Long-term Effects of Select Diarrheal Pathogens on Childhood Growth
Systematic Review and Meta-Analysis

Thesis Presentation

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March 8, 2025

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DEPARTMENT OF GLOBAL HEALTH

Agenda

1. Background
2. Research Question and Aims
3. Methods
4. Data Analysis
5. Expected Outcomes
6. Limitations
7. Acknowledgements
8. References

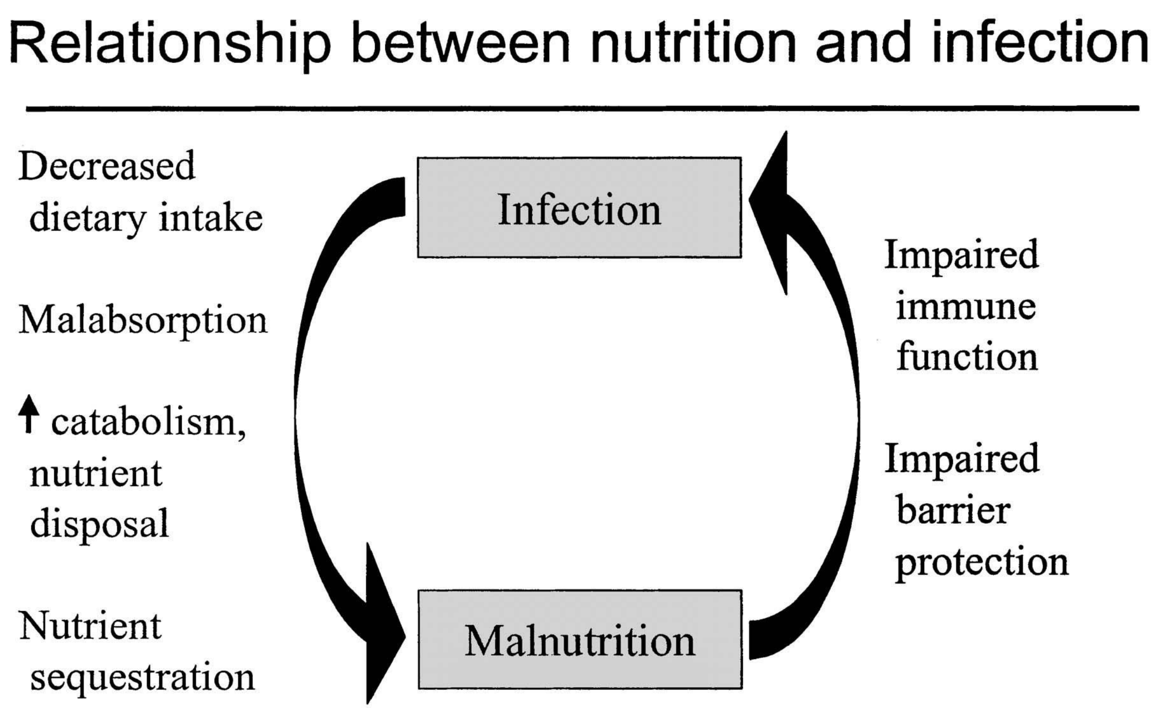
Background

- **Diarrheal diseases** due to certain **enteric pathogens** such as ***Cryptosporidium spp***. *and* ***Shigella spp***. remain one of the leading causes of **morbidity** and **mortality**[1,2].

- The burden of diarrhea extends beyond **acute illness**[3]
  - Children who experience **repeated diarrheal episodes** are at risk for
    - **Stunting**
    - **Being underweight**
    - **Wasting**

Interaction Between Diarrhea & Growth Impairment

- Relationship between **diarrhea** and **malnutrition** is **bi-directional.**[4]



Z-Scores as a Measure of Growth

- To evaluate the **impact** of diarrheal diseases on childhood growth, **Z-scores** are used to assessed **height-for-age (HAZ)**, **weight-for-age (WAZ)** and **weight-for-height (WHZ).**[5]

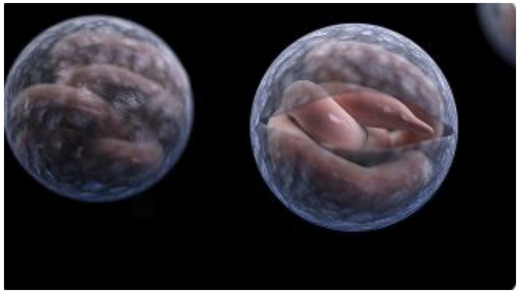
- These scores are derived from the **World Health Organization (WHO)** growth standards.

World Health Organization

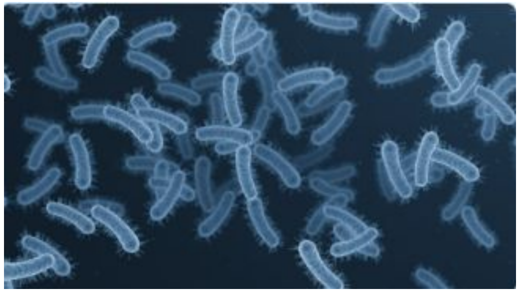
Why Cryptosporidium spp. and Shigella spp. ?

- ***Cryptosporidium spp.,*** is a parasitic cause of diarrhea and ***Shigella spp***., is a conventional enteric bacterial pathogen[5].

- Diarrheal diseases are not a **uniform group**, and different pathogens have **different impacts** and lead to **diverse outcomes** in terms of **growth impairment**[2].



Cryptosporidium



Shigella

Research Question and Aims

- **Research Question**
  - How do **diarrhea pathogen infections** (cryptosporidium spp., and shigella spp.,) **impact** childhood **height-for-age Z-scores** (HAZ), **weight-for-age Z-scores** (WAZ) and **weight-for-height Z scores (WHZ)**?
- **Aims**
  1. To conduct a new and updated **systematic review**
  2. To perform a **meta-analysis** using R

> Overall, my thesis aims to evaluate the **prevalence** and **magnitude** of **growth impairment** linked to **enteric infections.**

Positionality and Role in Data Collection and Analysis

> **Researcher Background**
  - Asian, cisgender female
  - MPH candidate at UW based in Seattle, WA (academic privilege)

> **Impact on Data Collection**
  - Potential bias towards established data sources and Western framework

> **Impact on analysis**
  - Potential of bias toward interpreting findings though a health equity lens

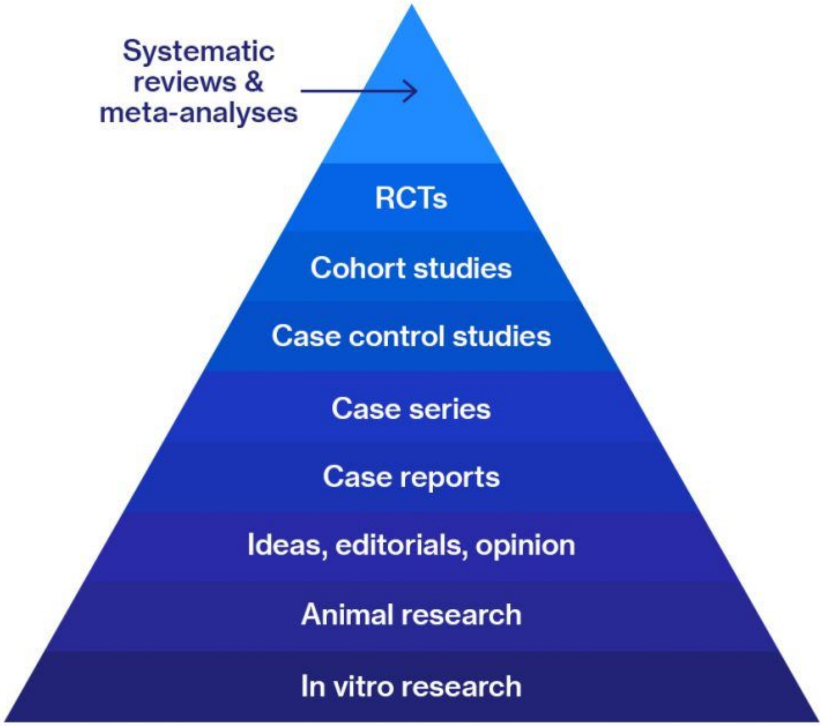
Methods

Systematic Review

- **Global** in scope and includes studies in **diverse geographic regions**
- Two databases (**PubMed and Embase**) searched for **peer reviewed** articles
- Search constrained to articles published between January 1st, 1990 and July 16th, 2024

Quantitative Meta-Analysis

- To estimate a **summary effect size** per **pathogen-specific** diarrhea episode

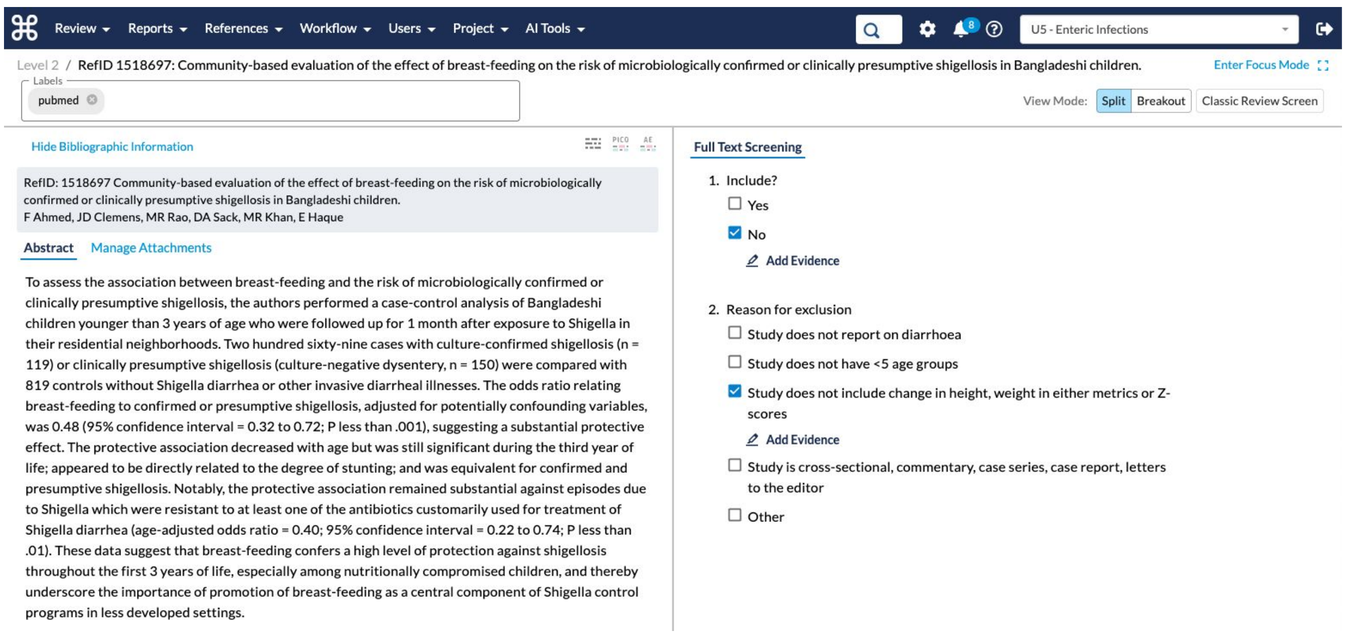


Research Population

- Sampling strategy
  - **Inclusion criteria**
    - **Diarrhea** as the case definition
    - Must include **age groups under 5** years
    - Reported data must include **change in height or weight** either measured in metric units (ex – kg, cm) or as Z-scores
    - Preferred that study include **case** and **control**
  - **Exclusion criteria**
    - Cross sectional studies, commentaries, case series, case reports and letters to the editor
    - Studies with title and abstract unavailable in English

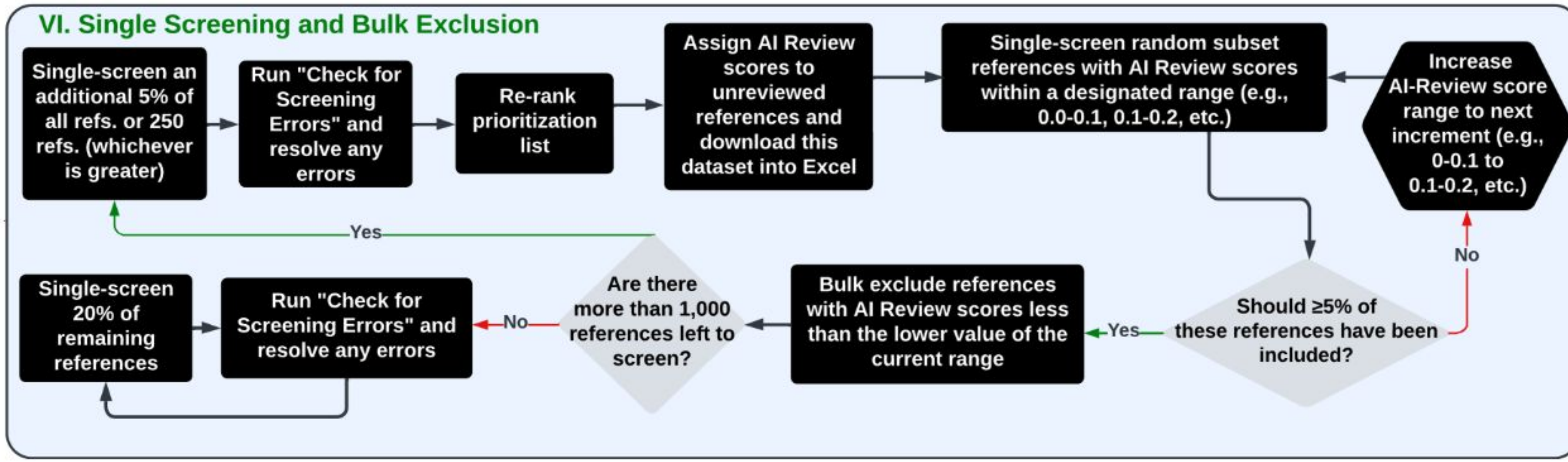
Data Collection

> Title Abstract (Ti/Ab) Screening with DistillerSR and Ye Htet Naing



When we began (Ti/Ab) screening there were 8838 references to begin with, and we got down to 212 for full text screening.

DistillerSR AI Bulk Screening Tool



and RGUD teams

Data Collection (Cont).

- **Data Extraction** using the **IHME standardized excel** \`epi_lit_GBD2023_19_march_2024.xlsx\`
  - Extract data on:
    - Children who have had **(case)** and have not had **(control)** **diarrhea** DUE TO PATHOGENS OF INTEREST
    - What their impact is on growth for weight or height, in form called **"effect size".**
      - Effect size was often (case – control)

Example of Extracted Data Table

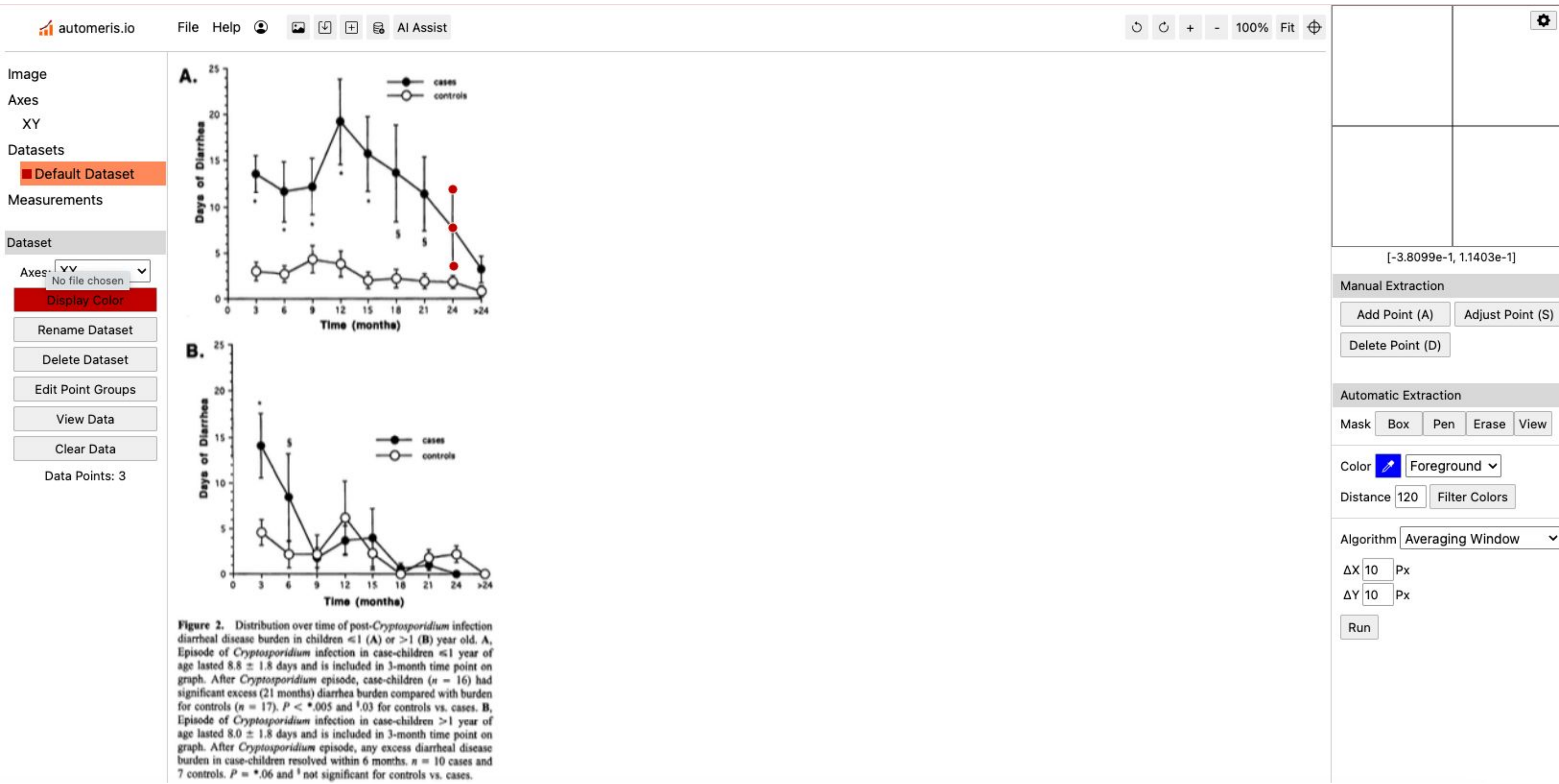
TABLE 2 The association between viral, bacterial, and parasitic infections detected at 18 months and children's LAZ at 24 months

Microbe	The proportion of positive samples	Children with negative test results (number of samples)	Children with positive test results (number of samples)	Difference (95% CI)	p-Value*
Mean ± SD LAZ at 24 months					
Enterovirus	84.5%	−1.82 ± 1.26 (91)	−1.76 ± 1.01 (495)	−0.07 (−0.30 to 0.17)	0.59
Parechovirus	15.5%	−1.74 ± 1.07 (495)	−1.92 ± 0.94 (91)	0.18 (−0.06 to 0.42)	0.13
Norovirus	7.7%	−1.78 ± 1.05 (541)	−1.62 ± 1.04 (45)	−0.15 (−0.47 to 0.17)	0.35
Rhinovirus	4.6%	−1.75 ± 1.04 (559)	−2.05 ± 1.26 (27)	0.29 (−0.12 to 0.70)	0.24**
Rotavirus	0.6%	−1.77 ± 1.05 (582)	−1.89 ± 1.63 (4)	0.12 (−2.47 to 2.70)	0.86**
Bacterial species					
Shigella	10.2%	−1.73 ± 1.03 (527)	−2.11 ± 1.11 (60)	0.39 (0.11–0.67)	0.006
Campylobacter	69.6%	−1.65 ± 1.09 (179)	−1.82 ± 1.02 (410)	0.17 (−0.01 to 0.36)	0.07
Parasitic species					
Cryptosporidium	2.7%	−1.77 ± 1.05 (570)	−1.80 ± 1.11 (16)	0.03 (−0.50 to 0.55)	0.85**
Giardia lamblia	53.8%	−1.78 ± 1.18 (271)	−1.76 ± 0.93 (315)	−0.02 (−0.20 to 0.15)	0.81
Blood malaria parasitemia	11.9%	−1.75 ± 1.04 (511)	−1.88 ± 0.92 (69)	0.13 (−0.10 to 0.37)	0.27

Abbreviations: CI, confidence interval; LAZ, length-for-age Z-score.
*p-value obtained using Student's t-test unless otherwise specified.
**p-value obtained using Wilcoxon sum of ranks test.

Luoma, Juho et al. "Association between asymptomatic infections and linear growth in 18-24-month-old Malawian children." *Maternal & child nutrition* vol. 19,1 (2023): e13417. doi:10.1111/mcn.13417

Example of Extracted Data on WebPlotDigitizer



Agnew, D G et al. “Cryptosporidiosis in northeastern Brazilian children: association with increased diarrhea morbidity.” *The Journal of infectious diseases* vol. 177,3 (1998): 754-60. doi:10.1086/514247

Extraction Template

	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU
1	case and control group	multi_single	exposure	definition exposure	exposure_m ure	exposure gth	time_of_outco	outcome	outcome finition	units	outcome easure	sample_ _crude	sample_	crude_effect_size	crude_effect_size_definition	lower	uppe	standard_error	standard_deviat	p-value
225	children with negative test results								months											
226	cases = children with positive test sults (number of samples), controls children with negative test results	single	norovirus		binary			LAZ	mean +- SD LAZ at 24 months				604	-0.15	difference (95% CI) (CASE - CONTROL)	-0.47	0.17			0.35
227	cases = children with positive test sults (number of samples), controls children with negative test results (number of samples)	single	rotavirus		binary			LAZ	mean +- SD LAZ at 24 months				604	0.12	difference (95% CI) (CASE - CONTROL)	-2.47	2.7			0.86
228	cases = children with positive test sults (number of samples), controls children with negative test results	single	shigella		binary			LAZ	mean +- SD LAZ at 24 months				604	0.39	difference (95% CI) (CASE - CONTROL)	0.11	-0.67			0.006
229	cases = children with positive test sults (number of samples), controls children with negative test results	single	campylobacter		binary			LAZ	mean +- SD LAZ at 24 months				604	0.17	difference (95% CI) (CASE - CONTROL)	-0.01	0.36			0.07
230	cases = children with positive test sults (number of samples), controls children with negative test results	single	cryptosporidium		binary			LAZ	mean +- SD LAZ at 24 months				604	0.03	difference (95% CI) (CASE - CONTROL)	-0.5	0.55			0.85
231	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	shigella	exposure was found in fecal stool sample and	binary		6 months	HAZ	change from baseline to 6-month		z-score	83	236	0.01	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as	-0.3	0.33			
232	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	cryptosporidium	exposure was found in fecal stool sample and	binary		6 months	HAZ	change from baseline to 6-month		z-score	11	236	0.37	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as outcomes and presence and quantities	-0.08	0.81			
233	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	ETEC	exposure was found in fecal stool sample and	binary		6 months	HAZ	change from baseline to 6-month		z-score		236	0.11	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as	-0.19	0.42			
234	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	campylobacter jejuni	exposure was found in fecal stool sample and	binary		6 months	HAZ	change from baseline to 6-month		z-score	127	236	0.09	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as	-0.15	0.34			
235	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	shigella	exposure was found in fecal stool sample and	binary		6 months	WHZ	change from baseline to 6-month		z-score	83	236	0.11	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as outcomes and presence and quantities	-0.2	0.42			
236	cases = pathogen or microbe presence found in stool, control = athogen or microbe prescence not	single	cryptosporidium	exposure was found in fecal stool sample and	binary		6 months	WHZ	change from baseline to 6-month		z-score	11	236	-0.41	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as outcomes and presence and quantities	-0.83	0.0008			
237	cases = pathogen or microbe presence found in stool, control =	single	ETEC	exposure was found in fecal	binary		6 months	WHZ	change from baseline to		z-score		236	-0.26	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as	-0.6	0.09			
238	cases = pathogen or microbe presence found in stool, control =	single	campylobacter jejuni	exposure was found in fecal	binary		6 months	WHZ	change from baseline to		z-score	127	236	0.11	change in HAZ, WAZ and WHLZ from baseline to 6-month follow-up as	-0.17	0.4			

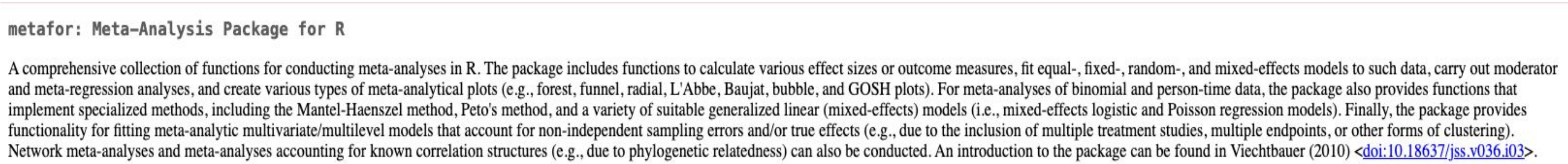
column

- nid
- field_citation_value
- file_path
- temp_id
- page_num
- table_num
- source_type
- location_name
- location_id
- ihme_loc_id
- smaller_site_unit
- site_memo
- sex
- sex_issue
- year_start
- year_end
- year_issue
- age_start
- age_end
- age_issue
- age_demographer
- multi_single
- exposure
- exposure_measure
- time_of_outcome
- outcome
- outcome_measure
- sample size crude
- sample_size
- crude_effect_size
- lower
- upper
- standard_error
- p-value
- CI or SE crude
- adjustment_covariates
- representative_name
- urbanicity_type
- note_SR
- extractor

Data Analysis

> Extracted data will be **analyzed** using R, taking into consideration different types of **biases** that are associated with each **data source.**

> Currently re-working Python code into an **R script** using the **`metafor`** package in R.


metafor: Meta-Analysis Package for R

A comprehensive collection of functions for conducting meta-analyses in R. The package includes functions to calculate various effect sizes or outcome measures, fit equal-, fixed-, random-, and mixed-effects models to such data, carry out moderator and meta-regression analyses, and create various types of meta-analytical plots (e.g., forest, funnel, radial, L'Abbe, Baujat, bubble, and GOSH plots). For meta-analyses of binomial and person-time data, the package also provides functions that implement specialized methods, including the Mantel-Haenszel method, Peto's method, and a variety of suitable generalized linear (mixed-effects) models (i.e., mixed-effects logistic and Poisson regression models). Finally, the package provides functionality for fitting meta-analytic multivariate/multilevel models that account for non-independent sampling errors and/or true effects (e.g., due to the inclusion of multiple treatment studies, multiple endpoints, or other forms of clustering). Network meta-analyses and meta-analyses accounting for known correlation structures (e.g., due to phylogenetic relatedness) can also be conducted. An introduction to the package can be found in Viechtbauer (2010) <doi:10.18637/jss.v036.i03>.

Expected Outcomes

> **My thesis is expected to**

1. Quantify the changes in **growth**, **height and/or weight** among **children under 5** after a reported case of infectious diarrhea from a pathogen of interest.

2. Highlight **potential gaps** in existing research, **guide future studies** and public **health interventions**.

Limitations

1. Challenges in **differentiating** types of diarrhea
2. **Bidirectional relationship** between diarrhea and growth
3. **Temporal relationship** between diarrhea and growth
4. Limitations due to **coinfection**
5. Data **sparsity**

Thank you to my Thesis Committee!

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Thank You to my Thesis Team!

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MD, MPHc
Dual (Ti/Ab) Screener

References

1. Mondal D, Haque R, Sack RB, Kirkpatrick BD, Petri WA. Attribution of Malnutrition to Cause-Specific Diarrheal Illness: Evidence from a Prospective Study of Preschool Children in Mirpur, Dhaka, Bangladesh. Am J Trop Med Hyg. 2009 May;80(5):824–6.
2. Khalil IA, Troeger C, Rao PC, Blacker BF, Brown A, Brewer TG, et al. Morbidity, mortality, and long-term consequences associated with diarrhoea from Cryptosporidium infection in children younger than 5 years: a meta-analyses study. Lancet Glob Health. 2018 Jul;6(7):e758–68.
3. Checkley W, Epstein LD, Gilman RH, Black RE, Cabrera L, Sterling CR. Effects of Cryptosporidium parvum Infection in Peruvian Children: Growth Faltering and Subsequent Catch-up Growth. Am J Epidemiol. 1998 Sep 1;148(5):497–506.
4. Opintan JA, Newman MJ, Ayeh-Kumi PF, Affrim R, Gepi-Attee R, Sevilleja JEAD, et al. Pediatric Diarrhea in Southern Ghana: Etiology and Association with Intestinal Inflammation and Malnutrition. Am Soc Trop Med Hyg. 2010 Oct 5;83(4):936–43.
5. The WHO Child Growth Standards [Internet]. [cited 2024 Dec 13]. Available from: https://www.who.int/tools/child-growth-standards