Long-Term Effects of Select Diarrheal Pathogens on Childhood Growth: A Systematic Review and Meta-Analysis

Sophie Mei Lin Whikehart

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Hmwe Hmwe Kyu

Peng Zheng

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Sophie Mei Lin Whikehart

University of Washington

Abstract

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Sophie Mei Lin Whikehart

Chair of the Supervisory Committee:

Hmwe Hmwe Kyu

Department of Health Metrics Sciences and Global Health

This systematic review and meta-analysis investigate the long-term impact of *Cryptosporidium spp.*, and *Shigella spp.*, on childhood growth outcomes, measured by height-for-age Z scores (HAZ), weight-for-age Z scores (WAZ) and weight-for-height Z scores (WHZ). *Cryptosporidium spp.*, infection was strongly associated with decreased HAZ ($p < 0.001$) and WHZ ($p < 0.001$), but not WAZ, with very high heterogeneity (I^2= 99.55% for HAZ and 99.20% for WHZ). S*higella spp.*, indicated a small but statistically negative effect only on HAZ ($p = 0.0122$) with moderate heterogeneity (I^2= 45.78%) suggesting some variability across studies. These findings highlight the differences in pathogen-specific effects.

Introduction

Diarrheal infections due to certain enteric pathogens such as *Cryptosporidium spp.*, and *Shigella spp.*, have been linked to malnutrition and stunted growth in children especially in resource limited settings. Diarrheal infections also remain one of the leading causes of morbidity and mortality in children under five (1,2). According to the Global Burden of Disease (GBD) study from 2021, diarrheal infections are responsible for an estimated 1.17 million deaths globally, particularly in low-income and middle-income countries (3). The burden of diarrhea extends beyond acute illness, as frequent episodes can lead to growth faltering, malnutrition and long-term developmental impairments. Children who experience repeated diarrheal episodes are at a higher risk for stunting, being underweight and wasting which all significantly impair physical growth and cognitive development (1,5).

To evaluate the impact of diarrheal diseases on childhood growth, Z-scores are commonly used to assess height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height WHZ). These scores are derived from the World Health Organization (WHO) growth standards, which provide reference populations either defined for the study country or from standard international reference charts (6). Children with a negative Z-score (below -2 standard deviations) are considered to be at risk for stunting or are considered underweight, both of which are key indicators for poor nutrition and growth faltering (7).

Malnutrition, particularly in the form of stunting (low height-for-age Z-score), underweight (low-weight-for age Z-score), and wasting (low weight-for-height Z-score), is a common outcome of diarrheal infections. It is important to understand that the relationship between diarrhea and malnutrition is bidirectional: diarrheal infections can lead to malnutrition and malnutrition can predispose children to diarrhea (1). This association is thought to be

mediated by environmental enteric dysfunction (EED) or environmental enteropathy which is a complex syndrome involving intestinal inflammation, impaired nutrient absorption, and a comprised intestinal barrier that arises from prolonged exposure to various enteric pathogens (2,7). While malnutrition can increase a child's susceptibility to infections, enteric infections can also impair nutrient absorption leading to malnutrition and initiating a recurrent cycle of infection (8).

Although numerous enteric pathogens contribute to growth impairment in children, this study focuses on two particularly important and distinct pathogens: *Cryptosporidium spp.*, a parasitic cause of diarrhea and *Shigella spp., a* conventional enteric bacterial pathogen (7). The decision to focus on two pathogens stems from the understanding the diarrheal infections are not a uniform group. Different pathogens can have vastly different impacts and lead to a diverse set of outcomes in terms of growth impairments. The mechanisms of infection for *Cryptosporidium spp.*, and *Shigella spp.*, are also distinct. *Cryptosporidium spp.*, causes persistent infection by invading the intestinal epithelial cells and induces chronic intestinal dysfunction, while *Shigella spp.*, causes acute intestinal inflammation and damage through its cytotoxic effects on intestinal lining (9,10). These differences lead to different pathways of nutrient malabsorption, intestinal damage and immune system dysregulation which in turn affects childhood growth in unique ways.

Despite the well documented relationship between diarrheal infections and growth impairment, significant gaps remain in understanding how specific enteric pathogens contribute to long term consequences. Previous research utilizing data from the GBD 2016 demonstrated that the impact of *Cryptosporidium spp.* infection on children's health, specifically in terms of growth impairment and increased risk of infectious disease, has been significantly

underestimated. It has been suggested that the burden of *Cryptosporidium spp.,* is 2.5 times greater than previously recognized (2). These insights underscore the need for targeted interventions to diminish the long-term consequences of *Cryptosporidium spp.,* and call for further research to explore the actual burden posed by other major diarrheal pathogens such as *Shigella spp.,* as well.

The main objective of this study is to assess the impact of select diarrheal pathogens on childhood growth by synthesizing findings from existing literature through a systematic review and conducting a meta-analysis. This will help identify the long-term impacts of the two key pathogens *Cryptosporidium spp.,* and *Shigella spp.,* on growth impairment in children. Additionally, this study helps aid in the design of targeted interventions to mitigate growth impairment caused by diarrheal infections and provide evidence to support policymaking for child health improvement. The first aim of this study is to conduct a new and updated systematic review identifying relevant studies that examine the long-term impact of specific diarrheal pathogens (*Cryptosporidium spp.,* and *Shigella spp.,*) on childhood growth metrics such as height-for-age Z scores (HAZ), weight-for-age Z scores (WAZ) and weight-for-height Z scores (WHZ). The second aim of this thesis is to perform a meta-analysis to estimate the relationship of pathogen specific effects on child growth indicators.

Methods

This study was conducted by a multidisciplinary team with expertise in global health, data extraction and epidemiology. The core research team involved Sophie Whikehart (SW) who led the systematic review and meta-analysis, managed the data collection and extraction process and conducted the statistical analysis. Ye Htet Naing (YN) who helped to conduct the title and abstract screening, support study selection and helped train the DistillerSR AI system, Regina-

Mae Dominguez (RD) who assisted with the study selection, verified data extraction and resolved discrepancies in study inclusion and Hmwe Hmwe Kyu (HK) who served as the subject matter expert, provided guidance on inclusion / exclusion conflicts and data interpretation.

Study setting

This study was a systematic review and quantitative meta-analysis in collaboration with the Institute for Health Metrics and Evaluation (IHME) to investigate the long-term effects of selected diarrheal pathogens (*Cryptosporidium spp.*, and *Shigella spp.*,) on childhood growth focusing on changes in height-for-age Z scores (HAZ), weight-for-age Z scores (WAZ) and weight-for-height Z scores (WAZ). The systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure comprehensive, transparent and replicable reporting. The meta-analysis used R to synthesize data and estimate pooled effects.

The systematic review was global in scope and included studies conducted in diverse geographic regions. Two data bases (PubMed and Embase) were searched for peer-reviewed articles using standard terms related to infectious diarrhea, diarrheal pathogens (*Cryptosporidium spp.,* and *Shigella spp.*,) and childhood growth and development (weight and height). It is to be noted that other pathogens (*Campylobacter, Norovirus, Enterotoxigenic E. coli, Enteropathogenic E. coli, Rotavirus, and Adenovirus*) were initially searched for as well to aid IHME's enteric diarrhea work but not included in the analysis for this thesis. The search was constricted to studies published between January 1st, 1990, and July 16th, 2024. No restrictions were applied for foreign language or study location during selection, ensuring a broad representation of settings. Foreign language studies were eligible for inclusion in the full-text phase, but the studies had to have an English title or abstract to review.

Study population

The population of interest included children under five years of age. Studies that reported on subpopulations were used if sufficient data was provided to assess potential biases and heterogeneity. Inclusion of the data from these subpopulations in the meta-analysis depended on whether there was sufficient data to adjust for bias in modeling for the overall target population. When relevant, unexposed (control) populations were used as a reference group for exposed populations (confirmed cases of infectious diarrhea caused by specified pathogens).

Sampling Strategy

The systematic review included studies based on specific inclusion and exclusion criteria. The inclusion criteria required that studies focus on children aged 0 to 5 years of age. Studies must report on infectious diarrhea with confirmed pathogen presence of the subset of pathogens of interest such as *Cryptosporidium spp.*, and *Shigella spp.*, and provide follow up information on height and weight after diarrhea cases are reported. Changes in height or weight must be reported as Z-scores (HAZ, WAZ, WHZ) or reported as raw metrics (i.e., cm, kg). Eligible study designs included cohort studies or longitudinal follow up studies). It was preferred the studies included a population without a confirmed infectious diarrhea case as the control group.

Studies that lacked a distinct control group or did not perform a comparative analysis (i.e., diarrhea vs. non-diarrhea or pathogen vs. no pathogen cases) were excluded. However, studies that did not explicitly state a “control group” but accounted for control comparable cases in their statistical models were eligible. This approach allowed flexibility in defining cases and controls while enabling further subgroup analysis based on variations in definitions.

The exclusion criteria eliminated cross-sectional studies, commentaries, case series, case reports and letters to the editor, Studies with population older than five years or those not focused on human subjects were excluded. Studies without follow up data on height or weight outcomes were also excluded. Finally, studies with titles and abstracts unavailable in English were not considered.

Data collection

Data collected was conducted in two phases: Title Abstract (Ti/Ab) screening and Full Text screening with dual data extraction. The initial search strategy combined standardized keywords related to infectious diarrhea, diarrheal pathogens, and childhood growth metrics in PubMed and Embase. The search terms are adapted from the larger study that includes more pathogens (see Appendix).

Once the searchers were complete, the combined references we de-duplicated and 8,883 references were uploaded into DistillerSR for Ti/Ab screening by SW and YN. RD served as a third reviewer and HK as the topic expert to provide guidance on inclusion or exclusion for conflict decisions. SW and YN utilized DistillerSR for study selection in this review and began with an independent, randomized manual screen of 10% of the article titles and abstracts. From there, they trained DistillerSR AI system to prioritize the remaining studies for manual review before using DistillerSR's AI bulk exclusion feature.

After manually screening 5% of the articles (~444) and having a good balance of included and excluded studies SW and YN ran the Check for Screening Errors. The output of this check showed the predicted inclusion likelihood scores of the REFIDs (Reference identification) that were excluded. As a note, Check for Screening Errors trains itself multiple

times using random samples of reviewed referenced for accuracy and performance. Due to random sampling to create these training sets it's possible that running these multiple times can yield varying results. Therefore, Check for Screening Errors was only run once before proceeding to the next step.

There were 75 observations that DistillerSR identified as potential accidental "false exclusions". The DAISY (DistillerSR Artificial Intelligence System) scores for these observations ranged from 0.852 – 0.994, with 44 counts for SW and 31 counts for YN. SW and YN corrected these accidental exclusions by exporting the data from DistillerSR to an Excel file and ordering the false exclusions by REFID to generate an even mix of uses and DAISY rank scores. They then split the Excel sheet in half and manually reviewed each reference. After this review it was determined that five references should be added back for full-text screening while the other 70 were correctly excluded (Table 1).

SW and YN then subset the data to unscreened references with AI Review Score within the range of < 0.1. The reviewers looked at a random sample of 5% and found that they should be excluded. They then repeated the previous steps for different ranges of AI Review Scores (i.e., 0.1-0.2, 0.2-0.3, etc.). SW and YN then ran bulk exclusion of the references with the AI Review Scores below a certain criterion. Once this step was done there were fewer "unreviewed" references assigned in the main DistillerSR dashboard. SW and YN proceeded with the remaining unreviewed references and continued until they reached a score range that contained more than 10% of the studies that should have been included. From there they continued to manually review 5% of the references to retrain DistillerSR AI system. SW and YN manually screened those with a score of > 0.85. At the end, 212 references were included for full-text screening and 8671 were excluded.

SW conducted the full text review and data extraction in tandem manually to confirm eligibility based on inclusion and exclusion criteria. Data extraction was performed by SW using the IHME standardized excel form `epi_lit_GBD2023_19_march_2024.xlsx` and adapted to collect information on study design, population characteristics, exposure type, outcomes and quality assessment metric etc. Once SW had completed 5 extractions, RD verified the extractions and marked inclusions and resolved extractions or exclusions. Once the extractions were found correct in the first 5 extraction reviews, SW screened and extracted another 5 sources for review by RD. Once the extractions were error free, RD verified all exclusions and checked one extraction out of every 5 – 10 until full text screening was complete by SW. There were 212 references in the beginning of full text screening and SW extracted 34 references at the end. A large reason why so many studies we excluded was if they contained data from the Global Enteric Multicenter Study (GEMS), Malnutrition and Enteric Disease Study (MAL-ED) or 1969-1973 Vellore Birth Cohort Study in South India which IHME already had the microdata for.

Analysis

The meta-analysis was intended to estimate the effect of *Cryptosporidium spp.,* and *Shigella spp.,* on physical growth in childhood and impacting childhood growth scores as measured by height-for-age Z scores (HAZ), weight-for-age Z scores (WAZ) and weight-for-height Z scores (WHZ). Specifically, the hypothesis is that children infected with *Cryptosporidium spp.,* or *Shigella spp.,* will exhibit lower growth scores in comparison to uninfected children. The key variables used in the meta-analysis and their definitions are shown in Table 2.

For conducting the meta-analysis for *Shigella spp.,* there were a limited number of studies from the systematic review that provided estimates on this relationship. Several studies

reported the upper and lower interval bounds but did not report standard error. To calculate the standard error for each study in the meta-analysis the following equation was used (Equation 1):

$$SE = \frac{(Upper\ Bound\ of\ Crude\ Effect\ Size - Lower\ Bound\ of\ Crude\ Effect\ Size)}{(2 \cdot 1.96)}$$

Upper Bound refers to the upper bound of the extracted crude effect size and Lower Bound refers to the lower bound of the extracted crude effect size. 1.96 is the Z-value corresponding to a 95% confidence interval. The Global Enteric Multicenter Study (GEMS), the Vellore birth cohort and the Malnutrition and Enteric Disease Study (MAL-ED) micro data are also included in the meta-analysis. The data from these studies show the change in HAZ among periods with symptomatic infection (diarrhea) compared to the change in periods without infections.

Five studies were included for the meta-analysis on *Shigella spp.*, and a random effects meta-analysis model for each outcome (HAZ, WAZ, WHZ) was fitted using the restricted maximum likelihood (REML) method from the `metafor` package in R. This approach was chosen to account for heterogeneity in effect sizes across studies and to generate a pooled estimated of the effect of infection on growth indices. There was insufficient data to estimate the effect of *Shigella spp.*, on WHZ, so this Z-score measurement was not run in the meta-analysis.

For *Cryptosporidium spp.,* four studies were included in the meta-analysis however, microdata from the GEMS, MAL-ED and Vellore birth cohort were not included. The same approach for fitting the meta-analysis from *Shigella* in R was used. Some of the studies did not report a standard error or upper or lower bounds of crude effect size estimates, therefore a standard error could not be calculated. For the studies that had no standard error, that study was removed from the meta-analysis.

Results

The meta-analysis included data from studies investigating the relationship between *Shigella* and *Cryptosporidium* infections and growth outcomes in children under five years of age.

For the *Shigella spp.,* meta-analysis a total of 29 measurements assessed the effect of Shigella spp., infection on HAZ, 16 measurements on WAZ and 13 measurements on WHZ. The random-effects model showed moderate heterogeneity for HAZ (I^2 = 45.78%) but no observed heterogeneity for WAZ and WHZ (I^2 = 0%). The effect size of HAZ was small but statistically significant (β = -0.0120, 95% CI = -0.0214, -0.0026, p = 0.0122). The effect sizes for WAZ and WHZ were small and statistically nonsignificant (p > 0.05).

For the *Cryptosporidium spp.*, meta-analysis a total of 25 measurements assessed the effect of *Cryptosporidium spp.*, infection on HAZ, 2 measurements for WAZ and 10 measurements on WHZ. The random effects model showed high heterogeneity for both HAZ and WHZ (I^2 = 99.55% and I^2 = 99.20%). WAZ shows no observed heterogeneity (I^2 = 0) %. *Cryptosporidium spp.*, infection was associated with a significant decrease in HAZ (β = -1.8399, 95% CI = -2.2427, -1.4371, p < 0.0001) which indicates a strong negative effect on linear growth. The effect of WAZ was small and not statistically significant (β = -0.0100, 95% CI = -0.0349, 0.0150, p = 0.4341). The effect size for WHZ was also statistically significant and a significant reduction was observed (β = -0.9192, 95% CI = -1.2511, -0.5872, p < 0.0001). This indicates a strong negative association between *Cryptosporidium* infection and weight-for-height (WHZ). A summary table and forest plots for each outcome can be viewed in the appendix (Tables 3-4, Figures 1-6).

Discussion

This meta-analysis attempted to evaluate the long-term impact of *Cryptosporidium spp.,* and *Shigella spp.,* infections on childhood growth outcomes from their height-for-age Z scores (HAZ), weigh-for-age Z scores (WAZ) and weight-for-height Z scores (WHZ). *Cryptosporidium spp.,* infection was significantly associated with decreased HAZ and WHZ which indicated a negative effect on both linear growth and wasting. In contrast, *Shigella spp.,* infection had a moderate effect on HAZ but little to no impact on WAZ and WHZ. These findings highlight the pathogen specific effects on childhood growth and emphasize the need for targeted interventions.

These strengths of this study come from incorporating a comprehensive and systematic approach using PRISMA guidelines to ensure a robust and transparent review process. The inclusion of both *Cryptosporidium spp.,* and *Shigella spp.,* also allowed for a comparative analysis of distinct pathogen specific effects on growth. The use of the random effects model using the REML method attempted to account for study heterogeneity and provide more accurate pooled estimates. And finally, the meta-analysis of *Shigella spp.,* included high quality data from well characterized studies such as GEMS and MAL-ED cohorts to increase the reliability of the findings.

However, this study has several limitations that go beyond the scope of this thesis. Studying heterogeneity remains a major limitation of this meta-analysis. Differences in study populations such as geographic variability, sample sizes and study designs introduced variability into the effect estimates. Two of the most cited sources of heterogeneity are differences in treatment effect parameters (typically expressed as β_1, β_2 which represent regression coefficients in linear regression, odds ratio in logistic regression, relative risks in regression analysis or mean and standard deviation) and differences in the variance of these parameters (i.e., σ_1^2, σ_2^2) (11).

Other sources of heterogeneity may include study populations, sample sizes, study designs and the modeling approaches. Despite the importance of addressing heterogeneity in meta-analysis, there has been limited research focused specifically on evaluating the accuracy of pooled meta-analysis results and due to time constraints, data limitations and scope of this study, subgroup analysis was not conducted.

While some studies included diagnostic level data, diagnostic information was not consistently extracted in the dataset. This limitation was identified later in the data collection process and to maintain consistency the analysis proceeded without including diagnostic specific data. The meta-analysis also required that all values be converted to Z-scores. Studies reporting beta coefficients in metric units (i.e., changes in weight in kg or changes in height in cm) were excluded because they could not be accurately converted to Z-scores due to inconsistencies and errors in the conversion formula. This exclusion may have reduced the overall sample size and influenced the strength of the pooled estimates.

This meta-analysis was also not able to distinguish the differential effects of acute, persistent and chronic diarrhea on growth outcomes. Some studies provided data on specific types of diarrheas while others combined them or did not specify duration. As a result, it is possible that the observed effect sizes reflect an average effect across different types of diarrheas rather than the true impact of each specific type. The effect of longer duration (i.e., persistent or chronic) may also be stronger than acute diarrhea due to prolonged nutritional and immune system stress. However, the lack of consistent reporting on diarrhea duration across studies makes it difficult to assess these differential effects.

In the introduction it was also mentioned about the well-established bidirectional relationship between diarrhea and malnutrition. This analysis focused on the effect of diarrhea on

growth, but it is difficult to establish a clear temporal relationship (i.e., whether malnutrition precedes or results from diarrhea). Studies included in this analysis primarily measured growth outcomes following diarrhea episodes but the potential for reverse causality remains and understanding whether growth failure leads to increased susceptibility to diarrhea or vice versa requires more detailed longitudinal data which is often unavailable.

This analysis also focused on pathogen specific effects of *Cryptosporidium spp.,* and *Shigella spp.,* but coinfections with other pathogens (i.e., *Rotavirus, Adenovirus, Norovirus)* are common in high-burden settings and could modify the observed associations. The role of co-infections was beyond the scope of this analysis but remains an important area for future research.

Finally, the last limitation of this study was data sparsity and geographic representation. Because of the specific inclusion criteria during the systematic review, at the end of the data extraction phase there was not that much data found on *Shigella spp.,* while more data was found on *Cryptosporidium*. This imbalance of data availability may have limited the ability to detect significant associations for *Shigella spp.,* and reduced the generalizability of the findings for that pathogen.

The findings on *Cryptosporidium spp.,* aligned with previous research such as the work done by Khali et al. They found that each episode of diarrhea caused by *Cryptosporidium spp.,* was associated with decreases in height-for-age Z scores (HAZ), weight-for-age Z scores (WAZ) and weight-for-height Z scores (WHZ). Their analysis also found that stratifying the data by diagnostic method (PCR-based vs non-PCR methods) revealed only minor differences in the magnitude of the effect on growth indicators (2). A study done by Checkley et al found that *Cryptosporidium parvum* had a lasting adverse effect on linear (height) growth, especially when

acquired during infancy and when children are stunted before they become infected (5). The lack of significant effects of WAZ and WHZ of *Shigella* on growth outcomes in this analysis also aligns with earlier studies such as one done by George et al. that suggest that *Shigella spp.,* infections are associated with stunting though the effect is typically less pronounced that that seen in other pathogens like *Cryptosporidium spp.,* that cause prolonged or chronic intestinal disruption (12).

The findings from this study provide strong support for the conceptual model that diarrheal infections particularly *Cryptosporidium spp.,* and *Shigella spp.,* can have lasting negative effects on childhood growth. The significant association between *Cryptosporidium spp.,* infections on both HAZ and WHZ strengthen the model's focus on long term impact of such infections on linear growth and nutritional status. The effects of HAZ for *Shigella spp.,* but lack of effect on WAZ and WHZ suggests that not all enteric pathogens contribute equally to growth failure which can help refine the conceptual model to include pathogen-specific pathways of growth disruption.

For public health practitioners and clinicians these findings have important implications for both clinical practice and public health strategies. The strong negative association between diarrheal infections and growth outcomes emphasizes the need for early diagnosis, targeted treatment and long-term monitoring of children affected by diarrheal pathogens especially in regions with high burden. Public health practitioners should prioritize interventions such as improving sanitation, access to clean water and ensure timely treatment of diarrheal diseases with oral rehydration therapy and global immunizations against different diarrheal infections (13).

The limitations of this study suggest several areas for future research. More research is needed to explore the sources of heterogeneity in meta-analysis especially concerning variations in study design, geographic settings and populations. Perhaps in the future a standardized growth metric data collection and reporting protocol could be developed to ensure consistency across studies. Such protocol would provide clear guidelines for reporting growth metrics (HAZ, WAZ, WHZ) including standardized methods for converting measurements to Z-scores and consistent diagnostic criteria. This would help future researchers produce more comparable and reliable data and improve the quality of meta-analyses and enhance ability to draw accurate conclusions about the impact of various pathogens on childhood growth. Subgroup analyses should be conducted to provide deeper insights into the different effects of *Cryptosporidium spp.,* and *Shigella spp.,* and other pathogens should be added such as (*Campylobacter, Norovirus, Enterotoxigenic E. coli, Enteropathogenic E. coli, Rotavirus, and Adenovirus).* Future studies should also examine the differential effects of acute, persistent and chronic diarrhea on growth outcomes. Longitudinal studies that track the duration of infections and their long-term consequences on nutritional status could provide valuable data. Better diagnostic data and standardized reporting are also necessary to evaluate the true effect on each pathogen. In addition, co-infections with other pathogens are common in high-burden settings and should be evaluated by future research to help refine public health recommendations and treatment protocols.

In conclusion, the meta-analysis provides evidence for the long-term negative impact of *Cryptosporidium spp.,* infections on childhood growth outcome. The findings emphasize the need for more targeted interventions. In contrast the results for *Shigella spp.,* which only showed an effect on HAZ, suggest that more research and data collection should be done for other

pathogens as well and that not all enteric pathogens contribute equally to growth failure. Although this analysis has provided valuable insights, the several limitations highlight the need for more standardized protocols and further research in this area. By advancing research in these areas, public health strategies, interventions and treatment protocols to reduce the long-term consequence of diarrheal diseases on childhood development can be achieved.

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Appendix

Tables

Table 1. Corrected “False Exclusions” from DistillerSR Check for Screening Errors

	Reason_for_Exclusion	Count
1	Other	5
2	Study does not have <5 age groups	5
3	Study does not include change in height or weight either in metrics or Z-scores	51
4	Study does not report on diarrhea	15
5	Study is cross-sectional, commentary, case series, case report, letters to the editor	10

Table 2. Key Variables used in the Meta-Analysis

	Code	Definition
1	Outcome	Type of Z-score (HAZ, WAZ, WHZ) or height or weight
2	Crude Effect Size	Value of difference in height or weight or Z-score measurement (typically case – control)
3	Standard Error	Standard error of the difference of the outcome, if not given, (Upper bound – Lower bound) / (2 * 1.96)
4	Study	What study this comes from (i.e., GEMS, MAL-ED, Vellore or Author’s Last Name)

Table 3. Summary of *Shigella spp.*, meta-analysis results

Summary Shigella Meta-Analysis

	I_Squared	Beta_Coefficient	CI	P_Value
HAZ	45.77781	-0.012	(-0.021, -0.003)	0.0122
WAZ	0.00000	0.005	(-0.004, 0.015)	0.285
WHZ	0.00000	0.006	(-0.008, 0.02)	0.385

Table 4. Summary of *Cryptosporidium spp.*, meta-analysis results

Summary Crypto Meta-Analysis

	I_Squared	Beta_Coefficient	CI	P_Value
HAZ	99.55284	-1.840	(-2.243, -1.437)	<0.001
WAZ	0.00000	-0.010	(-0.035, 0.015)	0.434
WHZ	99.19874	-0.919	(-1.251, -0.587)	<0.001

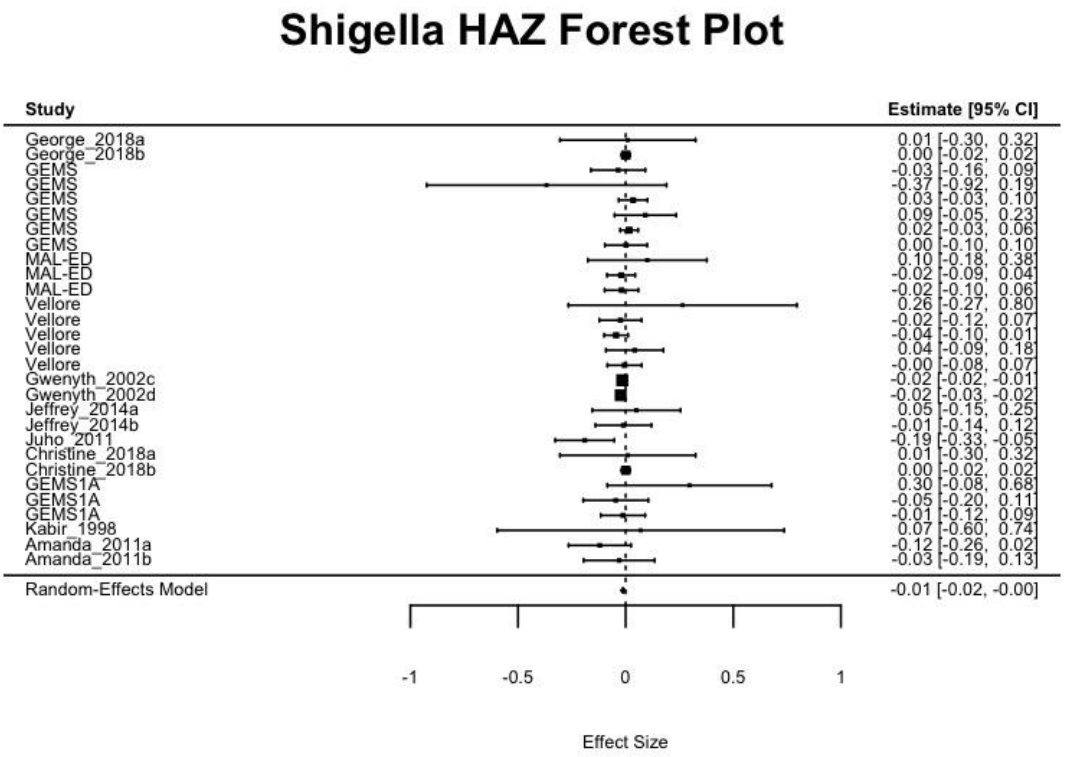
Equations

Equation 1. Standard Error Calculation

$$SE = \frac{(Upper\ bound\ of\ crude\ effect\ size - Lower\ bound\ of\ crude\ effect\ size)}{(2 \cdot 1.96)}$$

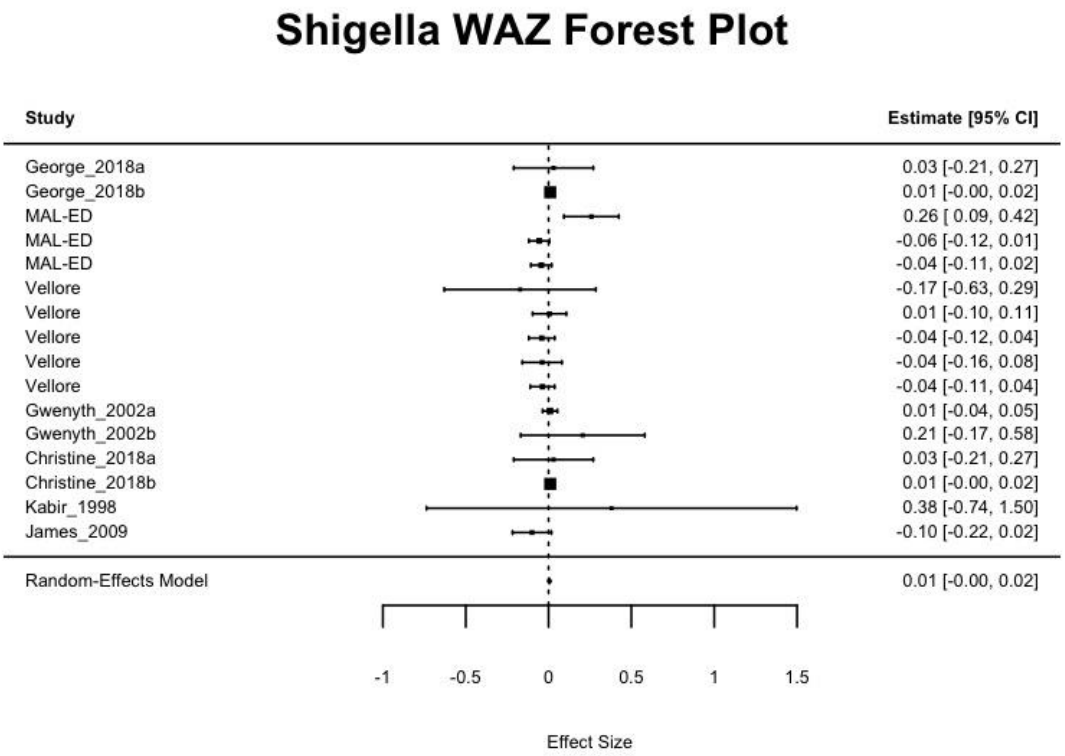
Figures

Figure 1. *Shigella spp.,* HAZ Forest Plot



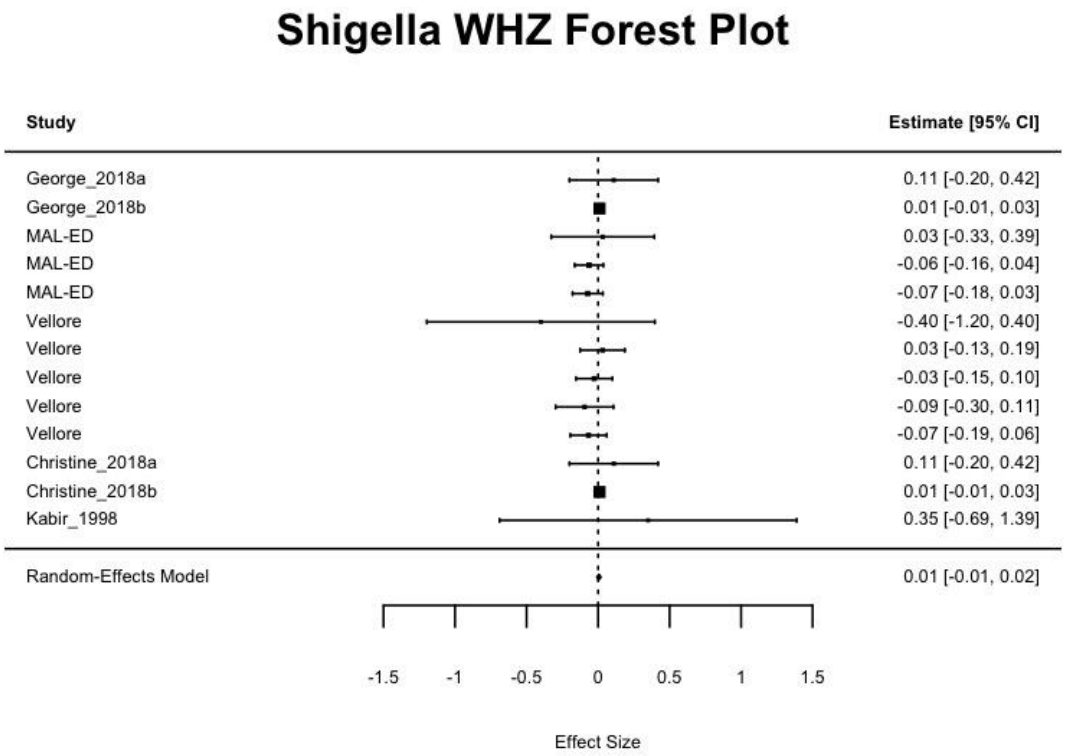
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool
*Gwenyth2002_c = time of outcome is 2 months, exposure is % of days with diarrhea
*Gwenyth2002_d = time of outcome is 9 months, exposure is incidence of diarrhea
*Jeffery_2014a = time of outcome is 12 months
*Jeffery_2014a = time of outcome is 24 months
*Christine_2018a = exposure is non log transformed presence vs absence
*Christine_2018b = exposure is log transformed presence vs absence
*Amanda_2011a = time of outcome 12 months
*Amanda_2011b = time of outcome 24 months

Figure 2. *Shigella spp.*, WAZ Forest Plot



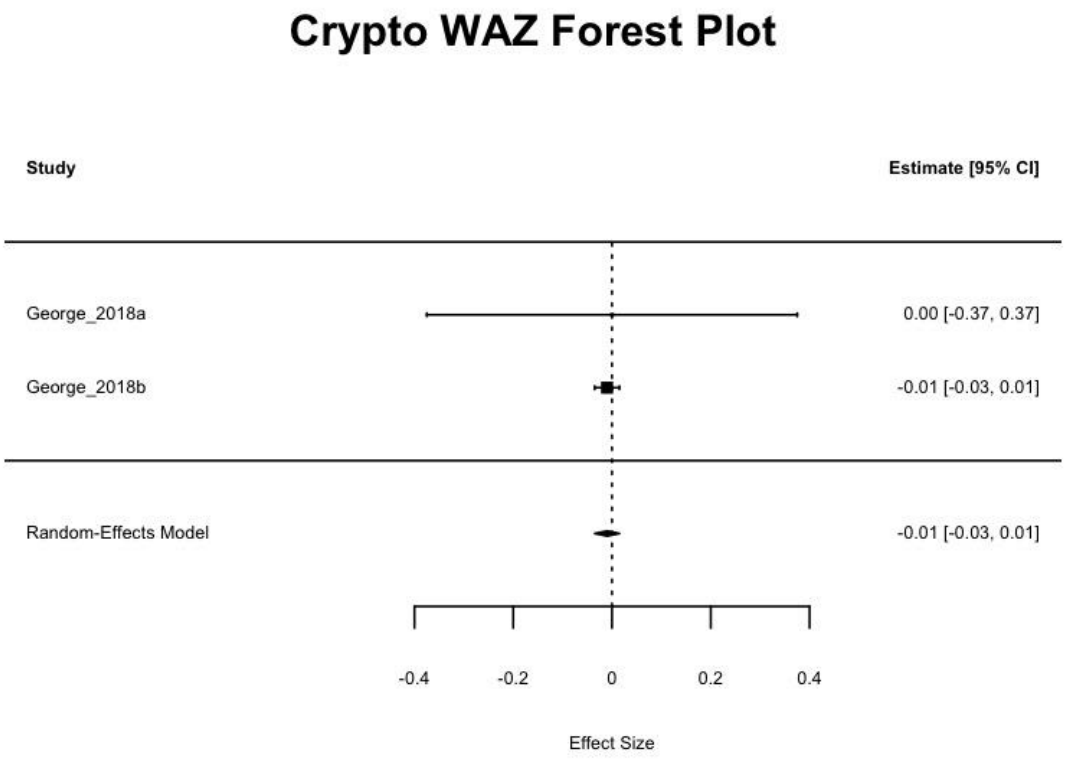
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool
*Gwenyth_2002a = time of outcome 2 months, exposure is % of days with diarrhea
*Gwenyth_2002b = time of outcome is 9 months, exposure is incidence of diarrhea

Figure 3. *Shigella spp.*, WHZ Forest Plot



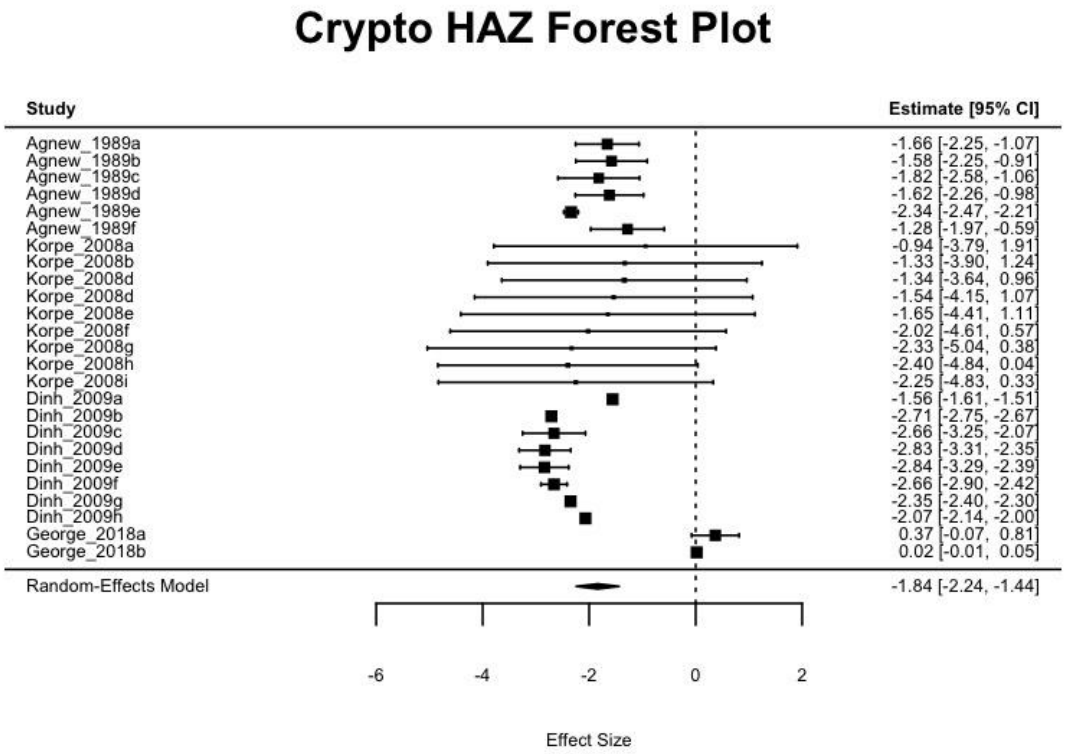
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool
*Christine_2018a = exposure is non log transformed presence vs absence
*Christine_2018b = exposure is log transformed presence vs absence

Figure 4. *Cryptosporidium spp.*, WAZ Forest Plot



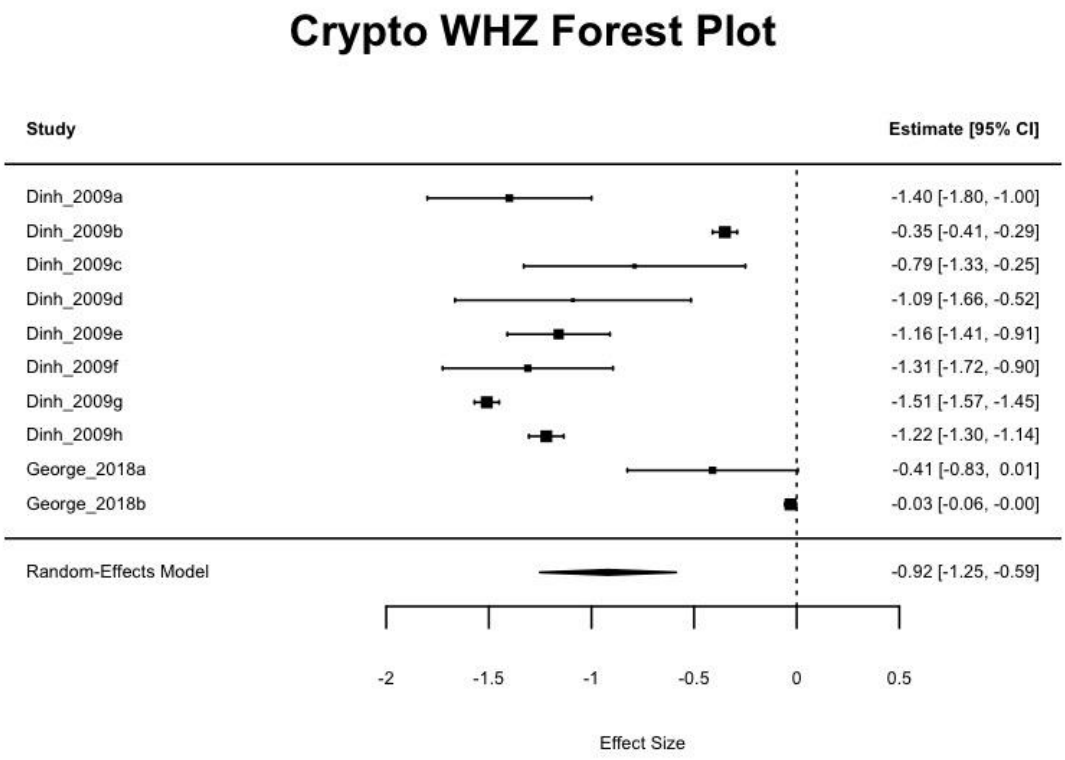
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool

Figure 5. *Cryptosporidium spp.*, HAZ Forest Plot



*Agnew_1989a = 1.5 months post exposure
*Agnew_1989b = 4.5 months post exposure
*Agnew_1989c = 7.5 months post exposure
*Agnew_1989d = 10.5 months post exposure
*Agnew_1989e = children ≤ 1 who had no prior diarrhea illnesses, 7.5 post exposure
*Agnew_1989f = children ≤ 1 who had no prior diarrhea illnesses, 10.5 post exposure
*Korpe_2008a = time of outcome birth
*Korpe_2008b = time of outcome 3 months
*Korpe_2008c = time of outcome 6 months
*Korpe_2008d = time of outcome 9 months
*Korpe_2008e = time of outcome 12 months
*Korpe_2008f = time of outcome 15 months
*Korpe_2008g = time of outcome 18 months
*Korpe_2008h = time of outcome 21 months
*Korpe_2008i = time of outcome 24 months
*Dinh_2009a = time of outcome 0 days
*Dinh_2009b = time of outcome 100 days
*Dinh_2009c = time of outcome 200 days
*Dinh_2009d = time of outcome 300 days
*Dinh_2009e = time of outcome 400 days
*Dinh_2009f = time of outcome 500 days
*Dinh_2009g = time of outcome 600 days
*Dinh_2009h = time of outcome 700 days
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool

Figure 6. *Cryptosporidium spp.*, WHZ Forest Plot



*Dinh_2009a = time of outcome 0 days
*Dinh_2009b = time of outcome 100 days
*Dinh_2009c = time of outcome 200 days
*Dinh_2009d = time of outcome 300 days
*Dinh_2009e = time of outcome 400 days
*Dinh_2009f = time of outcome 500 days
*Dinh_2009g = time of outcome 600 days
*Dinh_2009h = time of outcome 700 days
*George2018a = cases are non-log transformed presence found in stool
*George2018b = cases are log transformed presence found in stool

Search Terms

PubMed

("Campylobacter"[Mesh] OR "Campylobacter Infections"[Mesh] OR Campylobacter*[tiab] OR "Norovirus"[Mesh] OR Norovirus*[tiab] OR "Enterotoxigenic Escherichia coli"[Mesh] OR ETEC[tiab] OR "Enterotoxigenic E*"[tiab] OR “Cryptosporidium”[Mesh] OR “Cryptosporidiosis”[Mesh] OR “Rotavirus”[Mesh] OR “Adenovirus Infections, Human”[Mesh] OR “Shigella”[Mesh] OR “Shigell*”[tiab] OR “Enteropathogenic Escherichia coli”[Mesh] OR “Enteropathogenic E*”[tiab] OR “EPEC”[tiab]) AND

(stunting[Title/Abstract] OR wasting[Title/Abstract] OR growth[Title/Abstract] OR underweight[Title/Abstract] OR development[Title/Abstract] OR malnutrition[Title/Abstract] OR "Child Development"[Mesh] OR "Growth Disorders"[Mesh] OR "Body Size"[Mesh] OR "child development" OR "postnatal development" OR "post-natal development" OR growth[tiab] OR "Crown Rump Length") AND

(“1980/01/01”[Date - Publication] : “2024/07/16”[Date - Publication]) AND

Humans[Mesh] NOT (animals[MeSH] NOT humans[MeSH])

Embase

('campylobacter'/exp OR 'campylobacteriosis'/exp OR 'campylobacter*':ti,ab,kw OR 'norovirus'/exp OR 'norovirus*':ti,ab,kw OR 'enterotoxigenic escherichia coli'/exp OR 'etec':ti,ab,kw OR 'enterotoxigenic e*':ti,ab,kw OR 'cryptosporidium'/exp OR 'cryptosporidiosis'/exp OR 'rotavirus'/exp OR 'human adenovirus infection'/exp OR 'shigella'/exp OR 'shigell*':ti,ab,kw OR 'enteropathogenic escherichia coli'/exp OR 'enteropathogenic e*':ti,ab,kw OR 'epec':ti,ab,kw) AND ('stunting':ti,ab,kw OR 'wasting':ti,ab,kw OR 'underweight':ti,ab,kw OR 'development':ti,ab,kw OR 'malnutrition':ti,ab,kw OR 'child development'/exp OR 'growth disorder'/exp OR 'body size'/exp OR 'child development' OR 'postnatal development' OR 'post-natal development' OR 'growth':ti,ab,kw OR 'crown rump length') AND 'human'/exp NOT ('animal'/exp NOT 'human'/exp) AND [01-01-1980]/sd NOT [16-07-2024]/sd

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