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The Effect of Antibiotic Treatment of Subclinical Enteric Infection on Child Growth in the MAL-ED Cohort Study

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B.S.
Georgia Institute of Technology
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Abstract

The Effect of Antibiotic Treatment of Subclinical Enteric Infection on Child Growth in the MAL-ED Cohort Study

By Simone Anderson

Background: Stunting is prevalent in low- and middle-income countries. In the long term, it can lead to cognitive impairment and increased risk for infectious diseases. Diarrheal diseases in children under five have been found to decrease length-for-age and weight-for-age z-scores leading to stunting in the long term. Subclinical infection of these diseases may have a larger effect on this deficit. Antibiotics may have a positive impact on child growth. We wanted to see the effect of antibiotic treatment on these subclinical infections and its relationship to child growth.

Methods: We identified our 5 pathogens of interest in non-diarrheal stool samples collected monthly from children in the cohort. We defined an infection as treated if a child received antibiotics in the 7 days before or after the stool sample was collected. We evaluated the effect on length-for-age, weight-for-age, and weight-for-length z-scores 3 months, 6 months, and 2 years after infection. We used linear regression with generalized estimating equations to estimate the effect of antibiotic use on the infection for the 3- and 6-month z-scores. At 2 years, we used linear regression to assess the proportion of infections treated.

Results: Differences in z-score varied by both pathogen type and antibiotic class. Treatment of ETEC resulted in significant differences in WAZ and WFL when treated with fluoroquinolones or macrolides. Use of fluoroquinolones had the greatest differences in z-scores. Treatment of Shigella with cephalosporins resulted in significant negative differences in LAZ. Z-score differences 6 months after infection were slightly larger than those at 3 months. There were very small impacts of antibiotic use at 2 years after infection.

Conclusions: We found that antibiotic treatment had a larger impact on weight than length There appeared to be a larger effect on short term growth outcomes than long term growth. Other methods are needed to reduce the global burden of stunting.

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Introduction

Growth faltering is a cause for concern for children under five living in low- and middle-income countries (LMICs). Stunting, which is defined as more than two standard deviations below the WHO height-for-age standard, affects many children in these settings, and can lead to long term health consequences such as decreased cognitive development and increased mortality risk for infectious diseases [1]. Malnutrition and diarrhea are major contributors to this phenomenon. Approximately 84% of long-term disability adjusted life years (DALYs) lost were due to an increased risk of infectious disease and diarrhea induced undernutrition. Much of this burden falls disproportionately on children living in low- and middle-income countries in sub-Saharan Africa and South Asia [2].The relationship between diarrheal diseases and impaired child growth has been well described. Diarrheal disease has been associated with decreased height and weight attainment[3]. Specific pathogens including *Shigella*, *Campylobacter* and enteroaggregative *E. coli* have had the greatest impacts on mean length for age z-scores[4].

Studies are suggesting that subclinical infections of these pathogens are a greater threat to a child's growth than symptomatic infections. Prevalence of these infections appears to be high in LMICs with an average of 1.3 pathogens detected per non-diarrheal stool by the age of 2 [5]. These negative impacts persist leading to deficits into 5 years of age[4]. It was also seen that children who had more of these subclinical infections had a slower growth velocity than those who had fewer pathogens detected[5].

Antibiotic treatment for these enteric pathogens has been studied as an intervention that could mitigate the negative growth effects with variable success. In children with moderate to severe

diarrhea, Shigella episodes that were not treated with WHO-recommended antibiotics had a greater decline in linear growth than those who received treatment [6]. However, a clinical trial found that giving antibiotics to newborns every three months until 18 months did not produce a significant difference in length for age z-score from the placebo group[7]. Antibiotics appear to have a more positive effect on weight than on length[8]. Antibiotic use in the first year of life has been associated with weight gain and increased growth rate likely due to changes in the gut microbiome, anti-inflammatory effects, and treatment of subclinical infections[9, 10]. The studies that could not find an association between antibiotic treatment and growth could have missed subclinical infections in between doses or failed to adequately reduce pathogen carriage[6, 7].

In this study, we sought to understand how antibiotic treatment at the time of subclinical enteric infections modified their effect on child growth in children under 2 years of age from low-resource settings.

Methods

Study Design

The MAL-ED Study has previously been described [5]. The study was conducted from November 2009 to February 2014 in Dhaka, Bangladesh, Vellore, India, Bhaktapur, Nepal, Fortaleza, Brazil, Loreto, Peru, Venda, South Africa, Naushahro Feroze, Pakistan and Haydom, Tanzania. Newborns were enrolled within 17 days of their birth and followed until 2 years old. Inclusion criteria for the study were the child's mother had to be 16 years old or older, the family planned to remain in the area for at least 6 months from enrollment, they were a singleton

pregnancy, they had no other siblings enrolled in the study, and had an enrollment weight of more than 1500 grams. Fieldworkers visited children twice weekly to ask caregivers about any presence of illness, antibiotic use, and feeding practices. Stool samples were collected monthly and tested for presence of enteropathogens. Stool samples were also collected during or within 2 days before or after a diarrheal illness. Length and weight outcomes were measured at enrollment and at monthly intervals.

Variable Definitions

We defined a subclinical infection to be any pathogen detected by qPCR in the monthly non-diarrheal stool sample[11]. The 5 pathogens we explored were *Campylobacter*, *Shigella*, enteroaggregative *E. coli*, typical enteropathogenic *E. coli*, and enterotoxigenic *E. coli* as these were the most common bacterial pathogens assessed that could respond to antibiotics. We wanted to see if treatment of these infections led to improved growth outcomes at 3 and 6 months after infection and at 2 years using length and weight collected within a 30-day window of the desired outcome date. We defined an infection as treated if it was exposed to antibiotics in the 7 days before or after the stool sample was collected. The exposure of treated infection was modeled as a dichotomous variable: ≥ 1 day of use vs 0 days of use. We assessed the effect of any antibiotic use and the effect of any macrolide, fluoroquinolone, or cephalosporin specific use. To assess growth outcomes, we utilized weight-for-age, length-for-age, and weight-for-length z-scores. These growth outcomes compare each child's measured weight to an international reference standard based on WHO growth standards[12].

Analysis

We used multivariable linear regression to estimate the effect of antibiotic use at the time of bacterial infections on short-term growth. We used generalized estimating equations to account for the correlation between measurements within each child across the time points. We adjusted for site, sex, WAMI score, weight-for-age z-score at most recent measurement prior to infection, length-for-age at most recent previous measurement, proportion of days exclusively breastfed in the 30 days before stool collection, presence of acute lower respiratory infection, maternal report of symptoms, and presence of other pathogens in the 7 days before or after stool collection. For each pathogen, we subset the data to stools with that pathogen present and assessed the difference in growth outcomes for those who had received antibiotic versus not. We assessed this for any antibiotic use. We also assessed the effects of each antibiotic class on their own.

We also used multivariable linear regression to estimate the effect of antibiotic treatment during bacterial infections on growth at 2 years. We defined the exposure as the proportion of infections exposed to antibiotics out of the total number of infections experienced by each child over the study period. For this analysis we adjusted for site, sex, WAMI score, enrollment weight-for-age z-scores, enrollment length-for-age z-scores, the total number of days each child was exclusively breastfed, the total number of reports of presence of acute lower respiratory infection, maternal report of symptoms, the total number of *E. bieneusi* or *Giardia* infections, and total number of infections for each of the 5 pathogens explored. We examined the number of infections treated over the study period for each of the pathogens to assess the effect of more treated infection on growth outcomes. We assessed the antibiotics as above.

Results

Demographics

Among the 1,288 children with non-diarrheal stools testing positive for at least 1bacterial pathogen of interest, there were 26,647 samples obtained and utilized in the analysis. The mean LAZ and WAZ at enrollment were -0.979, and -0.947, respectively. At 2 years, the mean LAZ was -1.53 and the mean WAZ was -1.01.

3- and 6-Month Outcomes

Overall, we found that use of any antibiotics at the time of an enteric infection increases z-scores for short term growth outcomes. Increases were greater for weight-for-age and weight-for-length z-scores than for length-for-age. Among those that were infected with *Campylobacter*, length-for-age z-scores were 0.03 (-0.02, 0.08) z-scores higher 3 months after treatment with any antibiotic compared to no treatment. For weight-for-age and weight-for-length z-scores, z-scores were 0.06 (0.003, 0.11) and 0.05 (-0.01, 0.11) higher for those who received any antibiotic compared to those who did not, among those infected with *Campylobacter*. 6 months after infection, use of any antibiotics showed similar increases in WAZ and WFL as the 3-month outcomes. The largest difference in WAZ after treatment was 0.09 (-0.01, 0.20) comparing children who were treated to those who were not treated among those that were infected with *Shigella*.

Use of cephalosporins was associated with often negative impacts on short term growth outcomes. Cephalosporins resulted in significant decreases in LAZ after 3 months for *Shigella*, EAEC, and tEPEC (-0.20(-0.33, -0.04), -0.10 (-0.20, -0.03), -0.18 (-0.32, -0.04)). This result persisted after 6 months post infection (-0.20 (-0.34, -0.04), -0.06(-0.13, 0.02), -0.14 (-0.28, 0.01)). Cephalosporins slightly increased WAZ and WFL z-scores for those infected with

Campylobacter and ETEC at both 3- and 6-months post-infection (0.06 (-0.03, 0.16), 0.001 (-0.10, 0.10) for 3-month WAZ, 0.06 (-0.04, 0.17), 0.02 (-0.09, 0.12) for 6-month WAZ, 0.08 (-0.04, 0.21), 0.05 (-0.07, 0.17) for 3-month WFL, 0.07 (-0.06, 0.20), 0.02 (-0.10, 0.15) for 6-month WFL).

Those who used fluoroquinolones had the largest differences in growth outcomes compared to those who did not. At 3 months after infection, differences in WAZ and WFL z-scores are most prominent among those who were infected with ETEC. There was a 0.20 (0.08, 0.31) difference in WAZ and a 0.20 (0.06, 0.34) difference in WFL. After 6 months, fluoroquinolones were associated with larger differences in WAZ and WFL. Notably there was a 0.37 (0.10, 0.65) difference in WAZ for those infected with *Shigella*. Fluoroquinolones were also associated with some positive effects on LAZ at 6 months, especially on those infected with *Campylobacter* with a difference of 0.20 (0.01, 0.40).

We found macrolide use produced mixed results for growth outcomes. For all 5 of the pathogens investigated, macrolides produced negative differences in LAZ at 3 months. The greatest difference was among those who were infected with tEPEC with a difference of -0.04 (-0.14, 0.06). Similar to the other antibiotics, the effects were larger for WAZ and WFL. There was a significant difference in WAZ scores among those infected with ETEC at 0.07 (0.005, 0.13). For WFL, significant increases were seen among those who were infected with *Shigella*, EAEC, and ETEC (0.19 (0.01,0.37), 0.09 (0.01, 0.17), and 0.09 (0.01, 0.17)). The differences seen at 6 months were smaller for all the growth outcomes. For LAZ, small positive differences were seen among those infected with *Shigella* and tEPEC (0.004 (-0.13, 0.14), 0.01 (-0.10, 0.12)). Among

those infected with ETEC there was a 0.08 (0.01, 0.15) difference in LAZ. For WFL the largest difference was seen among those with *Shigella* at 0.09 (-0.13, 0.31).

2-Year Outcomes

The differences in z-scores associated with the proportion of infections treated with any antibiotics for all growth outcomes were small or slightly negative. The difference in LAZ was 0.003 (-0.04, 0.05) for treated *Campylobacter* infections. For WAZ, there was a -0.001 (-0.05, 0.05) difference in z-scores for treated infections. WFL at 2 years showed a similar pattern with a -0.01 (-0.06, 0.05) difference.

Infections treated with cephalosporins showed a similar pattern to the outcomes presented at 3 and 6 months. Some of the positive effects of treatment with this antibiotic were seen on LAZ, particularly in *Campylobacter* and ETEC infections, but the effects were very small (0.02 (-0.08, 0.12), 0.02 (-0.08, 0.12)). The effects on WAZ and WFL were mainly negative. There were significant decreases in WAZ and WFL in those with tEPEC infections with a -0.24 (-0.41, -0.07) difference in WAZ and a -0.28 (-0.45, -0.10) difference in WFL.

Treatment with fluoroquinolones once again demonstrated the most benefit of the antibiotic classes tested. It was associated with positive effects on LAZ for all the pathogens except for *Campylobacter* where there was a -0.01 (-0.21, 0.19) difference in treated infections. The greatest impact of this drug class on LAZ was on *Shigella* infections where there was a 0.21 (-0.10, 0.52) difference at 2 years. Treated infections of tEPEC resulted in positive differences in all 3 growth outcomes compared to those who did not have treated infections. For LAZ there was

a 0.14 (-0.19, 0.46) difference. For WAZ, there was a 0.31 (-0.04, 0.66) difference, and for WFL there was a 0.23 (-0.13, 0.59) difference.

Many of the pathogens treated with macrolides resulted in negative differences in LAZ at 2 years. *Shigella* infections treated with macrolides were associated with a -0.17 (-0.31, -0.02) difference in LAZ at 2 years. There was a similar but less pronounced pattern for WAZ and WFL with -0.07 (-0.22, 0.08) and -0.003 (-0.16, 0.16) difference in z-score, respectively. The greatest impact of this antibiotic was seen in tEPEC infections where there was a 0.08 (-0.06, 0.23) difference in the WFL scores at 2 years.

Discussion

Treatment of subclinical infections was associated with higher growth z-scores 3 and 6 months after infection. This effect was more pronounced for WAZ and WFL compared to LAZ. This finding is consistent with previous literature that antibiotic use may have a larger impact on weight than length [8]. Fluoroquinolones was consistently associated with the largest differences. For all three growth outcomes, it was associated with larger differences at 6 months than 3 months. Fluoroquinolone use was significantly associated with a 0.20 (0.08, 0.3) increase in z-scores at 3 months and 0.21(0.08, 0.34) increase at 6 months compared to those who had no use, among those infected with ETEC. A similar pattern for WFL was observed with a 0.20 (0.06, 0.34) and 0.23 (0.09, 0.38) difference, respectively. Macrolide use was associated with similar yet smaller increases in z-scores than fluoroquinolones. The effect is greatest at 3 months after infection and decreased slightly at 6 months. Cephalosporin use was associated with some negative differences in z-scores particularly among those infected with Shigella. It was

significantly associated with negative differences in LAZ. Shigella has been associated with some of the largest deficits in mean LAZ [6,8]. Cephalosporins apparent inability to treat Shigella in this study is in contradiction to current use as a recommended antibiotic for the pathogen. Specific information about each antibiotic was not available, so we were unable to separate first or second generation cephalosporins from the third generation cephalosporins. First and second generations are not effective against Shigella like third generations which could account for some of the differences.

At 2 years, having treated infections was associated with minimal results on growth outcomes. We found little association between antibiotic treatment and long-term LAZ for any of the antibiotics. Among those with who were infected with Shigella infections, fluoroquinolones use was associated with a 0.21 (-0.10, 0.52) increase in LAZ whereas macrolides were associated with a -0.17 (-0.31, -0.02) decrease. These results are not consistent with the short-term results which demonstrates the opposite trend. In terms of WAZ and WFL at 2 years, there appeared to be small differences between those that were treated and those who were not. There are many determinants of growth at this age, so short-term impacts may better reflect the true treatment effect. The long-term effects of antibiotics on weight are not well studied. Previous studies have found that antibiotic use is associated with greater weight gain in children[9, 13]. Potentially, antibiotic treatment did not reduce overall pathogen carriage enough to see these effects. Another explanation for this is that changes in the gut's microbiome could mediate weight gain more than treatment of subclinical infections.

A limitation of this study is that there was no information available about the dose of antibiotic or specific drug within each class used, so we were unable to determine whether the amount of antibiotics used was able to eliminate carriage of the pathogen. Further studies could examine whether there exists a dose-response effect of antibiotic treatment on growth outcomes. Although we controlled for any reported illness symptoms and presence of other pathogens, it is possible that there was still residual confounding leading to biased estimates.

In summary, targeting subclinical infections via antibiotic therapy may improve child weight in low- and middle-income countries in the short term, but the effect is not long lasting and other methods are required to promote long term growth. Interventions aimed at prevention of exposure to enteric infection and reduction in pathogen carriage are needed to lessen the global burden of stunting.

Figure 1. Comparison of differences in LAZ and WAZ at 3 months among those treated with any antibiotics

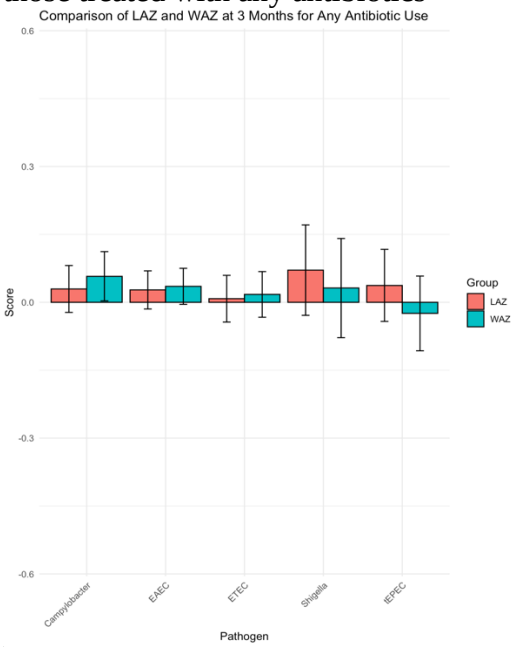

Figure 2. Comparison of differences in LAZ and WAZ at 3 months among those treated with cephalosporins

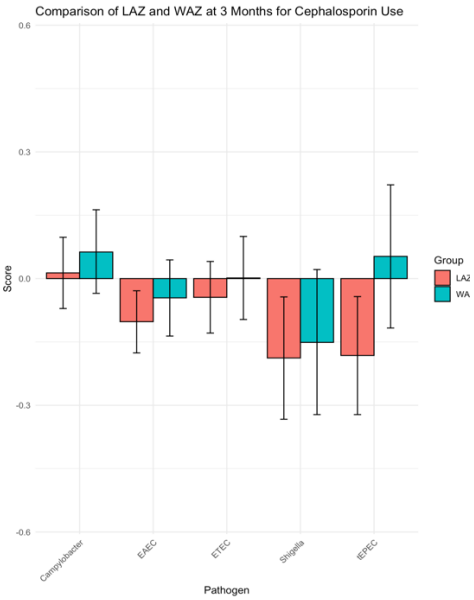

Figure 3. Comparison of differences in LAZ and WAZ at 3 months among those treated with fluoroquinolones

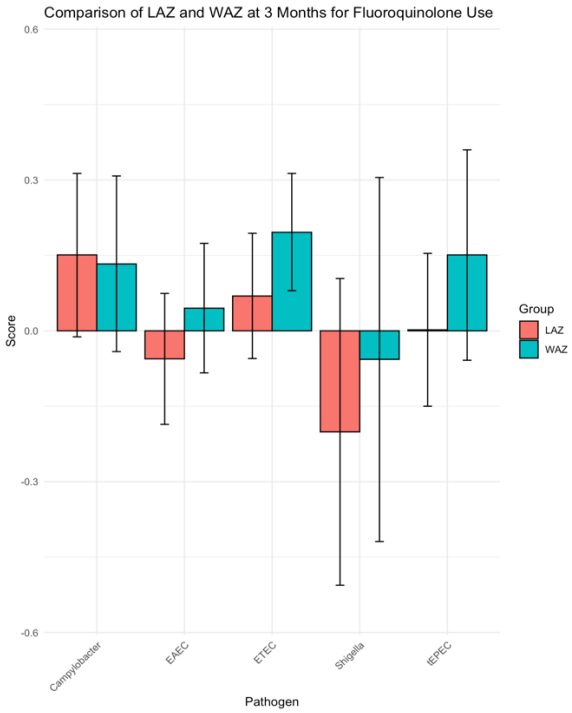

Figure 4. Comparison of differences in LAZ and WAZ at 3 months among those treated with macrolides

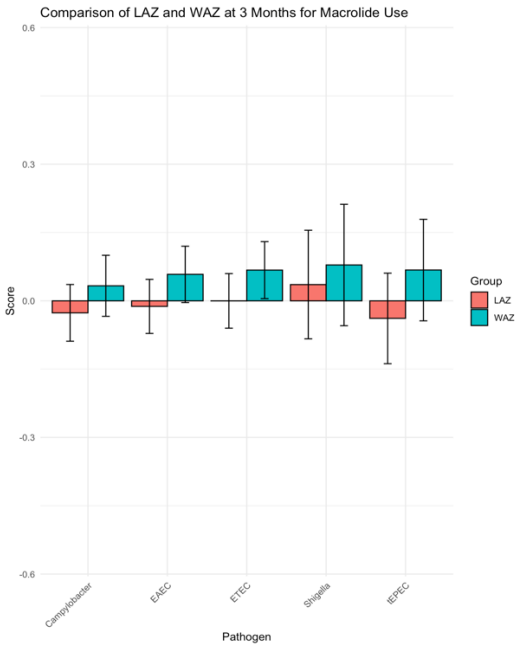

Table 1. Baseline characteristics and growth outcomes

	BG (n=210)	BR (n=165)	IN (n=227)	NP (n=227)	PE (n=194)	PK (n=246)	SA (n=19)	Total (n=1288)
Non-diarrhoeal stools that tested positive for ≥1 pathogen of interest, n	4372	2970	4929	5066	4249	4680	381	26647
Median per child (IQR)	21.0(19.0, 22.8)	19.0(16.0, 21.0)	22.0(21.0, 23.0)	23(22,23.5)	22.0(21.0, 23.0)	19.5(17.0, 21.0)	20.0(18.0, 23.0)	22.0(19.0, 23.0)
Sex								
Female, n (%)	2124 (48.6%)	1323(44.5 %)	2659(53.9 %)	2361(46.6%)	1967(46.3 %)	2434(52%)	206(54.1 %)	13074
Male, n (%)	2248(51.4%)	1647(55.5 %)	2270(46.1 %)	2705(53.4%)	2282(53.7 %)	2246(48%)	175(45.9 %)	13573
Mean WAMI Score	0.55	0.84	0.49	0.70	0.55	0.49	0.78	0.59
Mean enrollment WAZ	-1.26	-0.15	-1.29	-0.92	-0.62	-1.39	-0.01	-0.98
Mean enrollment LAZ	-0.95	-0.78	-1.01	-0.71	-0.95	-1.32	0.02	-0.95
Mean WAZ at 2 years	-1.61	0.40	-1.65	-0.92	-0.79	---------	-0.51	-1.01

Mean LAZ at 2 years	-2.03	-0.03	-1.91	-1.34	-1.88	---------	-1.30	-1.53
Mean WFL at 2 years	-0.75	0.52	-0.90	-0.32	0.26	---------	0.21	-0.30

Table 2. Differences in LAZ, WAZ, and WFL for each of the 5 pathogens and antibiotic classes at 3 months post-infection

3-month LAZ				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.03 (-0.02, 0.08)	0.01 (-0.07, 0.10)	0.15 (-0.01, 0.31)	-0.03 (-0.09, 0.04)
Shigella	0.07 (-0.03, 0.17)	-0.19 (-0.33, -0.04)	-0.20 (-0.50, 0.10)	0.04 (-0.08,0.16)
EAEC	0.03 (-0.01,0.07)	-0.10 (-0.18, -0.03)	-0.06 (-0.19, 0.07)	-0.01 (-0.07, 0.05)
tEPEC	0.04 (-0.04,0.12)	-0.18 (-0.32, -0.04)	0.002 (-0.15, 0.15)	-0.04 (-0.14, 0.06)
ETEC	0.01 (-0.04, 0.06)	-0.04 (-0.13, 0.04)	0.07 (-0.06, 0.19)	-0.0001 (-0.06, 0.06)
3-month WAZ				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.06 (0.003, 0.11)	0.06 (-0.03, 0.16)	0.13 (-0.04, 0.31)	0.03 (-0.03, 0.10)
Shigella	0.03 (-0.08, 0.14)	-0.15 (-0.32, 0.02)	-0.06 (-0.42, 0.31)	0.08 (-0.05, 0.21)
EAEC	0.04 (-0.004, 0.08)	-0.05 (-0.14, 0.04)	0.05 (-0.08, 0.17)	0.06 (-0.004, 0.12)
tEPEC	-0.02 (-0.11, 0.06)	0.05 (-0.12, 0.22)	0.15 (-0.06, 0.36)	0.07 (-0.04, 0.18)
ETEC	0.02 (-0.03, 0.07)	0.001 (-0.10, 0.10)	0.20 (0.08, 0.31)	0.07 (0.005, 0.13)
3-month WFL				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.05 (-0.01, 0.11)	0.08 (-0.04, 0.20)	0.10 (-0.12, 0.31)	0.07 (-0.02, 0.15)
Shigella	-0.01 (-0.14, 0.11)	-0.11(-0.33, 0.11)	0.14 (-0.17, 0.45)	0.19 (0.01,0.37)
EAEC	0.04 (-0.01, 0.08)	-0.02 (-0.12, 0.09)	0.14 (-0.001 ,0.29)	0.09 (0.01, 0.17)
tEPEC	-0.03 (-0.14, 0.07)	0.11 (-0.09, 0.31)	0.25 (-0.04, 0.55)	0.11 (-0.02, 0.23)
ETEC	0.0004 (-0.06, 0.06)	0.05 (-0.07, 0.17)	0.20 (0.06, 0.34)	0.09 (0.009, 0.17)

Table 3. Differences in LAZ, WAZ, and WFL for each of the 5 pathogens and antibiotic classes at 6 months post-infection

6-month LAZ				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.04 (-0.01, 0.09)	0.06 (-0.03, 0.15)	0.20 (0.01, 0.40)	-0.02 (-0.09, 0.05)

Shigella	0.07 (-0.04, 0.18)	-0.19 (-0.34, -0.04)	-0.25 (-0.57, 0.06)	0.004 (-0.13, 0.14)
EAEC	0.02 (-0.02, 0.07)	-0.06 (-0.13, 0.02)	0.02 (-0.12, 0.15)	-0.001 (-0.07, 0.06)
tEPEC	0.02 (-0.07, 0.11)	-0.14 (-0.28, 0.01)	0.05 (-0.12, 0.22)	0.01 (-0.11, 0.12)
ETEC	-0.01 (-0.07, 0.04)	-0.03 (-0.12, 0.06)	0.07 (-0.07, 0.21)	0.05 (-0.01, 0.12)
6-month WAZ				
Pathogen	Any Antibiotic	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.07 (0.02, 0.13)	0.06 (-0.04, 0.17)	0.09 (-0.08, 0.27)	0.05 (-0.02, 0.13)
Shigella	0.09 (-0.01, 0.20)	-0.15 (-0.31, 0.02)	0.11 (-0.06, 0.28)	0.01 (-0.15, 0.16)
EAEC	0.05 (0.003, 0.09)	-0.01 (-0.10, 0.08)	0.14 (0.02, 0.26)	0.06 (-0.01, 0.12)
tEPEC	0.02 (-0.06, 0.10)	0.01 (-0.16, 0.18)	0.12 (-0.07, 0.30)	0.10 (-0.004, 0.20)
ETEC	0.02 (-0.03, 0.08)	0.02 (-0.09, 0.12)	0.21 (0.08, 0.33)	0.08 (0.01, 0.15)
6 month-WFL				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.07 (0.004, 0.13)	0.07 (-0.06, 0.20)	0.08 (-0.14, 0.30)	0.06 (-0.03, 0.16)
Shigella	0.06 (-0.07, 0.19)	-0.08 (-0.31, 0.15)	0.37 (0.10, 0.65)	0.09 (-0.13, 0.31)
EAEC	0.06 (0.01, 0.11)	-0.01 (-0.11, 0.10)	0.23 (0.08, 0.38)	0.08 (-0.01, 0.16)
tEPEC	0.06 (-0.04, 0.16)	-0.02 (-0.22, 0.18)	0.09 (-0.14, 0.32)	0.07 (-0.06, 0.20)
ETEC	0.05 (-0.01, 0.12)	0.02 (-0.10, 0.15)	0.23 (0.09, 0.38)	0.04 (-0.04, 0.13)

Table 4. Differences in LAZ, WAZ, and WFL for each of the 5 pathogens and antibiotic classes at 2 years

2-year LAZ				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	0.003 (0.04, 0.05)	0.02 (-0.08, 0.12)	-0.01 (-0.21, 0.19)	-0.002 (-0.10, 0.10)
Shigella	-0.01 (-0.09, 0.08)	-0.05 (-0.22, 0.12)	0.21 (-0.10, 0.52)	-0.17 (-0.31, -0.02)
EAEC	0.02 (-0.02, 0.05)	0.003 (-0.07, 0.08)	0.10 (-0.07, 0.27)	0.04 (-0.03, 0.11)
tEPEC	0.01 (-0.06, 0.08)	-0.07 (-0.23, 0.09)	0.14 (-0.19, 0.46)	-0.04 (-0.17, 0.09)
ETEC	0.002 (-0.04, 0.05)	0.02 (-0.08, 0.12)	0.02 (-0.16, 0.19)	0.04 (-0.04, 0.12)
2-year WAZ				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	-0.002 (-0.05, 0.05)	0.04 (-0.06, 0.14)	-0.01 (-0.22, 0.21)	0.02 (-0.08, 0.13)
Shigella	-0.02 (-0.11, 0.06)	-0.15 (-0.33, 0.03)	0.05 (-0.29, 0.38)	-0.07 (-0.22, 0.08)
EAEC	0.002 (-0.04, 0.04)	-0.003 (-0.08, 0.08)	0.15 (-0.03, 0.32)	0.02 (-0.06, 0.09)
tEPEC	0.02 (-0.06, 0.09)	-0.24 (-0.41, -0.07)	0.31 (-0.04, 0.66)	0.034 (-0.11, 0.17)

ETEC	0.003 (-0.04, 0.05)	0.001 (-0.10, 0.10)	0.02 (-0.17, 0.21)	0.06 (-0.03, 0.14)
2-year WFL				
Pathogen	Any Antibiotics	Cephalosporin	Fluoroquinolone	Macrolide
Campylobacter	-0.01 (-0.06, 0.05)	0.04 (-0.07, 0.14)	-0.00002 (-0.22, 0.22)	0.02 (-0.09, 0.13)
Shigella	-0.03 (-0.12, 0.06)	-0.15 (-0.34, 0.04)	-0.12 (-0.46, 0.23)	-0.003 (-0.16, 0.16)
EAEC	-0.02 (-0.06, 0.02)	-0.01 (-0.10, 0.07)	0.11 (-0.08, 0.29)	-0.01 (-0.09, 0.07)
tEPEC	0.02 (-0.06, 0.09)	-0.28 (-0.45, -0.10)	0.23 (-0.13, 0.59)	0.08 (-0.06, 0.23)
ETEC	0.01 (-0.04, 0.06)	-0.001 (-0.11, 0.11)	0.01 (-0.19, 0.21)	0.05 (-0.04, 0.14)

1. Wierzba, T.F. and F. Muhib, *Exploring the broader consequences of diarrhoeal diseases on child health.* The Lancet Global Health, 2018. **6**(3): p. e230-e231.
2. Troeger, C., et al., *Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases in children younger than 5 years.* The Lancet Global Health, 2018. **6**(3): p. e255-e269.
3. Lee, G., et al., *Symptomatic and asymptomatic Campylobacter infections associated with reduced growth in Peruvian children.* PLoS Negl Trop Dis, 2013. **7**(1): p. e2036.
4. Rogawski, E.T., et al., *Use of quantitative molecular diagnostic methods to investigate the effect of enteropathogen infections on linear growth in children in low-resource settings: longitudinal analysis of results from the MAL-ED cohort study.* Lancet Glob Health, 2018. **6**(12): p. e1319-e1328.
5. *Relationship between growth and illness, enteropathogens and dietary intakes in the first 2 years of life: findings from the MAL-ED birth cohort study.* BMJ Glob Health, 2017. **2**(4): p. e000370.
6. Nasrin, D., et al., *Pathogens Associated With Linear Growth Faltering in Children With Diarrhea and Impact of Antibiotic Treatment: The Global Enteric Multicenter Study.* J Infect Dis, 2021. **224**(12 Suppl 2): p. S848-s855.
7. DeBoer, M.D., et al., *Effect of scheduled antimicrobial and nicotinamide treatment on linear growth in children in rural Tanzania: A factorial randomized, double-blind, placebo-controlled trial.* PLoS Med, 2021. **18**(9): p. e1003617.
8. Gough, E.K., et al., *The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials.* BMJ : British Medical Journal, 2014. **348**: p. g2267.
9. Dawson-Hahn, E.E. and K.E. Rhee, *The association between antibiotics in the first year of life and child growth trajectory.* BMC Pediatrics, 2019. **19**(1): p. 23.
10. Vallianou, N., et al., *Do Antibiotics Cause Obesity Through Long-term Alterations in the Gut Microbiome? A Review of Current Evidence.* Curr Obes Rep, 2021. **10**(3): p. 244-262.
11. Platts-Mills, J.A., et al., *Use of quantitative molecular diagnostic methods to assess the aetiology, burden, and clinical characteristics of diarrhoea in children in low-resource settings: a reanalysis of the MAL-ED cohort study.* Lancet Glob Health, 2018. **6**(12): p. e1309-e1318.
12. WHO, U. *The World Bank Group Levels and trends in child malnutrition. Joint child malnutrition estimates*. 2017.
13. Rogawski, E.T., et al., *Early Antibiotic Exposure in Low-resource Settings Is Associated With Increased Weight in the First Two Years of Life.* J Pediatr Gastroenterol Nutr, 2017. **65**(3): p. 350-356.