are not accessible. However, while these guidelines are intended to treat *Shigella* episodes with antibiotics, not all Shigella episodes cause bloody diarrhea. A previous analyses of MAL-ED data found that 85.5% of Shigella episodes were non-bloody (Platts-Mills 2018). The WHO guidelines, adopted in 2005, miss episodes that could be effectively treated by antibiotics.

At the same time, numerous studies have found that the WHO guidelines are not followed closely, and antibiotics are used much more broadly. One study that interviewed caretakers in low resource settings found that diarrhea episodes are often treated incorrectly with

antibiotics (Zwisler 2013). Data from the MAL-ED study likewise indicates that non-bloody diarrhea is often treated with antibiotics, counter to the WHO guidelines (Rogawski 2017).

A better understanding of the subset of diarrhea episodes that could benefit from antibiotic treatment is needed to inform treatment decisions given the limited scope of the WHO guidelines and the current practice of treating most episodes. Several studies have shown that antibiotics are effective at treating diarrhea caused by specific pathogens. Treating *Shigella*-positive non-bloody diarrhea episodes with WHO recommended antibiotics resulted in a significant reduction in growth stunting (Nasrin 2021). A 2006 clinical review found that antibiotics can reduce diarrheal duration (Diniz-Santos 2006). A more recent clinical review indicates that antibiotic use can reduce diarrheal duration in cases of travelers' diarrhea (Leung 2019). This paper will evaluate the impact of antibiotic treatment on diarrheal duration and short-term growth, adding to the growing body of research to identify diarrhea episodes that are effectively treated by antibiotics.

Methods

Study Introduction

We used data from the MAL-ED study. The MAL-ED study was a multisite study, with 8 sites: Dhaka (Bangladesh), Venda (South Africa), Naushahro Feroze (Pakistan), Vellore (India), Bhaktapur (Nepal), Haydom (Tanzania), Loreto (Peru) and Fortaleza (Brazil) (The MAL-ED Network Investigators 2014). The study recruited healthy infants who were 17 days old or younger and followed them to 24 months of age (The MAL-ED Network Investigators 2014). Upon enrollment, basic demographic information was collected (The MAL-ED Network Investigators 2014). Homes were visited twice a week to collect basic information, such as diet

and general health (The MAL-ED Network Investigators 2014). During these twice weekly visits, information was collected about diarrhea episodes and diarrhea stool samples were collected (The MAL-ED Network Investigators 2014). Length and weight measurements were taken once a month (The MAL-ED Network Investigators 2014). Growth measurements were biased for the Pakistan site, so results from Pakistan were not included in the growth analysis.

Variable Definitions

The MAL-ED study defined diarrhea as "≥3 loose stools in a 24-hour period and separated by ≥2 diarrhea-free days." (The MAL-ED Network Investigators 2014). Antibiotic use was defined as any antibiotic use during a diarrhea episode. The class of antibiotic used was also recorded by the MAL-ED study. Short-term growth was defined as the change in length-for-age (LAZ) between the most recent measurement prior to the diarrhea episode (within a maximum of 30 days before the diarrhea episode) and the closest measurement to 90 days after the first day of diarrhea (within a range of 60-120 days). Diarrheal duration was defined as the total number of days with diarrhea. Diarrhea etiology was determined by qPCR analysis of collected stool samples (Platts-Mills 2018). Diarrhea was considered to be caused by a given pathogen if the episode-specific attributable fraction for that pathogen was above 0.5 (Rogawski 2018).

Data Analysis

The association between antibiotics and short-term growth following a diarrhea episode was assessed by linear regression. Confounders included SES, age, duration of diarrhea episode, fever, blood in diarrhea, dehydration, vomiting, breastfeeding, maternal height, and length at

episode. The severity measures (fever, blood in diarrhea, dehydration, and vomiting) were binary variables, and were counted as having occurred if they occurred at any point during the episode.

The association between antibiotics and diarrheal duration was assessed using survival analysis with a time varying exposure to account for antibiotic treatments that started after the first day of diarrhea and the potential for a longer duration of diarrhea to indicate treatment. Individuals were followed from the first day of their diarrhea to resolution of the diarrhea, which is defined as 1 day after the last day of symptoms. Antibiotics were a time varying exposure that began on the date of antibiotic treatment initiation and continued until diarrhea resolution. Deaths were counted as conclusions of diarrhea, not censored outcomes. Confounders included SES, age, fever, blood in diarrhea, dehydration, vomiting, and duration of diarrhea before treatment. Duration of diarrhea before treatment was created by finding the number of days between the onset of diarrhea and the initiation of antibiotic treatment.

Both analyses were stratified by the 9 most common causes of childhood diarrhea disease in MAL-ED: adenovirus, astrovirus, *Campylobacter*, *Cryptosporidium*, ETEC, norovirus, rotavirus, sapovirus, and *Shigella*. We also estimated the effect of each of the 6 antibiotic types reported: Penicillin, Cephalosporins, Sulfonamides, Macrolides, Metronidazole, and Fluoroquinolones, comparing episodes that received each drug class to those that did not receive that drug class.

Results

Growth

A total of 6,600 diarrhea episodes were recorded among the 1,355 children included in the growth analysis. 2,618 (39.67%) of the episodes were treated with antibiotics. Without

stratifying by antibiotic type or diarrheal episode cause, there was no significant association between antibiotic treatment and short-term growth. When stratified by drug class, there was also no significant association between antibiotic treatment and short-term growth. When stratified by diarrheal cause, children with *Campylobacter* diarrhea who were treated with antibiotics of any drug class had 0.26 lower LAZ (95% CI: 0.11, 0.41) 3 months after the episode compared to children with *Campylobacter* diarrhea who were not treated with antibiotics. There were no other significant associations present when stratifying by only drug class or diarrheal cause.

The drug class specific associations for *Campylobacter* were variable. Treatment with sulfonamides, macrolides, and metronidazole resulted in reduced short-term growth, while cephalosporin treatment resulted in improved short-term growth. Sulfonamide treatment had the largest negative effect: children with *Campylobacter* diarrhea who were treated with sulfonamides had 0.43 lower LAZ (95% CI: 0.26, 0.61) 3 months after the episode compared to children with *Campylobacter* diarrhea who were not treated with antibiotics or were treated with other antibiotics. Cephalosporin treatment resulted in improved short term growth outcomes: children with *Campylobacter* diarrhea who were treated with cephalosporins had 0.53 higher LAZ (95% CI: 0.35, 0.72) 3 months after the episode compared to children with *Campylobacter* who were not treated with antibiotics or were treated with other antibiotics.

The drug class specific associations for adenovirus were also variable. Children with adenovirus diarrhea who were treated with cephalosporins had 0.26 higher LAZ (95% CI: 0.07, 0.44) 3 months after the episode compared to children with adenovirus diarrhea who were not treated with antibiotics or were treated with other antibiotics. Children with adenovirus diarrhea who were treated with sulfonamides, however, had 0.19 lower LAZ (95% CI: 0.07, 0.30) 3

months after the episode compared to children with adenovirus diarrhea who were not treated with antibiotics or were treated with other antibiotics.

The drug class specific associations for both *Cryptosporidium* and astrovirus were negative. Treatment of *Cryptosporidium* with cephalosporins or metronidazole significantly reduced growth, with cephalosporins having the largest impact. Children with *Cryptosporidium* diarrhea who were treated with cephalosporins had 0.09 lower LAZ (95% CI: 0.01, 0.18) 3 months after the episode compared to children with *Cryptosporidium* diarrhea who were not treated with antibiotics or were treated with other antibiotics. Treatment of astrovirus with cephalosporins or sulfonamides significantly reduced growth, with cephalosporins again having the largest impact. Children with astrovirus diarrhea who were treated with cephalosporins had 0.22 lower LAZ (95% CI: 0.03, 0.42) 3 months after the episode compared to children with astrovirus diarrhea who were not treated with antibiotics or were treated with other antibiotics.

The drug class specific associations for norovirus were positive. Norovirus-caused episodes only showed a significant short-term growth difference when treated with fluoroquinolones: children who had norovirus diarrhea and were treated with fluoroquinolones had 0.61 higher LAZ (95% CI: 0.27, 0.96) 3 months after the episode compared to children with norovirus diarrhea who were not treated with antibiotics or were treated with other antibiotics.

Duration

A total of 10,260 diarrhea episodes were recorded amongst the 1,686 children included in the duration analysis. 4,693 (45.74%) of the episodes were treated with antibiotics. The only significant associations between antibiotic treatment and diarrheal duration were negative; treatment with antibiotics always led to no change in diarrheal duration or a reduction in

diarrheal duration. Without stratifying by antibiotic type or diarrheal episode cause, antibiotic treatment was associated with a 36% (95% CI: 33%, 39%) reduction in diarrheal duration compared to children who were not treated with antibiotics. When stratified by diarrhea cause only, overall antibiotic treatment significantly reduced diarrheal duration for all causes, with ETEC showing the largest reduction in duration, with a 45% (95% CI: 33%, 55%) reduction in diarrheal duration for ETEC-caused episodes compared to children with ETEC who were not treated with antibiotics. When stratified by antibiotic type only, penicillin, cephalosporins, and macrolides significantly reduced diarrheal duration for all-cause diarrheal episodes. Macrolides were the most effective, resulting in a 30% (95% CI: 24%, 35%) reduction in diarrheal duration, compared to children who were not treated with antibiotics or were treated with other antibiotics.

Cryptosporidium showed the largest response to antibiotic treatment, with cephalosporins causing a 75% (95% CI: 42%, 90%) reduction in diarrheal duration and fluoroquinolones causing a 78% (95% CI: 65%, 86%) reduction in diarrheal duration, both compared to children with *Cryptosporidium* who were not treated with antibiotics or were treated with other antibiotics.

Adenovirus, *Campylobacter*, *Cryptosporidium*, ETEC, and sapovirus showed a significant reduction in duration in response to the most antibiotics, with each responding to overall antibiotic treatment and two specific antibiotics. Norovirus and rotavirus showed a significant reduction in duration in response to the fewest antibiotics, with each having shorter duration after overall antibiotic treatment only. The bacteria-caused episodes showed a significant reduction in duration in response to an average of 1.67 individual antibiotics, while the virus-caused episodes showed a significant reduction in response to an average of 0.8

individual antibiotic. *Cryptosporidium*, the sole protozoa, had shorter duration when treated with 2 individual antibiotics.

Macrolides were the most effective antibiotics, significantly reducing duration for all-cause diarrhea as well as five out of nine individual causal pathogens (55.56%). Metronidazole was the least effective antibiotic, only significantly reducing the duration of *Campylobacter*-caused episodes.

Discussion

The analysis of the impact of antibiotic treatment on growth yielded no consistent results; antibiotic treatment improved growth outcomes for some antibiotic-pathogen pairs, but it worsened growth outcomes for other antibiotic-pathogen pairs. There was no pattern for which antibiotic-pathogen pairs had significant changes in growth. These results were also unexpected, as viruses were often responsive to antibiotic treatment. Another additional unexpected result was the fact that *Shigella* cases were not impacted by antibiotic treatment. The GEMS study found that treating *Shigella*-positive with WHO recommended antibiotics significantly reduces growth stunting (Nasrin 2021). There are two primary reasons we may have this result. The first is confounding by indication: *Shigella* cases that had more severe symptoms such as vomiting or blood in diarrhea were more likely to be treated. This prompts antibiotic treatment and causes worse growth outcomes, therefore acting as a confounder. The second possible reason is the analysis methods used. In our analysis, we compared treatment with a given antibiotic to treatment by any other antibiotic or no antibiotics. Changing the analysis to compare treatment with a given antibiotic to treatment with no antibiotics may yield a different result that is more consistent with existing literature.

The analysis of the impact of antibiotic treatment on duration yielded consistent results, with antibiotics always either decreasing duration or having no significant effect on it. These results are consistent with a 2006 clinical review and a recent study of travelers' diarrhea (Diniz-Santo 2006, Leung 2019). However, this contradicts results from the ABCD study, which found that antibiotic treatment does not impact the duration of non-bacterial diarrhea episodes (Manuscript Under Review). The ABCD study is more recent, more relevant to the population in the MAL-ED study, and is a clinical trial. As a result, we would expect our results to align with it. This discrepancy may be resolved with another analysis method, such as matching, that emulates a clinical trial more closely.

The MAL-ED dataset is well-suited to the analysis performed in this paper, as it contains records of over ten thousand diarrhea episodes, along with stool samples, symptom information, length measurements, and numerous other datapoints. In addition, the multi-site nature of MAL-ED helps to limit biases that may occur in single site studies. However, the MAL-ED study is inherently limited by being an observational study, rather than a trial with randomized exposure. The analyses performed benefited from the wealth of information in the MAL-ED dataset, as it ensured that there were enough results within antibiotic-pathogen pairs to perform analyses, and these analyses were able to control for numerous confounders. However, there is room to improve on the analysis methods, as noted earlier in this discussion. The growth analysis is limited by the comparison group including other antibiotic classes, which may be the reason for the unclear results we have obtained. The duration analysis may be improved by implementing matching, which may help it to be more in line with the results the ABCD study obtained. Overall, the large scope of the MAL-ED dataset is a strength, and this scope will be useful moving forward.

Improving upon guidelines for treating childhood diarrhea is essential. Childhood diarrhea impacts some of the most vulnerable populations in the world, and the effects of childhood diarrhea leave lasting impacts on these communities. One major element needed to improve these guidelines is information on which diarrheal episodes can be effectively treated with antibiotics. Of particular importance is identifying treatable episodes that are not currently treated under WHO guidelines. This paper adds to this growing body of research, and it indicates that, while growth may not have a clear response to antibiotic treatment, diarrheal duration is significantly reduced in many cases by antibiotic treatment. Further refinement of our methods may more specifically identify which diarrhea cases can be effectively treated with antibiotics.

Table 1. Number of episodes, antibiotic treatment rate, severity, duration, growth, and confounders (SES, age, fever, blood in diarrhea, dehydration, and vomiting) by study site.

Country	Overall	Bangladesh	Brazil	India	Nepal	Peru	Pakistan	South Africa	Tanzania
Number of episodes	10,260	1,682	188	981	1,083	2,129	3,250	322	625
Number of episodes treated with antibiotics	4,693/10,260 (45.74%)	979/1,682 (58.20%)	20/188 (10.64%)	251/981 (25.59%)	327/1,083 (30.19%)	802/2,129 (37.67%)	1,920/3,250 (59.08%)	71/322 (22.05%)	323/625 (51.68%)
Average severity ***mean(sd)***	3.75 (2.04)	3.94 (2.12)	3.49 (1.69)	3.43 (2.09)	4.48 (1.91)	3.69 (2.08)	4.71 (2.70)	2.54 (1.48)	3.30 (1.93)
Average duration (days) ***mean(sd)***	4.29 (4.48)	3.73 (2.75)	4.29 (2.19)	3.21 (3.19)	5.05 (3.43)	4.01 (3.11)	5.38 (6.50)	2.31 (1.62)	2.45 (1.64)
Average growth change 3 months after the episode* ***mean(sd)***	-0.16 (0.51)	-0.20 (0.41)	-0.12 (0.58)	-0.15 (0.48)	-0.11 (0.44)	-0.12 (0.53)	N/A	-0.19 (0.60)	-0.36 (0.65)
SES Score ***mean(sd)***	0.52 (0.18)	0.53 (0.12)	0.80 (0.10)	0.48 (0.15)	0.69 (0.13)	0.54 (0.11)	0.49 (0.18)	0.76 (0.11)	0.21 (0.10)
Age at episode (days) ***mean(sd)***	336.75 (197.44)	364.51 (190.75)	437.90 (181.34)	325.14 (188.33)	343.72 (199.51)	365.60 (189.95)	307.52 (206.27)	350.01 (187.87)	284.68 (173.20)
Fever	3,291/10,260 (32.08%)	394/1,682 (23.42%)	29/188 (15.43%)	261/981 (26.61%)	321/1,083 (29.64%)	506/2,129 (23.77%)	1,582/3,250 (48.68)	44/322 (13.66%)	154/625 (24.64%)
Blood in Diarrhea	506/10,260 (4.93%)	72/1,682 (4.28%)	4/188 (2.13%)	62/981 (6.32%)	50/1,083 (4.62%)	116/2,129 (5.45%)	106/3,250 (3.26%)	11/322 (3.42%)	85/625 (13.60%)
Dehydration	1,010/10,260 (9.84%)	75/1,682 (4.46%)	1/188 (0.53%)	43/981 (4.38%)	47/1,083 (4.34%)	210/2,129 (9.86%)	583/3,250 (17.94%)	11/322 (3.42%)	40/625 (6.40%)
Vomiting	1,996/10,260 (19.45%)	370/1,682 (22.00%)	38/188 (20.21%)	156/981 (15.90%)	143/1,083 (13.20%)	267/2,129 (12.54%)	768/3,250 (23.63%)	56/322 (17.39%)	198/625 (31.68%)

***** From subset of data with growth measurements, which included 6,600 episodes

Table 2. Associations between short-term growth and antibiotic treatment, stratified by antibiotic type and cause of diarrhea.

	Antibiotic Type						
Cause of Diarrhea	Any	Penicillin	Cephalosporins	Sulfonamides	Macrolides	Metronidazole	Fluoroquinolones
All diarrhea episodes (n=6,600)	0.02 (-0.01, 0.04)	0.01 (-0.03, 0.05)	-0.01 (-0.06, 0.04)	-0.00 (-0.05, 0.04)	-0.00 (-0.03, 0.03)	0.03 (-0.01, 0.08)	0.02 (-0.02, 0.06)
Adenovirus (n=271)	0.03 (-0.07, 0.14)	-0.01 (-0.21, 0.19)	**0.26 (0.07, 0.44)**	**-0.19 (-0.30, -0.07)**	0.07 (-0.04, 0.17)	-0.09 (-0.30 0.12)	0.01 (-0.18, 0.20)
Astrovirus (n=197)	0.02 (-0.14, 0.17)	-0.08 (-0.22, 0.07)	**-0.22 (-0.42, -0.03)**	**-0.15 (-0.30, -0.01)**	0.07 (-0.06, 0.20)	0.18 (-0.14, 0.49)	0.11 (-0.20, 0.41)
Campylobacter (n=123)	**-0.26 (-0.41, -0.11)**	-0.03 (-0.22, 0.17)	**0.53 (0.35, 0.72)**	**-0.43 (-0.61, -0.26)**	**-0.30 (-0.43, -0.18)**	**-0.19 (-0.29, -0.09)**	0.00 (-0.37, 0.38)
Cryptosporidium (n=94)	0.02 (-0.03, 0.06)	0.03 (-0.04, 0.09)	**-0.09 (-0.18, -0.01)**	-0.55 (-1.17, 0.07)	0.02 (-0.09, 0.14)	**-0.06 (-0.08, -0.03)**	0.05 (-0.02, 0.13)
ETEC (n=316)	0.02 (-0.08, 0.12)	0.01 (-0.17, 0.19)	0.02 (-0.22, 0.26)	-0.09 (-0.36, 0.53)	-0.07 (-0.18, 0.04)	0.08 (-0.04, 0.19)	0.09 (-0.06, 0.23)
Norovirus (n=234)	0.03 (-0.08, 0.14)	-0.03 (-0.20, 0.14)	-0.09 (-0.36, 0.17)	0.02 (-0.21, 0.25)	0.02 (-0.13, 0.18)	0.06 (-0.01, 0.13)	**0.61 (0.27, 0.96)**
Rotavirus (n=321)	0.04 (-0.07, 0.16)	-0.15 (-0.33, 0.03)	-0.13 (-0.36, 0.09)	0.08 (-0.16, 0.32)	0.03 (-0.11, 0.16)	0.13 (-0.04, 0.30)	0.04 (-0.11, 0.19)
Sapovirus (n=387)	-0.01 (-0.10, 0.08)	0.10 (-0.09, 0.28)	-0.05 (-0.22, 0.12)	-0.03 (-0.22, 0.16)	0.03 (-0.07, 0.14)	-0.12 (-0.27, 0.04)	-0.02 (-0.15, 0.11)
Shigella (n=548)	-0.01 (-0.06, 0.05)	0.08 (-0.02, 0.19)	-0.06 (-0.17, 0.05)	-0.03 (-0.19, 0.14)	0.03 (-0.03, 0.10)	-0.07 (-0.16, 0.03)	-0.00 (-0.08, 0.08)

Table 3. Associations between diarrheal duration and antibiotic treatment, stratified by antibiotic type and cause of diarrhea.

	Antibiotic Type						
Cause of Diarrhea	Any	Penicillin	Cephalosporins	Sulfonamides	Macrolides	Metronidazole	Fluoroquinolones
All diarrhea episodes (n=10,260)	**0.64 (0.61, 0.67)**	**0.89 (0.83, 0.96)**	**0.89 (0.81, 0.96)**	0.97 (0.89, 1.06)	**0.70 (0.65, 0.76)**	**0.91 (0.86, 0.98)**	0.90 (0.81, 1.00)
Adenovirus (n=430)	**0.58 (0.47, 0.71)**	0.68 (0.47, 1.00)	0.88 (0.51, 1.54)	0.66 (0.39, 1.14)	**0.69 (0.55, 0.87)**	1.31 (0.85, 2.02)	**0.73 (0.54, 0.99)**
Astrovirus (n=345)	**0.66 (0.52, 0.84)**	0.79 (0.54, 1.16)	0.93 (0.65, 1.34)	1.13 (0.76, 1.66)	**0.66 (0.45, 0.96)**	0.91 (0.65, 1.29)	0.97 (0.55, 1.71)
Campylobacter (n=183)	**0.60 (0.39, 0.92)**	1.14 (0.74, 1.75)	0.88 (0.44, 1.75)	**0.39 (0.24, 0.63)**	0.74 (0.41, 1.34)	**0.38 (0.19, 0.75)**	3.38 (0.60, 18.87)
Cryptosporidium (n=138)	**0.56 (0.38, 0.81)**	0.83 (0.50, 1.40)	**0.25 (0.10, 0.58)**	0.92 (0.56, 1.49)	0.88 (0.46, 1.67)	0.74 (0.43, 1.30)	**0.22 (0.14, 0.35)**
ETEC (n=508)	**0.55 (0.45, 0.67)**	0.94 (0.66, 1.33)	**0.57 (0.36, 0.88)**	1.20 (0.80, 1.79)	**0.68 (0.51, 0.90)**	0.90 (0.69, 1.19)	0.82 (0.54, 1.23)
Norovirus (n=376)	**0.61 (0.48, 0.78)**	0.75 (0.53, 1.07)	1.41 (0.77, 2.57)	0.75 (0.54, 1.03)	0.71 (0.49, 1.02)	0.90 (0.58, 1.40)	0.91 (0.55, 1.53)
Rotavirus (n=614)	**0.71 (0.59, 0.85)**	1.23 (0.94, 1.60)	1.05 (0.75, 1.47)	0.77 (0.56, 1.04)	0.79 (0.61, 1.02)	0.79 (0.61, 1.03)	0.80 (0.59, 1.08)
Sapovirus (n=611)	**0.64 (0.54, 0.77)**	0.83 (0.61, 1.13)	1.02 (0.64, 1.63)	0.96 (0.70, 1.32)	**0.64 (0.50, 0.83)**	0.92 (0.71, 1.21)	1.22 (0.76, 1.95)
Shigella (n=854)	**0.54 (0.46, 0.63)**	0.96 (0.76, 1.22)	1.01 (0.75, 1.35)	0.87 (0.67, 1.13)	**0.56 (0.46, 0.70)**	1.03 (0.83, 1.27)	1.01 (0.76, 1.34)

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