

BIOMARKERS OF GUT HEALTH FOR MATERNAL, NEONATAL, AND CHILD HEALTH (MNCH)

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September 7, 2021



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STRATEGIC ANALYSIS,
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Department of Global Health | University of Washington

AGENDA

- Project Overview
- Introduction
- Methods
- Results
- Questions and Discussion

INTRODUCTIONS

PROJECT TEAM MEMBERS



Miranda Delawalla, MPH
PhD Student, Epidemiology
Project Manager



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Research Assistant



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PhD Student, Epidemiology
Research Assistant



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Assistant Professor, Global Health
Faculty Lead

START OVERVIEW



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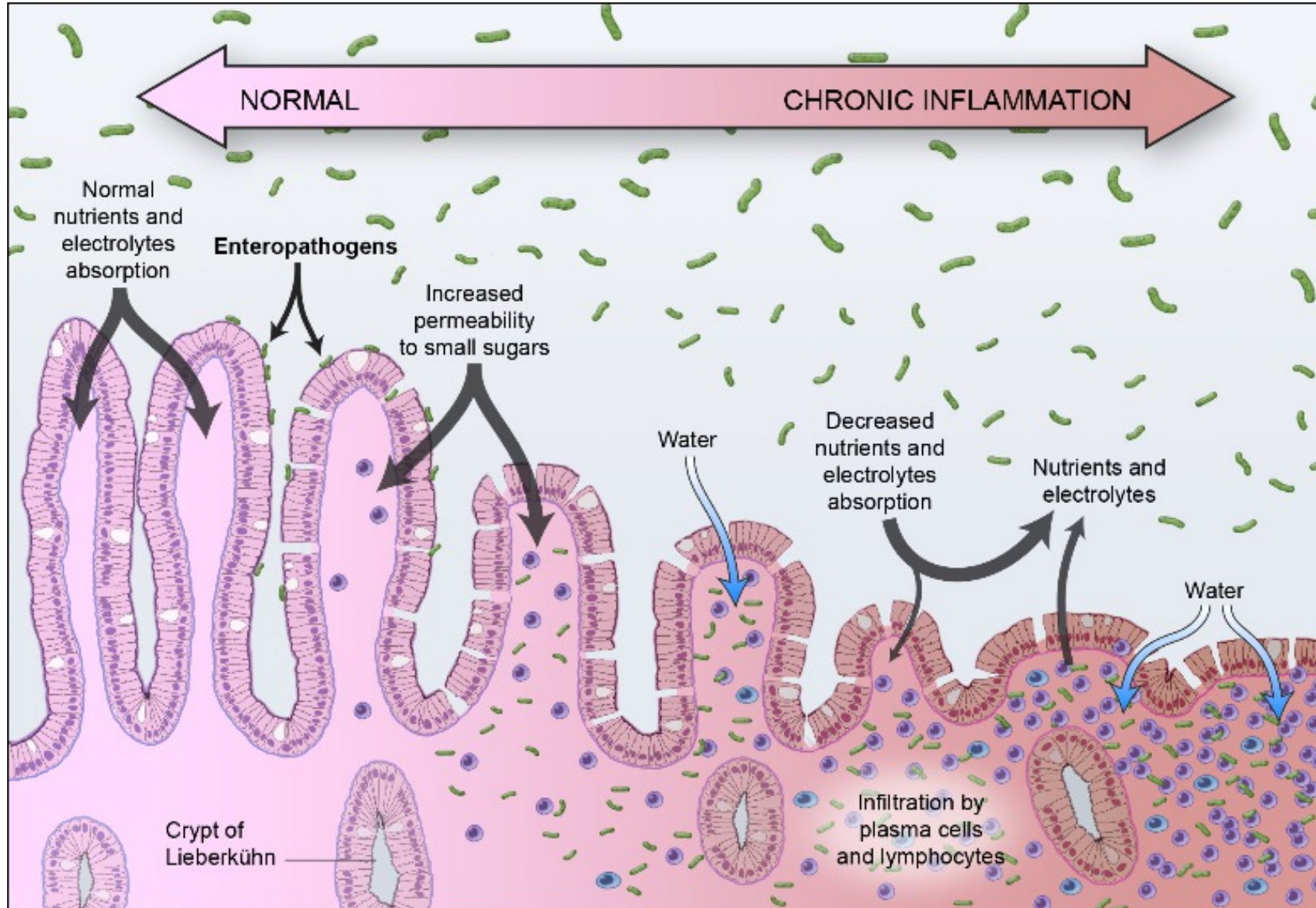


Provides structured mentorship and training to University of Washington graduate research assistants

PROJECT OVERVIEW

To review and summarize the literature around biomarkers for environmental enteric dysfunction in pregnant/lactating women and children

ENVIRONMENTAL ENTERIC DYSFUNCTION



MOTIVATIONS FOR THIS WORK

IMPACTS OF EED ON HEALTH

- Large strides in improving diarrheal incidence and mortality among children, but opportunities remain¹
- Among children, EED is associated with:²⁻⁴
 - Stunting
 - Chronic inflammation
 - Inadequate response to oral polio and rotavirus vaccines
- Among pregnant women, possible implications for birth outcomes⁵

¹ Troeger et al. 2018 doi: 10.1016/S1473-3099(18)30362-1

² Crane et al. 2015 doi: 10.1177/15648265150361S113

³ Tickell et al. 2019 doi: 10.1186/s12916-019-1417-3

⁴ Marie et al. 2018 doi: 10.1038/s41385-018-0036-1

⁵ Lauer et al. 2018 doi: 10.1093/ajcn/nqy176

MOTIVATIONS FOR THIS WORK

NEED FOR EED BIOMARKERS

- Currently, there is high interest in intervening on EED to prevent poor health outcomes
- But, knowledge gaps, particularly for pregnant and lactating women, remain in:
 - Standard definition(s) of EED
 - Distributions of biomarkers of EED
 - Associations between EED and clinical outcomes
- Practical, safe, and readily accessible biomarkers will support the design, evaluation, and implementation of prevention methods and treatments



INITIAL

PROJECT REQUEST

RESEARCH OBJECTIVES

1. Identify **EED definitions** for non-pregnant women, pregnant women, lactating women, & infants/children
2. Identify **biomarkers for EED** and relevant descriptive statistics and descriptions of populations (e.g. well-nourished vs. undernourished)
3. Identify **associations** between EED/EED-related biomarkers and clinical outcomes among non-pregnant women, pregnant women, lactating women, and infants/children

METHODS

BUILDING UPON EXISTING WORK

<https://digitalcommons.wustl.edu/tropicalenteropathybook/1/>

ENVIRONMENTAL ENTERIC DYSFUNCTION: ADVANCING CURRENT KNOWLEDGE



Environmental enteric dysfunction: Advancing current knowledge

Donna M. Denno, *University of Washington*

Kelley M. VanBuskirk

Zakia C. Nelson

Christine A. Musser

Phillip I. Tarr, *Washington University School of Medicine in St. Louis*

WORKSTREAMS

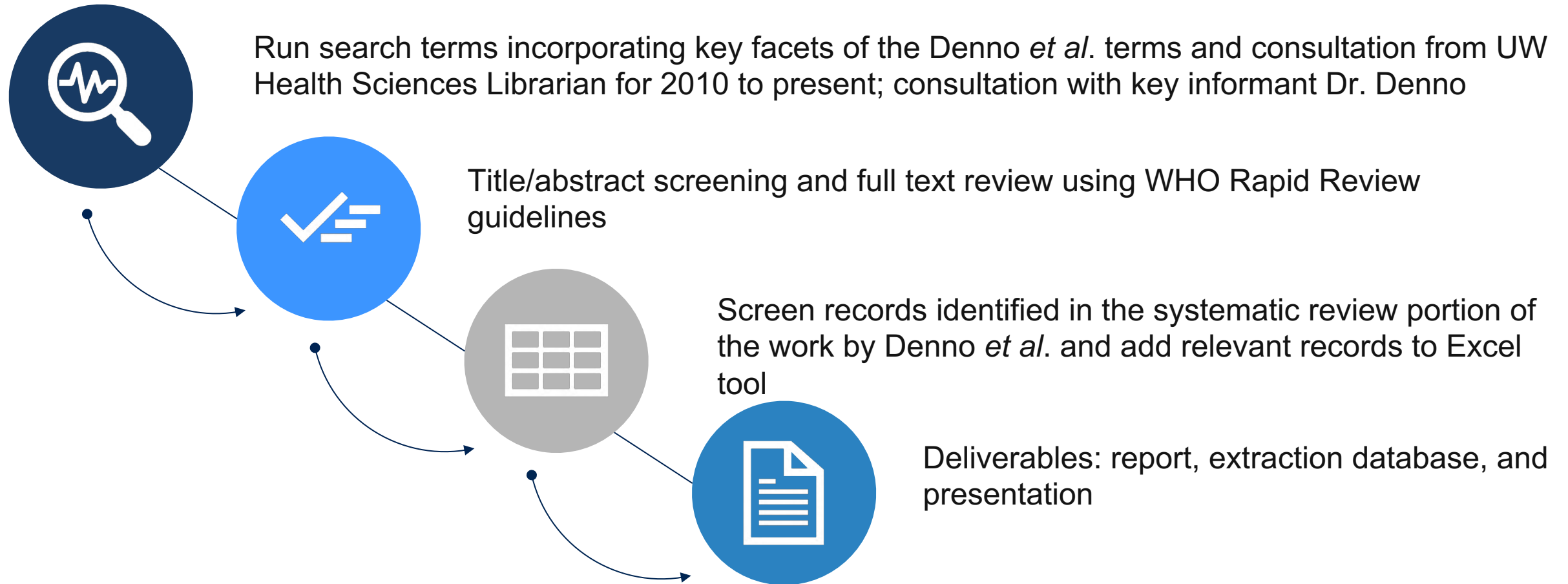
2010 – Present Updates

- Incorporate key additions from the Denno *et al.* terms to run searches for 2010 to present
- Using [WHO Rapid Review guidelines](#), single review for title/abstract screening, single review for full text screening, and single extraction
- Report including methods and results
- Excel-based tool with record details

Review of Denno *et al.* Records

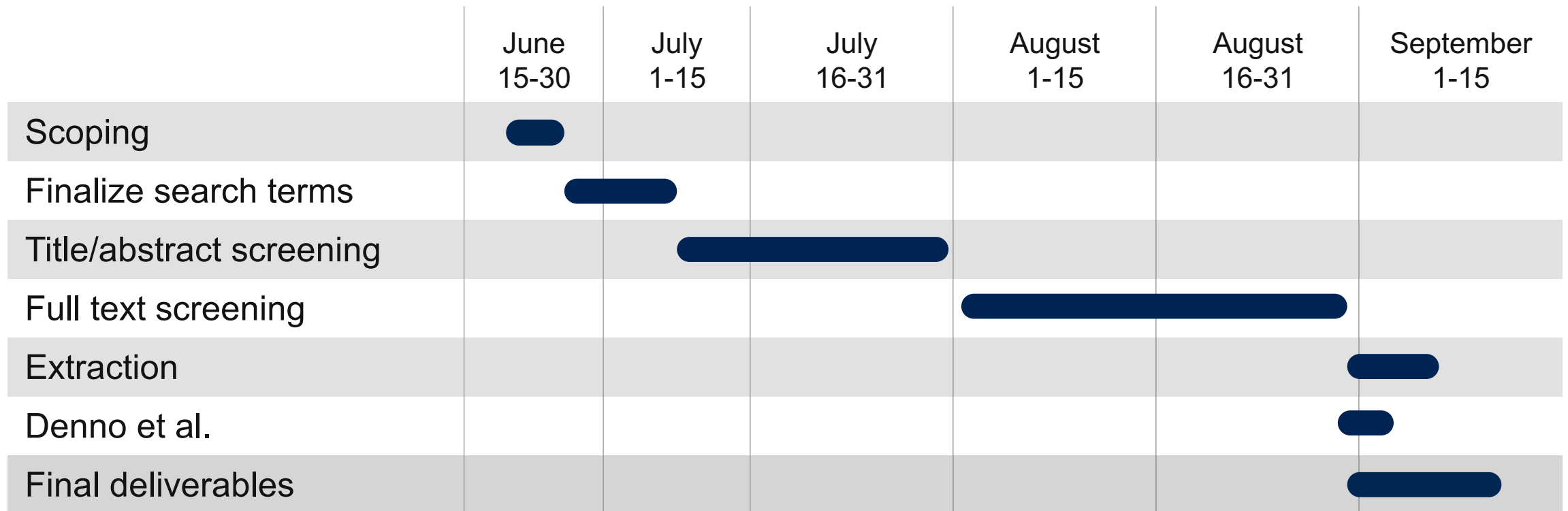
- Review records (n=77) identified in the systematic review by Denno *et al.* using [WHO Rapid Review guidelines](#), with single review for title/abstract screening, single review for full text screening, and single extraction
- Incorporate records identified to be relevant into the Excel-based tool
- Records from 2000 to 2010

WORKFLOW



TIMELINE

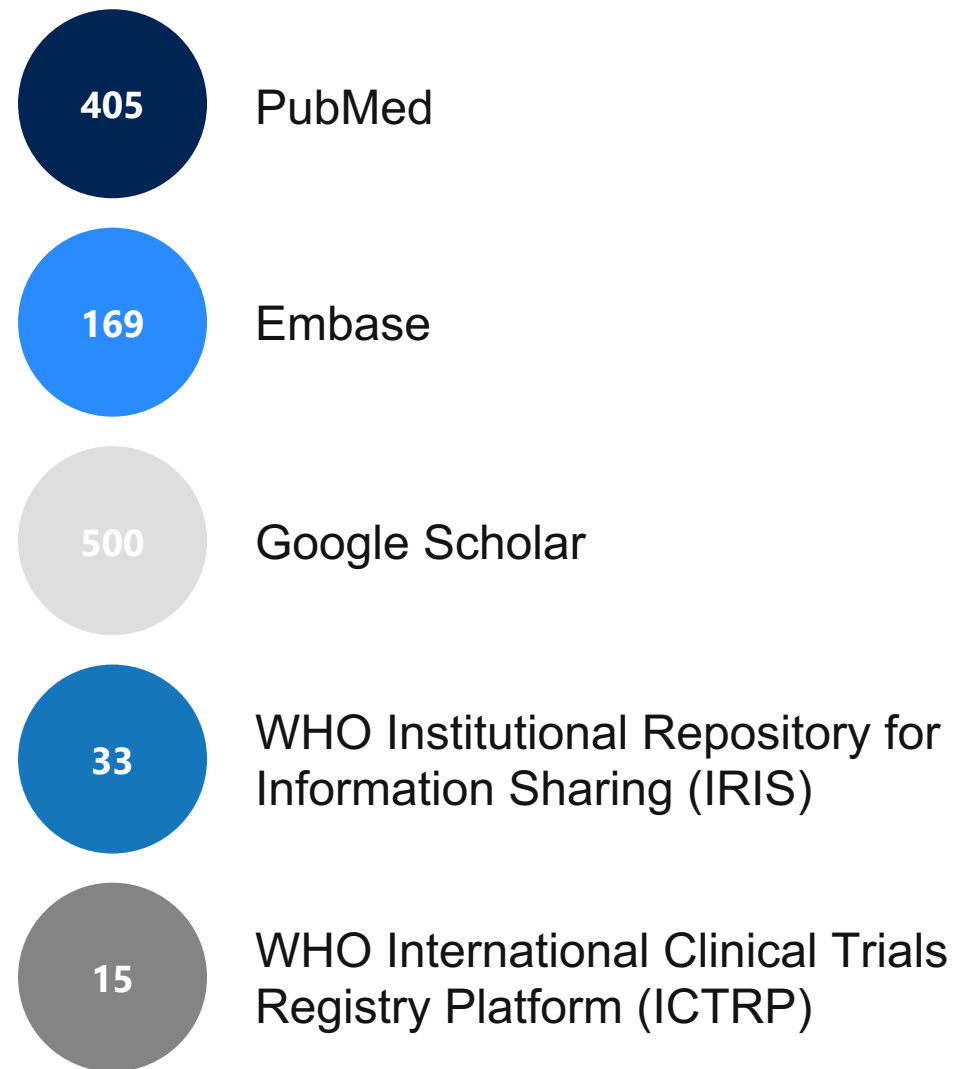
JUNE 21, 2021 – SEPTEMBER 10, 2021



INITIAL SEARCH RESULTS

Search Strategy

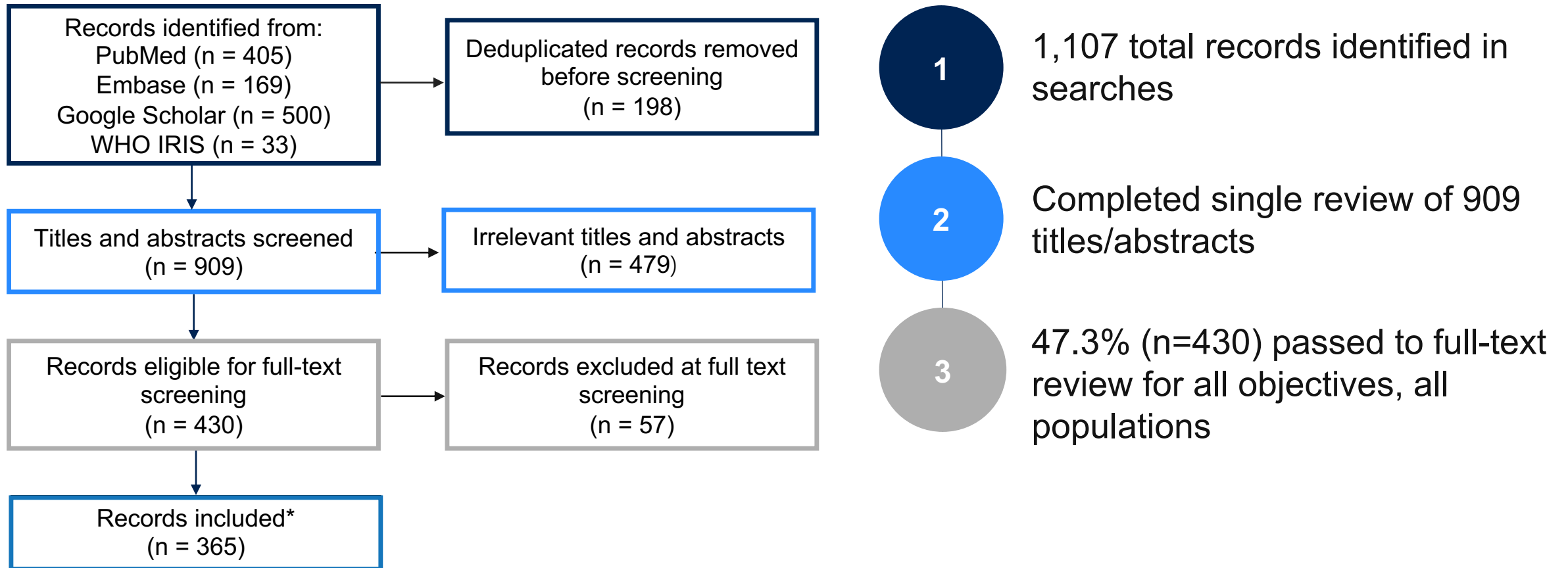
- Environmental enteric dysfunction
- Women, neonates, and children
- Sub-Saharan Africa (World Bank) and Southeast Asia (WHO Southeast Asia region)
- 2010 - present



SCREENING RESULTS

2010 – PRESENT RECORDS

PRISMA FLOW DIAGRAM

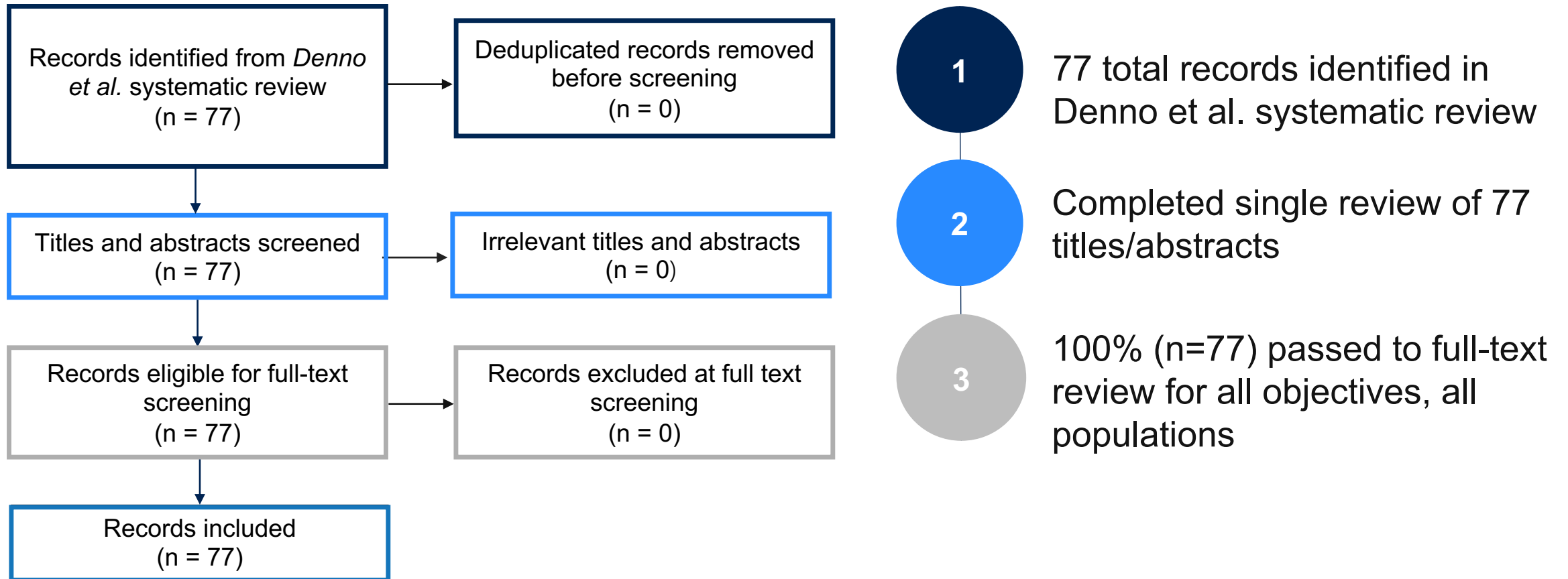


* Note: some records merged in extraction stage (e.g. conference abstract and corresponding article).

SCREENING RESULTS

BUILDING ON DENNO ET AL. REVIEW (2000 to 2010)

PRISMA FLOW DIAGRAM



SCREENING RESULTS

INCLUDED FOR OBJECTIVES 1, 2, & 3

909 records from
PubMed, Embase,
Google Scholar, &
WHO IRIS

77 records from
Denno et al.

441 reports eligible for extraction

~20 reports including **adult women**
for objectives 2 & 3

~180 reports including **children** for
objectives 2 & 3

UPDATED STRATEGY

GIVEN NUMBER OF RESULTS AND TIMELINE

- Focus only on studies with **maternal populations**
 - Pregnant women
 - Lactating women
 - Women of reproductive age (15 to 49 years)
- Qualitative, non-systematic summary of definitions (Objective 1)
- Focus extraction only on objectives 2 and 3

OBJECTIVES 2 & 3 INCLUSION CRITERIA

DESCRIPTIVES OF BIOMARKERS OF EED & ASSOCIATIONS

Record Characteristic	Criteria
Record Type	Primary research that presents the analysis of primary data (i.e. exclude meta-analyses, commentaries, etc.)
Population	Women of reproductive age, pregnant women, and lactating women
Geography	Sub-Saharan Africa and Southeast Asia
Exposures	EED Biomarkers
Outcomes	Objective 2: Distributions of biomarkers (including normal ranges and abnormal values) Objective 3: Any clinical outcome

EXTRACTION

COMPLETED WITH EXCEL BASED TOOL

Publication Details		Title	Abstract	Publication URL	Study design	Study Aim	Primary Study	Primary Study Publication URL (hyperlinked)	Language
Author first and Last name	Year of Publication								

Study Details								
Country	Setting	Population	Age for Enrollment	Number Enrolled	Population II	Population III	Main Inclusion Criteria	Comorbidities

Nutritional Status	EED at enrollment	Interventions	Outcome	Methods	Time points of data collection	Other comments	Key limitations

Non-biomarker					
Non-biomarker tests relevant to EED	Biomarker 1	Category	Cutoffs used for Biomarker 1	Findings for Biomarker 1	Effect size

EXTRACTION

BIOMARKER DOMAINS

EED Biomarker Domain Markers	EED Biomarkers Delineated by Harper et al.
Intestinal damage and repair	Citrulline, Intestinal fatty acid binding protein (I-FABP), Regenerating (REG) family proteins [fecal REG], Glucagon-like peptide 2 (GLP-2)
Permeability and absorption	Dual-sugar absorption test: lactulose-mannitol (LM) or lactulose-rhamnose (LR) ratio, D-xylose, Alpha-1-antitrypsin (AAT), Claudin: claudin-2, -15, -4, Zonulin
Microbial translocation	Lipopolysaccharide (LPS), Flagellin, Elevated plasma endotoxin core antibody (EndoCAb) titers, Anti-LPS immunoglobulin G (IgG) and A (IgA)
Intestinal inflammation	Translocated LPS neutrophils, macrophages, and dendritic cells, Myeloperoxidase (MPO), Neopterin (NEO), EED Composite score: comprised of three fecal biomarkers - AAT, MPO, and NEO, Calprotectin (calcium- and zinc-binding protein)
Systemic inflammation	Interferon gamma (IFN-gamma), Tumor necrosis factor (TNF), Interleukins (e.g., IL-6, IL-10), Alpha-1-acid glycoprotein, C-reactive protein, Ferritin, Soluble CD14 (sCD14), Total IgG and IgM, Kynurenine-tryptophan ratio (KTR)
Morphometry	Villous height, Crypt depth, Other morphological characteristics

* Note: Morphometry domain not included in Harper et al. but added in accordance with extraction findings and additional literature in Donna et al.

RESULTS: KEY EED DEFINITIONS

KEY EED DEFINITIONS

OBJECTIVE 1: GENERAL AND CHILDREN

- Broadly, “*an acquired subclinical disorder of the small intestine, characterized by villous atrophy and crypt hyperplasia*”¹
- Proposed definition for children includes three domains and conceptualizes EED as a sliding scale²
 - *Domain 1*: age 2-36 months, linear growth faltering, and negative screening for celiac disease
 - *Domain 2*: confirmation via histopathology or two or more biomarkers
 - *Domain 3*: other criteria which may support EED diagnosis such as markers for systemic inflammatory and metabolic effects

¹ Harper et al. 2018 doi: 10.1371/journal.pntd.0006205

² Denno et al. 2017 doi: 10.4269/ajtmh.17-0183

KEY EED DEFINITIONS

OBJECTIVE 1: ADULTS AND MATERNAL POPULATIONS

- Among adults, it presents as low BMI due to malabsorption induced malnutrition, as opposed to stunting as seen in children¹
- A study of EED biomarkers among pregnant women and their infants describes EED, citing 2 other sources, as: "*a subclinical inflammatory disorder of the small intestine characterized by altered gut morphology, reduced absorptive capacity, and impaired barrier function*"²
- A 2019 study of maternal EED biomarkers also includes a discussion of EED that focuses more on subclinical inflammation and permeability of the intestine and systemic inflammation³

¹ Hossain et al. 2021 doi: 10.1038/s41598-021-82079-6

² Lauer et al. 2018 doi: 10.1093/ajcn/nqy176

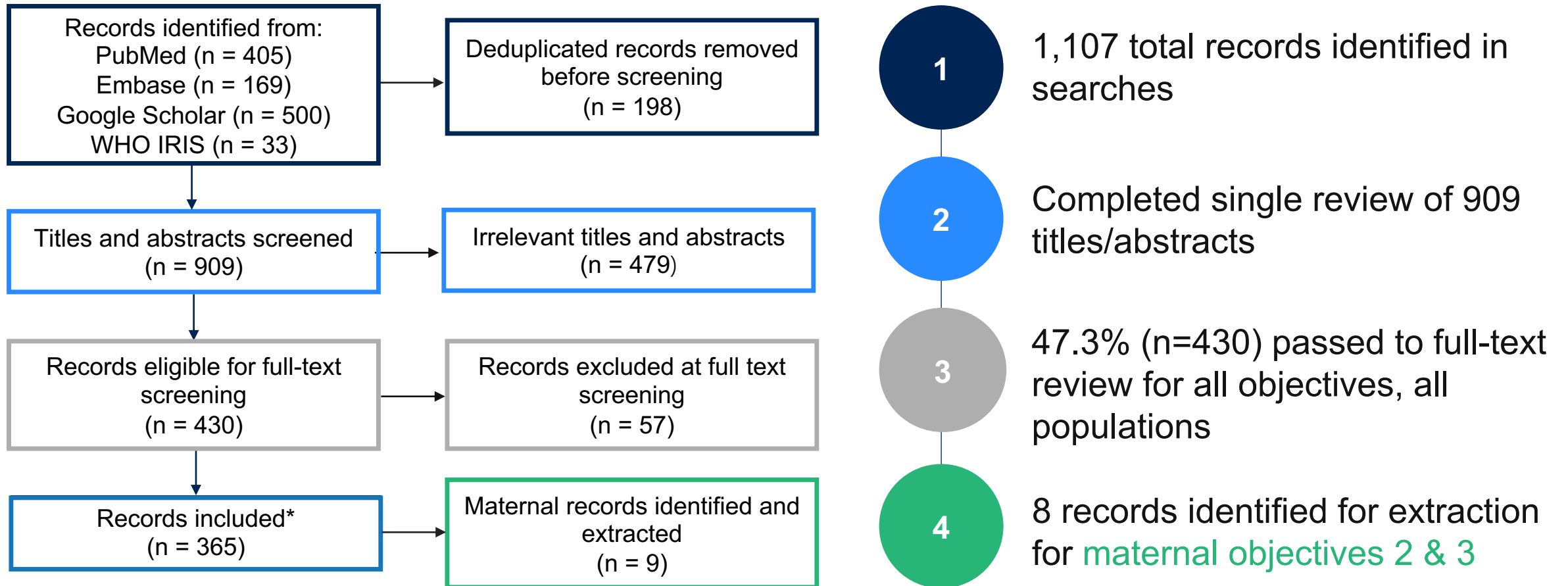
³ Lauer et al. 2020 doi: 10.1093/jn/nxaa141

RESULTS: SCREENING

SCREENING RESULTS

2010 – PRESENT RECORDS

PRISMA FLOW DIAGRAM



* Note: some records merged in extraction stage (e.g. conference abstract and corresponding article).

EXCLUSION REASONS

2010 – PRESENT RECORDS

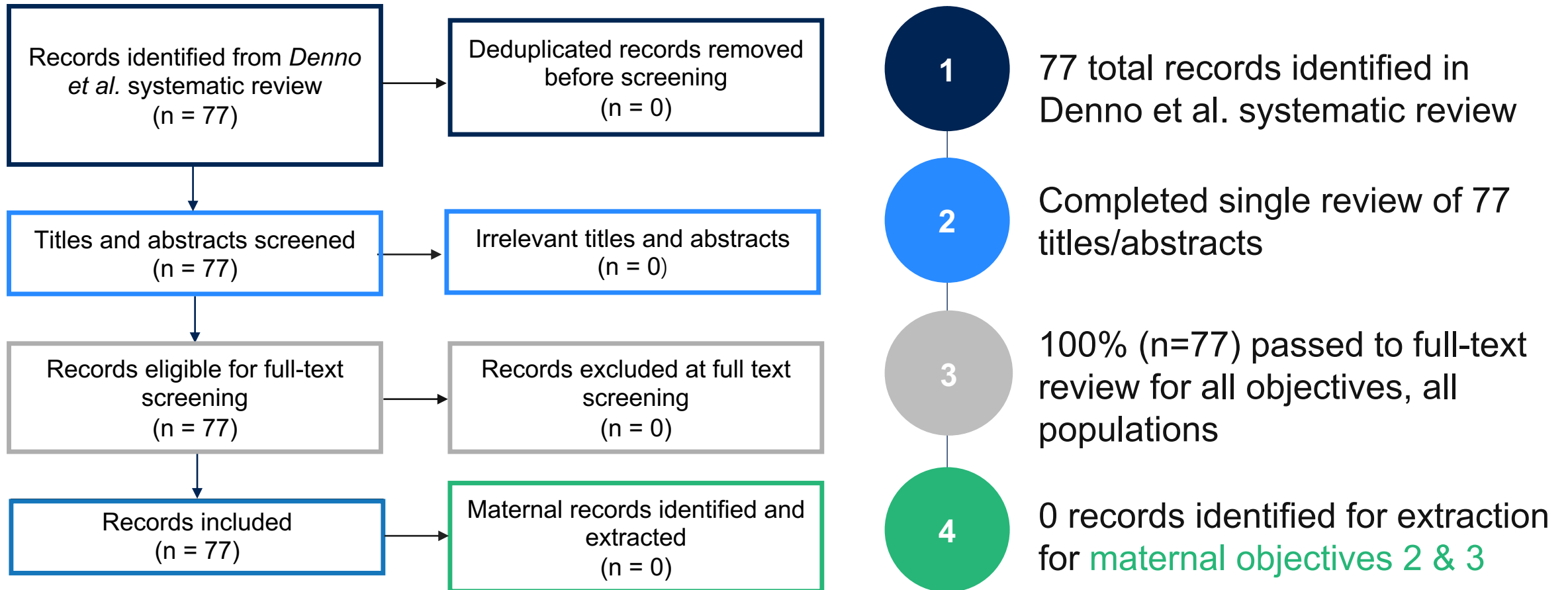
Exclusion Criteria	Number of Records Excluded
Published before 2010	3
EED not defined or delineated	44
No MNCH populations included	8
Not primary data	0
Not Sub-Saharan Africa or Southeast Asia	0
No results stratified to Sub-Saharan Africa or Southeast Asia	0
No results stratified to MNCH populations	2

* Note: reasons 3 to 7 refer only to Objectives 2 & 3

SCREENING RESULTS

BUILDING ON DENNO ET AL. REVIEW (2000 to 2010)

PRISMA FLOW DIAGRAM



RESULTS: EXTRACTION OF INCLUDED REPORTS

INCLUDED REPORTS:

KEY CHARACTERISTICS

Author and Year	Study Design	Country of Data Collection	Age Range (Years)	Sample Size
Amadi 2017	Cross-sectional study	Zambia	Not specified	61 (43 women)
Hossain 2021	Case-control study	Bangladesh	18 - 45	64 (39 women)
Karim 2015	Cross-sectional study	Bangladesh	18 - 60	116 (32 women)
Kashyap 2021	Interventional trial	India	20 - 35	7
Kelly 2016	Cross-sectional study	Zambia	18 - 55	49
Lauer 2018	Prospective cohort	Uganda	18 - 45	220
Patnayak 2016	Case study	India	15	1
Ramya 2020	Cross-sectional study	India	Above age 18	485 (181 women)
Shetty 2016	Case series	India	16 - 80	50 (18 women)

INCLUDED REPORTS

KEY CHARACTERISTICS

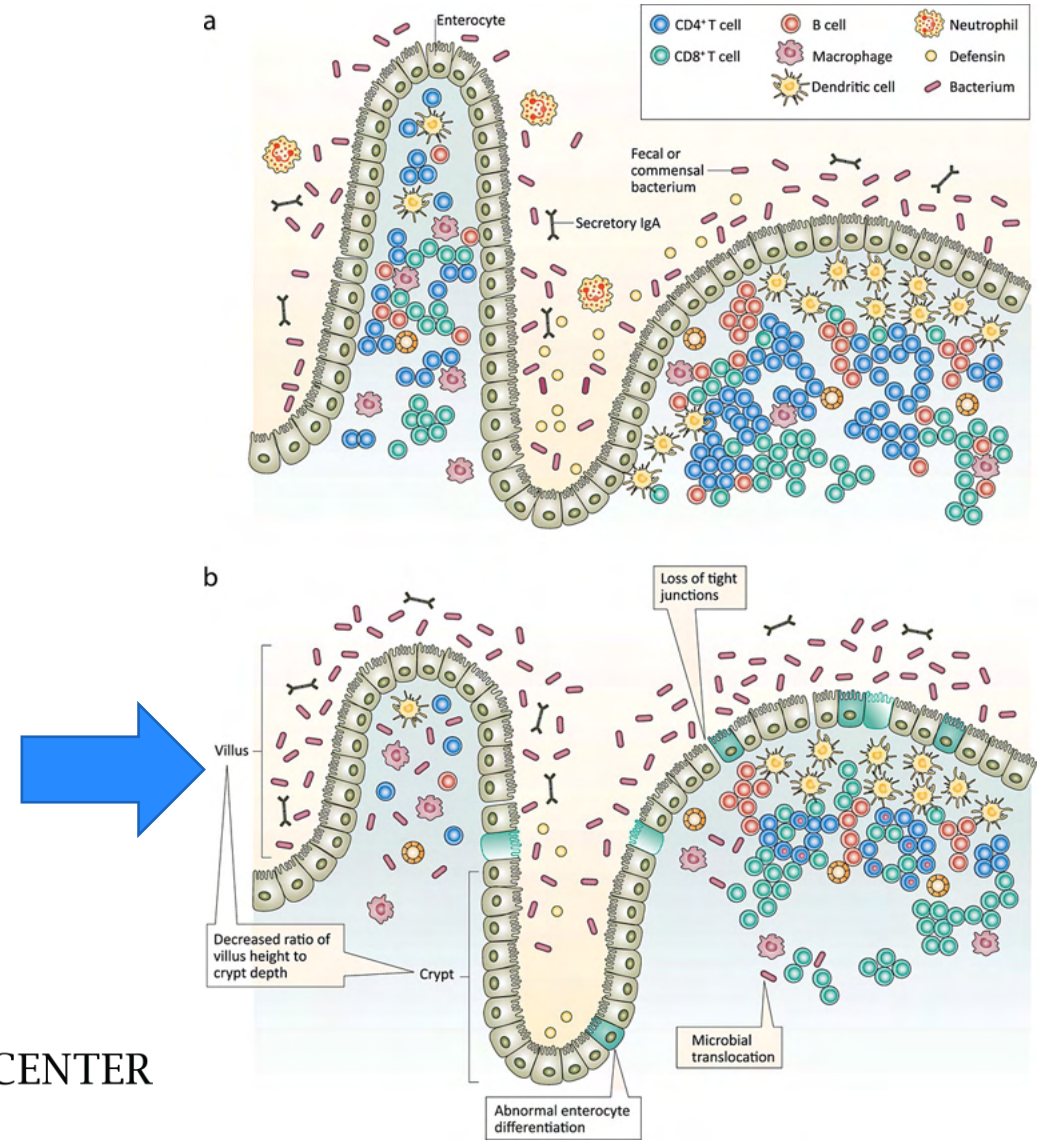
- **Participants:**
 - Women of reproductive age (n=8)
 - Pregnant women (n=1)
- **Setting:**
 - Community (n=5)
 - Clinical (n=3)
 - Recruited from staff at research institute (n=1)
- **Intervention:**
 - Goat milk protein (n=1)
 - Nutritional intervention (n=1)
 - Vitamins K,D,E,B12 and tetracycline (n=1)
 - No intervention (n=6)



INCLUDED REPORTS

OBJECTIVE 2: EED BIOMARKER DISTRIBUTIONS

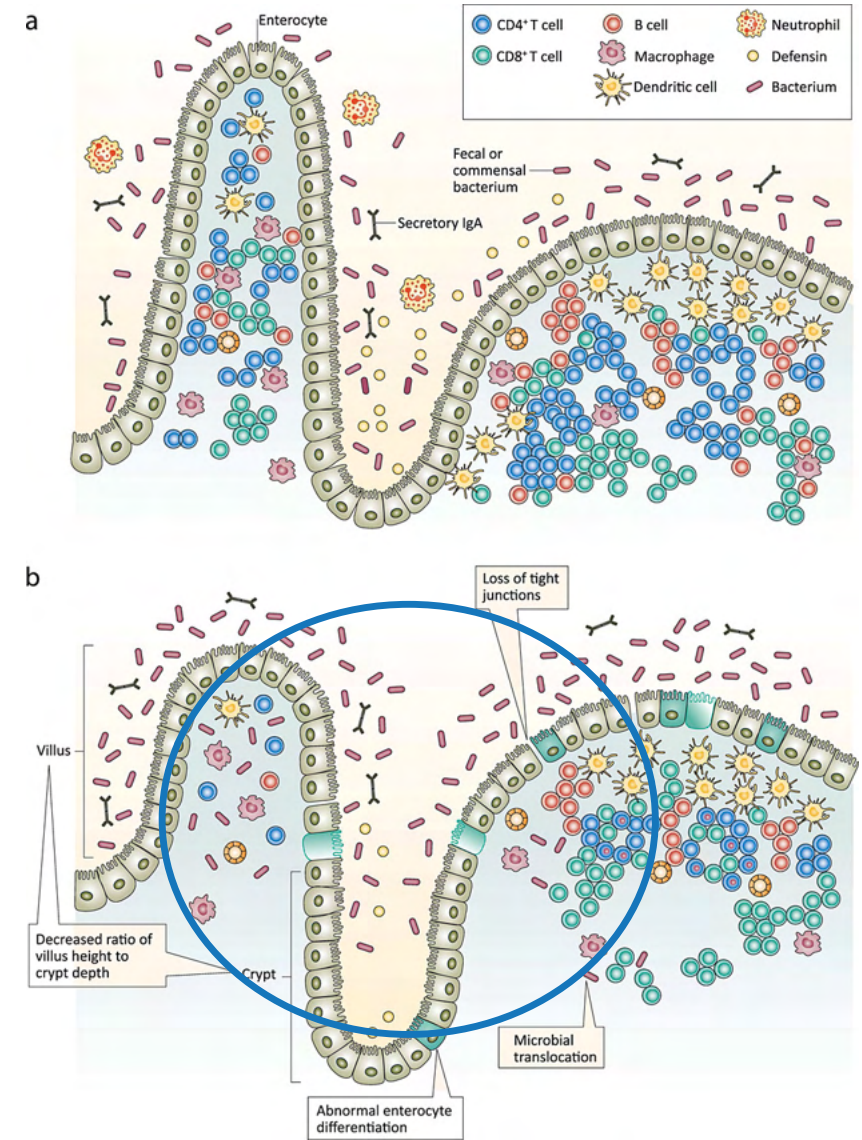
- Morphometry (n = 6)
 - Villous blunting and crypt lengthening
 - Lamina propria inflammation
 - Villous height: crypt depth ratios below normal values
 - Evidence of cellular infiltrates
 - Among healthy adults, normal villous to crypt ratio or only mild reduction in villous height



INCLUDED STUDIES

OBJECTIVE 2: EED BIOMARKER DISTRIBUTIONS

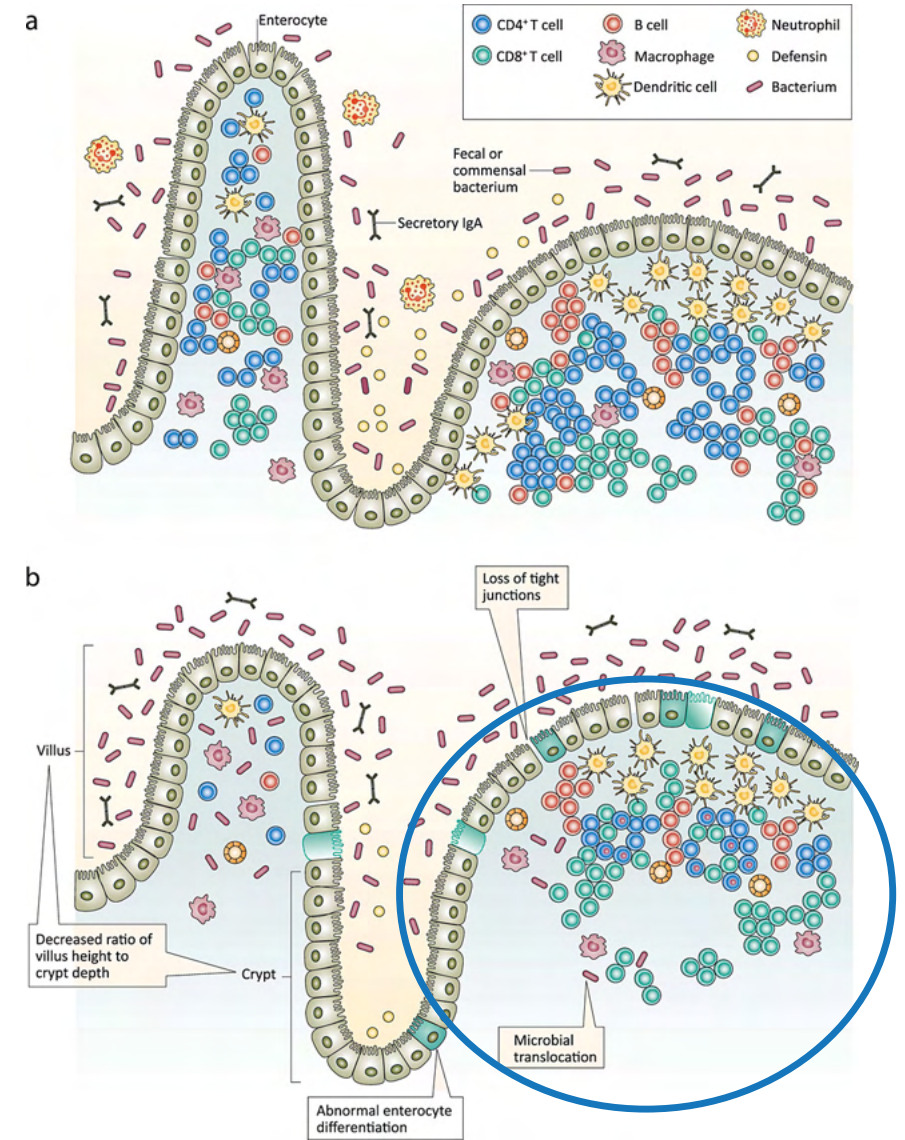
- Permeability and absorption (n = 4)
 - Abnormal values of D-xylose excretion
 - Reduced claudin-4 expression
 - Presentation of measures of phenylalanine, allo-isoleucine, and urinary concentration and percent recovery of lactulose and mannitol (and corresponding L:M ratios)
 - Not compared to reference values



INCLUDED STUDIES

OBJECTIVE 2: EED BIOMARKER DISTRIBUTIONS

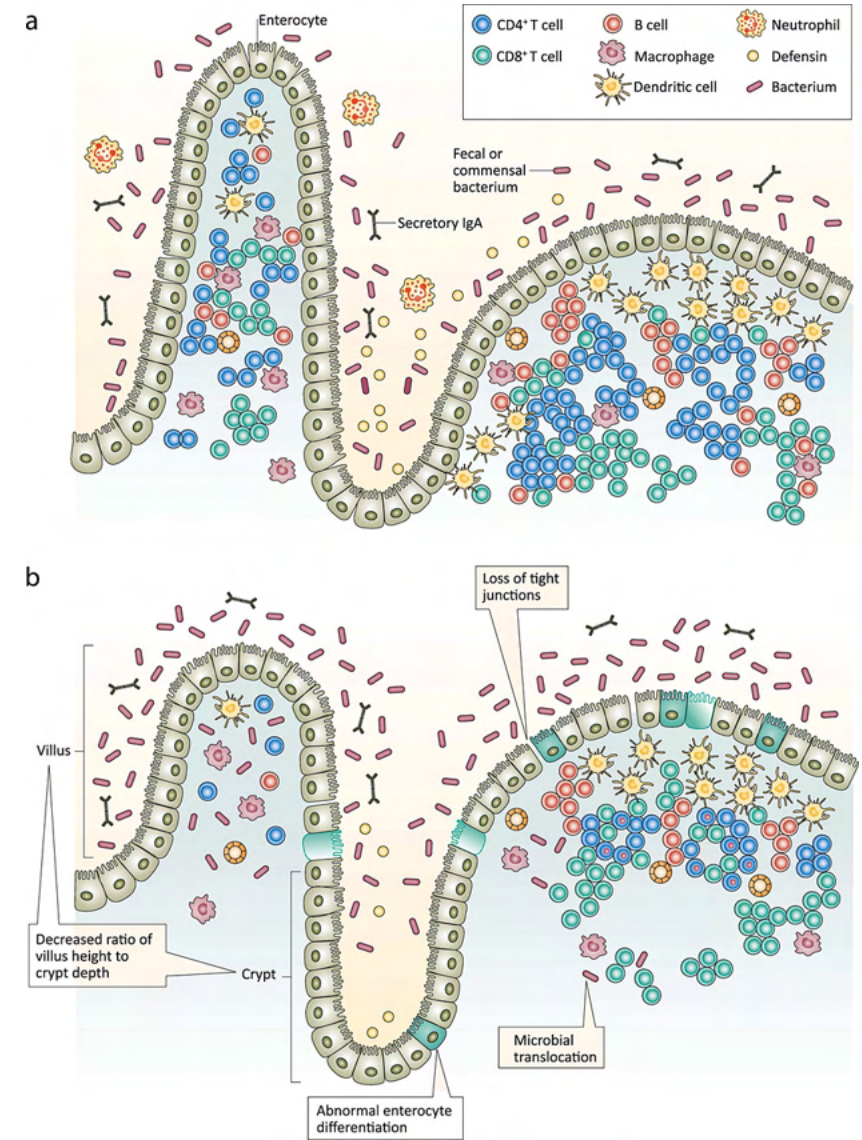
- Microbial translocation (n = 2)
 - Detectable levels of plasma lipopolysaccharide (LPS)
 - Mean values of anti-LPS IgA and IgG
 - Not compared to reference values
 - Mean values of anti-flagellin IgA and anti-flagellin IgG
 - Not compared to reference values



INCLUDED STUDIES

OBJECTIVE 2: EED BIOMARKER DISTRIBUTIONS

- Intestinal damage and repair (n = 1)
 - Serum GLP-2 lower than pediatric reference range



INCLUDED STUDIES

OBJECTIVE 3: EED BIOMARKERS AND CLINICAL OUTCOMES

- 1 reported identified
- Identified associations after statistical adjustment between higher levels of anti-flagellin IgG and anti-LPS IgG and:
 - Shorter length of gestation
 - Anti-flagellin IgG: β : -0.89, 95% CI: (-1.77, -0.01), $p = 0.047$
 - Anti-LPS IgG: β : -1.01, 95% CI: (-1.87, -0.17), $p = 0.019$
 - Reduced length at birth
 - Anti-flagellin IgG: β : -0.80, 95% CI: (-1.55, -0.05), $p = 0.036$
 - Anti-LPS IgG: β : -0.79, 95% CI: (-1.54, -0.04), $p = 0.039$
 - LAZ at birth
 - Anti-flagellin IgG: β : -0.44, 95% CI: (-0.83, -0.05), $p = 0.029$
 - Anti-LPS IgG: β : -0.40, 95% CI: (-0.79, -0.01), $p = 0.043$

INCLUDED STUDIES

BIOMARKERS NOT IDENTIFIED

- 2 biomarker domains not identified in reports for extraction:
 - Markers of intestinal inflammation
 - Markers of systemic inflammation
- Notably, many markers of intestinal inflammation commonly used for identification of EED in children were not identified:
 - Myeloperoxidase (MPO)
 - Neopterin (NEO)
 - C-reactive protein
- Some additional biomarkers identified in studies of adults, but not stratified to population of interest (women ages 15 to 49 years)
 - Potential for limited generalizability of unstratified results to women of reproductive age

ICTRP RESULTS

CLINICAL TRIALS

- One registered and recently published trial titled “Stunting and Bangladesh Environmental Enteric Dysfunction (BEED) Study”
- Includes adults 18-45 years
- Completion date marked in ICTRP as December 2021

INCLUDED STUDIES

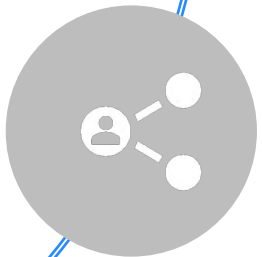
KEY LIMITATIONS



Lack of longitudinal data and small sample sizes



Limited comparison of identified EED biomarkers to reference values



Limited stratification of adult studies to report findings specifically among women of reproductive age

EXTRACTION DATABASE

Author first and Last name	Year of Publication	Publication Details							
		Title	Abstract	Publication URL	Study design	Study Aim	Primary Study	Primary Study Publication URL (hyperlinked)	Language
Paul Kelly	2016	Endomicroscopic and Transcriptomic	Introduction Environmental	https://journals.plos.org/plosntds/article?id=1	Cross-sectional study	To define cellular mechanisms of	Not applicable	Not applicable	English
Rashmi Patnayak	2016	The maladies of malabsorption	Malabsorption syndrome (MAS) is a	https://www.ncbi.nlm.nih.gov/pmc/articles/P	Case report	To describe a case of malabsorption	Not applicable	Not applicable	English
Shiran Shetty	2016	A Profile of Tropical Sprue	Tropical Sprue is an enigmatic	http://ejournal-tomgmu.ac.id/index.n	Cross-sectional study	To describe the clinical profile of Tropical	Not applicable	Not applicable	English

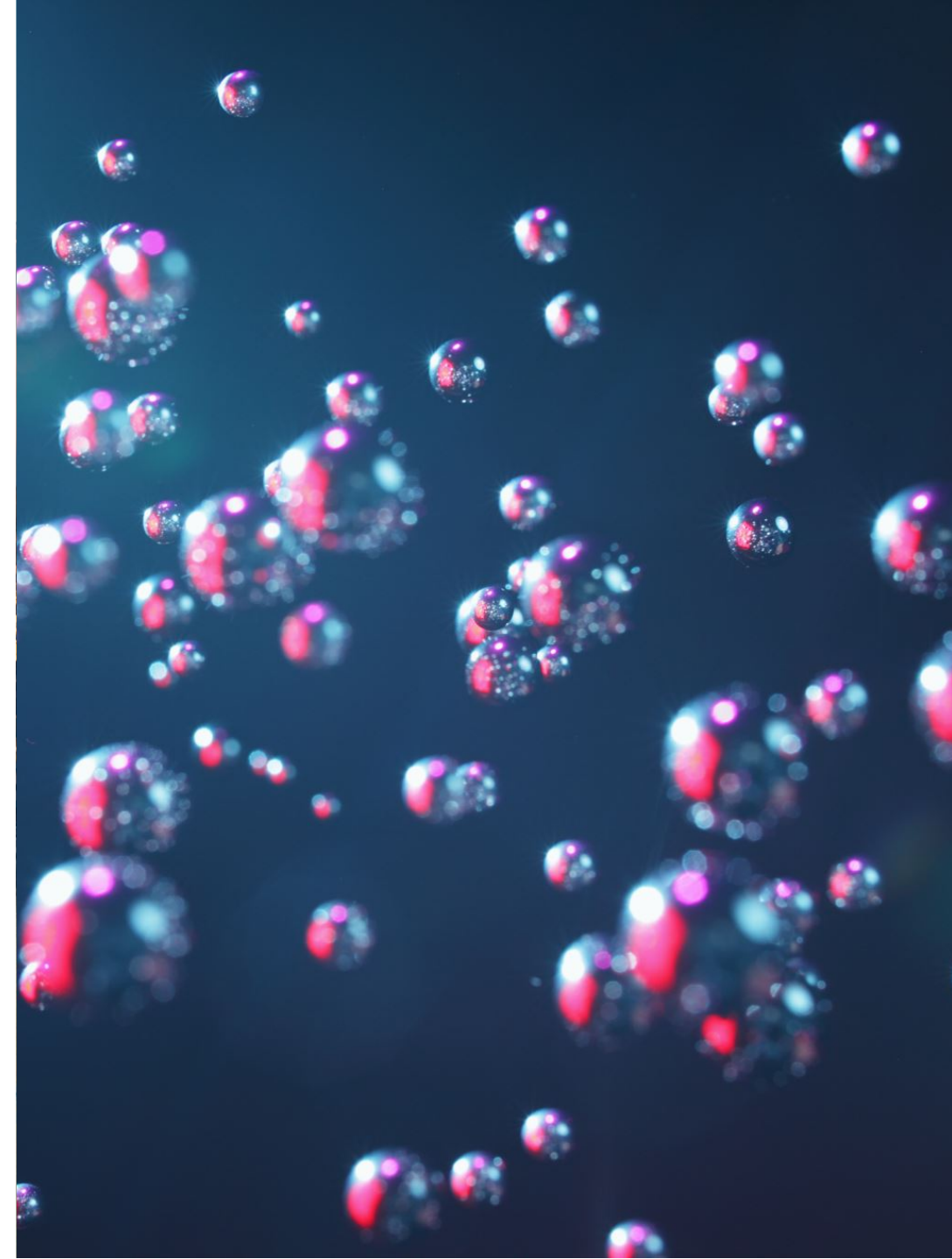
Country	Setting	Population	Age for Enrollment	Number Enrolled	Population II	Population III	Main Inclusion Criteria	Study Details									Other comments	Key limitations
								Comorbidities	Nutritional Status	EED at enrollment	Interventions	Outcome	Methods	Time points of data collection				
Zambia	Community	Women of reproductive age	18 to 55 years	49	Study enrolled adults, hence males were	Not applicable	Male or female adults recruited from the	14 participants were HIV seropositive, with	BMI ranged from 16.9 to 52.0	Yes	Not applicable	Not applicable	Recruited participants from the	At time of enrollment in study (cross-	The median CD4 count in 14 HIV	No longitudinal data (cross sectional);		
India	Clinical	Women of reproductive age	15 years	1	Not applicable	Not applicable	Not applicable	She was previously diagnosed with	Weight for age below the 3rd percentile	Yes	She was treated with megadose oral Vitamin E (400 IU)	Neurological symptoms	Case study of 15 year-old girl that details	Followed up to 6 years after	She became asymptomatic	Case study		
India	Clinical	Women of reproductive age	16 to 80 years	50 (18 women)	Study enrolled adults, hence males were	Not applicable	Patients with admission and	None described	Not specified	Yes	Not applicable	Not applicable	Hospital chart review for 50 individuals	Admission and discharge files were	None	Biomarkers not stratified by sex		
Zambia	Community	Women of reproductive age	For adults, target age not specified	61(43 women)	Children hospitalised with severe acute	Children in the community identified	Residing in the community and not	22/61 adults were HIV seropositive. Out of	Not specified; IQRs for BMI were 20.8-	Yes	Not applicable	Not applicable	Adults from the community were	At time of enrollment in study (cross-	Morphometry was also done: biopsies	No longitudinal data; limited to no		
Uganda	Community	Pregnant women	18-45 years	220	Not applicable	Not applicable	Pregnant women were recruited during	None described	Not used as an inclusion criteria	Yes	Not applicable	Infant parameters (Gestational age,	An ultrasound scan was performed by a	18 weeks gestational age	None	This study had a small sample size as it was		
India	Clinical	Women of reproductive age	Above age 18	485 (181 women)	Study enrolled adults, hence males were	Not applicable	Well oriented duodenal biopsy from	Tropical sprue; participants	Not specified	Yes	Not applicable	Not applicable	Duodenal biopsies were selected from	At time of enrollment in study (cross-	None	No longitudinal data		
India	Recruited from staff at research institute	Women of reproductive age	20 to 35 years	7	Not applicable	Not applicable	Non-pregnant, non-lactating women with	None	Not-specified; normal BMI	Unclear	Animal Source Food (Goat milk)	Ileal Indispensable Amino Acid (IAA)	2H-labeled milk protein was	3 days, through 5 hours for dual sugar	All experiments were conducted during the	Does not provide reference ranges for		

Non-Biomarker and Biomarker Tests					
Non-Biomarker Tests Relevant to EED	Biomarker 1	Category	Cutoffs used for Biomarker 1	Findings for Biomarker 1	Effect Size
None	Tissue_Morphology	Morphometry	Non-specific duodenitis was defined as	Among malnourished adults, 0% had a normal	Not specified

WRAP UP

WRAP UP

- START Team to share final report and extraction database including women of reproductive age, pregnant women, and lactating women
- Potential next phases for the project:
 - Extracting data for studies of children
 - Expanding geographic scope
 - Consideration of findings of unstratified studies of adults or follow up with authors
 - Further exploration of EED definitions
 - Consider scalability of biomarkers
 - Examine differences between biomarkers in children and adult women
 - Additional context of inflammatory mechanisms



QUESTIONS AND DISCUSSION

THANK YOU



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STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

APPENDIX: SEARCH TERMS



2010 - PRESENT

Embase®

PubMed (n = 404)

("environmental enteric dysfunction"[Tiab] OR "EED"[Tiab] OR "tropical sprue"[Tiab] OR "sprue, tropical"[MeSH Terms] OR "idiopathic tropical malabsorption syndrome"[Tiab] OR "idiopathic tropical malabsorption syndromes"[Tiab] OR ("environment"[MeSH Terms] OR "environment*" [Tiab] OR "tropic*" [Tiab]) AND ("enteropath*" [Tiab] OR "enteric" [Tiab]))

AND

("women"[MeSH Terms] OR "women*" [TIAB] OR "woman*" [TIAB] OR "mother" [TIAB] OR "maternal" [TIAB] OR "pregnant" [TIAB] OR "infant" [MeSH Terms] OR "infant*" [TIAB] OR "newborn" [TIAB] OR "child" [MeSH Terms] OR "child*" [TIAB] OR "kid" [TIAB] OR "kids" [TIAB] OR "baby" [TIAB] OR "babies" [TIAB])

AND

Sub-Saharan Africa and Southeast Asia terms

Embase (n = 169)

('environmental enteric dysfunction':ti,ab OR 'eed':ti,ab OR 'tropical sprue':ti,ab OR 'idiopathic tropical malabsorption syndrome':ti,ab OR 'idiopathic tropical malabsorption syndromes':ti,ab OR (('enteric*':ti,ab OR 'enteropath*':ti,ab) AND ('environ*':ti,ab OR 'tropic*':ti,ab)))

AND

('female'/exp OR 'female':ti,ab OR 'infant'/exp OR 'infant':ti,ab OR 'newborn'/exp OR 'newborn':ti,ab OR 'child'/exp OR 'child*':ti,ab)

AND

Sub-Saharan Africa and Southeast Asia terms

APPENDIX: SEARCH TERMS

PUBMED SUB-SAHARAN AFRICA AND SOUTHEAST ASIA SEARCH TERMS

((((Deprived Countries[tw] OR Deprived Population[tw] OR Deprived Populations[tw] OR Developing Countries[tw] OR Developing Country[tw] OR Developing Economies[tw] OR Developing Economy[tw] OR Developing Nation[tw] OR Developing Nations[tw] OR Developing Population[tw] OR Developing Populations[tw] OR Developing World[tw] OR LAMI Countries[tw] OR LAMI Country[tw] OR Less Developed Countries[tw] OR Less Developed Country[tw] OR Less Developed Economies [tw] OR Less Developed Nation[tw] OR Less Developed Nations[tw] OR Less Developed World[tw] OR Lesser Developed Countries[tw] OR Lesser Developed Nations[tw] OR LMIC[tw] OR LMICS[tw] OR Low GDP[tw] OR Low GNP[tw] OR Low Gross Domestic[tw] OR Low Gross National[tw] OR Low Income Countries[tw] OR Low Income Country[tw] OR Low Income Economies [tw] OR Low Income Economy[tw] OR Low Income Nations[tw] OR Low Income Population[tw] OR Low Income Populations[tw] OR Lower GDP[tw] OR lower gross domestic[tw] OR Lower Income Countries[tw] OR Lower Income Country[tw] OR Lower Income Nations[tw] OR Lower Income Population[tw] OR Lower Income Populations[tw] OR Middle Income Countries[tw] OR Middle Income Country[tw] OR Middle Income Economies [tw] OR Middle Income Nation[tw] OR Middle Income Nations[tw] OR Middle Income Population[tw] OR Middle Income Populations[tw] OR Poor Countries[tw] OR Poor Country[tw] OR Poor Economies [tw] OR Poor Economy[tw] OR Poor Nation[tw] OR Poor Nations[tw] OR Poor Population[tw] OR Poor Populations[tw] OR poor world[tw] OR Poorer Countries[tw] OR Poorer Economies [tw] OR Poorer Economy[tw] OR Poorer Nations[tw] OR Poorer Population[tw] OR Poorer Populations[tw] OR Third World[tw] OR Transitional Countries[tw] OR Transitional Country[tw] OR Transitional Economies[tw] OR Transitional Economy[tw] OR Under Developed Countries[tw] OR Under Developed Country[tw] OR under developed nations[tw] OR Under Developed World[tw] OR Under Served Population[tw] OR Under Served Populations[tw] OR Underdeveloped Countries[tw] OR Underdeveloped Country[tw] OR underdeveloped economies[tw] OR underdeveloped nations[tw] OR underdeveloped population[tw] OR Underdeveloped World[tw] OR Underserved Countries[tw] OR Underserved Nations[tw] OR Underserved Population[tw] OR Underserved Populations[tw]) OR (Angola[tw] OR Bangladesh[tw] OR Benin[tw] OR Bhutan[tw] OR Botswana[tw] OR "Burkina Faso"[tw] OR Burma[tw] OR Burundi[tw] OR "Cabo Verde"[tw] OR "Cape verde"[tw] OR Cameroon[tw] OR "Central African Republic"[tw] OR Chad[tw] OR Comoros[tw] OR Comores[tw] OR Comoro[tw] OR Congo[tw] OR "Côte d'Ivoire"[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR "Guinea Bissau"[tw] OR "Guinea-Bissau"[tw] OR India[tw] OR Indonesia[tw] OR Kenya[tw] OR Korea[tw] OR Lesotho[tw] OR Liberia[tw] OR Madagascar[tw] OR Malawi[tw] OR Maldives[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mozambique[tw] OR Myanmar[tw] OR Namibia[tw] OR Nepal[tw] OR Niger[tw] OR Nigeria [tw] OR Principe[tw] OR Rwanda[tw] OR Ruanda[tw] OR "Sao Tome"[tw] OR Senegal[tw] OR Seychelles[tw] OR "Sierra Leone"[tw] OR Somalia[tw] OR "South Africa"[tw] OR "South Sudan"[tw] OR "Sri Lanka"[tw] OR Sudan[tw] OR Swaziland[tw] OR "Eswatini"[tw] OR Tanzania[tw] OR Thailand[tw] OR Timor[tw] OR "Timor-Leste"[tw] OR Togo[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw]))))

APPENDIX: SEARCH TERMS

EMBASE SUB-SAHARAN AFRICA AND SOUTHEAST ASIA SEARCH TERMS

('deprived countries':de,ti,ab OR 'deprived country':de,ti,ab OR 'deprived nation':de,ti,ab OR 'deprived nations':de,ti,ab OR 'deprived population':de,ti,ab OR 'deprived populations':de,ti,ab OR 'deprived world':de,ti,ab OR 'developing countries':de,ti,ab OR 'developing country':de,ti,ab OR 'developing economies':de,ti,ab OR 'developing economy':de,ti,ab OR 'developing nation':de,ti,ab OR 'developing nations':de,ti,ab OR 'developing population':de,ti,ab OR 'developing populations':de,ti,ab OR 'developing world':de,ti,ab OR 'lami countries':de,ti,ab OR 'lami country':de,ti,ab OR 'less developed countries':de,ti,ab OR 'less developed country':de,ti,ab OR 'less developed economies':de,ti,ab OR 'less developed economy':de,ti,ab OR 'less developed nation':de,ti,ab OR 'less developed nations':de,ti,ab OR 'less developed population':de,ti,ab OR 'less developed populations':de,ti,ab OR 'less developed world':de,ti,ab OR 'lesser developed countries':de,ti,ab OR 'lesser developed 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nation':de,ti,ab OR 'lower income nations':de,ti,ab OR 'lower income population':de,ti,ab OR 'lower income populations':de,ti,ab OR 'middle income countries':de,ti,ab OR 'middle income country':de,ti,ab OR 'middle income economies':de,ti,ab OR 'middle income economy':de,ti,ab OR 'middle income nation':de,ti,ab OR 'middle income nations':de,ti,ab OR 'middle income population':de,ti,ab OR 'middle income populations':de,ti,ab OR 'poor countries':de,ti,ab OR 'poor country':de,ti,ab OR 'poor economies':de,ti,ab OR 'poor economy':de,ti,ab OR 'poor nation':de,ti,ab OR 'poor nations':de,ti,ab OR 'poor population':de,ti,ab OR 'poor populations':de,ti,ab OR 'poor world':de,ti,ab OR 'poorer countries':de,ti,ab OR 'poorer country':de,ti,ab OR 'poorer economies':de,ti,ab OR 'poorer economy':de,ti,ab OR 'poorer nation':de,ti,ab OR 'poorer nations':de,ti,ab OR 'poorer population':de,ti,ab OR 'poorer populations':de,ti,ab OR 'poorer world':de,ti,ab OR 'third world':de,ti,ab OR 'transitional 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'underdeveloped populations':de,ti,ab OR 'underdeveloped world':de,ti,ab OR 'underserved countries':de,ti,ab OR 'underserved country':de,ti,ab OR 'underserved nation':de,ti,ab OR 'underserved nations':de,ti,ab OR 'underserved population':de,ti,ab OR 'underserved populations':de,ti,ab OR 'underserved world':de,ti,ab OR 'angola':de,ti,ab OR 'bangladesh':de,ti,ab OR 'benin':de,ti,ab OR 'bhutan':de,ti,ab OR 'botswana':de,ti,ab OR 'burkina faso':de,ti,ab OR 'burma':de,ti,ab OR 'burundi':de,ti,ab OR 'cabo verde':de,ti,ab OR 'cape verde':de,ti,ab OR 'cameroon':de,ti,ab OR 'central african republic':de,ti,ab OR 'chad':de,ti,ab OR 'comoros':de,ti,ab OR 'comores':de,ti,ab OR 'comoro':de,ti,ab OR 'congo':de,ti,ab OR 'côte d ivoire':de,ti,ab OR 'eritrea':de,ti,ab OR 'ethiopia':de,ti,ab OR 'gabon':de,ti,ab OR 'gambia':de,ti,ab OR 'ghana':de,ti,ab OR 'guinea':de,ti,ab OR 'guinea bissau':de,ti,ab OR 'guinea-bissau':de,ti,ab OR 'india':de,ti,ab OR 'indonesia':de,ti,ab OR 'kenya':de,ti,ab OR 'korea':de,ti,ab OR 'lesotho':de,ti,ab OR 'liberia':de,ti,ab OR 'madagascar':de,ti,ab OR 'malawi':de,ti,ab OR 'maldives':de,ti,ab OR 'mali':de,ti,ab OR 'mauritania':de,ti,ab OR 'mauritius':de,ti,ab OR 'mozambique':de,ti,ab OR 'myanmar':de,ti,ab OR 'namibia':de,ti,ab OR 'nepal':de,ti,ab OR 'niger':de,ti,ab OR 'nigeria':de,ti,ab OR 'principe':de,ti,ab OR 'rwanda':de,ti,ab OR 'ruanda':de,ti,ab OR 'sao tome':de,ti,ab OR 'senegal':de,ti,ab OR 'seychelles':de,ti,ab OR 'sierra leone':de,ti,ab OR 'somalia':de,ti,ab OR 'south africa':de,ti,ab OR 'south sudan':de,ti,ab OR 'sri lanka':de,ti,ab OR 'sudan':de,ti,ab OR 'swaziland':de,ti,ab OR 'eswatini':de,ti,ab OR 'tanzania':de,ti,ab OR 'thailand':de,ti,ab OR 'timor':de,ti,ab OR 'timor-leste':de,ti,ab OR 'togo':de,ti,ab OR 'uganda':de,ti,ab OR 'zambia':de,ti,ab OR 'zimbabwe':de,ti,ab)Populations[tw] OR Middle Income Countries[tw] OR Middle Income Country[tw] OR Middle Income Economies [tw] OR Middle Income Nation[tw] OR Middle Income Nations[tw] OR Middle Income Population[tw] OR Middle Income Populations[tw] OR Poor Countries[tw] OR Poor Country[tw] OR Poor Economies [tw] OR Poor Economy[tw] OR Poor Nation[tw] OR Poor Nations[tw] OR Poor Population[tw] OR Poor Populations[tw] OR poor world[tw] OR Poorer Countries[tw] OR Poorer Economies [tw] OR Poorer Economy[tw] OR Poorer Nations[tw] OR Poorer Population[tw] OR Poorer Populations[tw] OR Third World[tw] OR Transitional Countries[tw] OR Transitional Country[tw] OR Transitional Economies[tw] OR Transitional Economy[tw] OR Under Developed Countries[tw] OR Under Developed Country[tw] OR under developed nations[tw] OR Under Developed World[tw] OR Under Served Population[tw] OR Under Served Populations[tw] OR Underdeveloped Countries[tw] OR Underdeveloped Country[tw] OR underdeveloped economies[tw] OR underdeveloped nations[tw] OR underdeveloped population[tw] OR Underdeveloped World[tw] OR Underserved Countries[tw] OR Underserved Nations[tw] OR Underserved Population[tw] OR Underserved Populations[tw] OR (Angola[tw] OR Bangladesh[tw] OR Benin[tw] OR Bhutan[tw] OR Botswana[tw] OR "Burkina Faso"[tw] OR Burma[tw] OR Burundi[tw] OR "Cabo Verde"[tw] OR "Cape verde"[tw] OR Cameroon[tw] OR "Central African Republic"[tw] OR Chad[tw] OR Comoros[tw] OR Comores[tw] OR Comoro[tw] OR Congo[tw] OR "Côte d'Ivoire"[tw] OR Eritrea[tw] OR Ethiopia[tw] OR Gabon[tw] OR Gambia[tw] OR Ghana[tw] OR Guinea[tw] OR "Guinea Bissau"[tw] OR "Guinea-Bissau"[tw] OR India[tw] OR Indonesia[tw] OR Kenya[tw] OR Korea[tw] OR Lesotho[tw] OR Liberia[tw] OR Madagascar[tw] OR Malawi[tw] OR Maldives[tw] OR Mali[tw] OR Mauritania[tw] OR Mauritius[tw] OR Mozambique[tw] OR Myanmar[tw] OR Namibia[tw] OR Nepal[tw] OR Niger[tw] OR Nigeria [tw] OR Principe[tw] OR Rwanda[tw] OR Ruanda[tw] OR "Sao Tome"[tw] OR Senegal[tw] OR Seychelles[tw] OR "Sierra Leone"[tw] OR "Somalia[tw] OR "South Africa"[tw] OR "South Sudan"[tw] OR "Sri Lanka"[tw] OR Sudan[tw] OR Swaziland[tw] OR "Eswatini"[tw] OR Tanzania[tw] OR Thailand[tw] OR Timor[tw] OR "Timor-Leste"[tw] OR Togo[tw] OR Uganda[tw] OR Zambia[tw] OR Zimbabwe[tw]))

APPENDIX: SEARCH TERMS

2010 - PRESENT

**Google
Scholar
(n = 500)**

Screen the first 500 records:
“Tropical sprue” OR “Environmental
enteric dysfunction” OR “Tropical
enteropathy” OR “Environmental
enteropathy” OR “Idiopathic Tropical
Malabsorption Syndrome”

**WHO
IRIS
(n = 33)**

Search each of the following terms
independently:
“Tropical sprue”
“Environmental enteric dysfunction”
“Tropical enteropathy”
“Environmental enteropathy”
“Idiopathic Tropical Malabsorption
Syndrome”

**WHO
ICTRP
(n = 15)**

Search each of the following terms
independently:
“Tropical sprue”
“Environmental enteric dysfunction”
“Tropical enteropathy”
“Environmental enteropathy”
“Idiopathic Tropical Malabsorption
Syndrome”

APPENDIX: EXCLUSION CRITERIA

RECORD SCREENING

Reasons 1-3 apply to all objectives; reasons 4-7 apply only to studies that could be relevant for objectives 2 and 3. If a record is not relevant for objective 1, it will not be relevant for objectives 2 and 3.

1. Record was published before 2010.
2. Record does not define EED, delineate distributions of EED biomarkers, or describe associations between EED/EED biomarkers and clinical outcomes.
3. Record does not include any of the following populations: women of reproductive age (ages 15 to 49), pregnant women, lactating women, children under 5 years (< 61 months) of age.
4. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, record does not present research that presents the analysis of primary data (i.e. exclude meta-analyses, commentaries, textbooks, etc.).
5. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, geographic location is not Sub-Saharan Africa or Southeast Asia.
6. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, geographic location is not stratified to Sub-Saharan Africa or Southeast Asia (e.g. results are aggregated across Brazil and Kenya, etc.).
7. For studies that delineate distributions of EED biomarkers or describe associations between EED/EED biomarkers and clinical outcomes, distributions and/or associations are not stratified to include only the populations of interest (e.g. record presents distribution of a biomarker for children 10+, record presents association between biomarker and clinical outcome for female and male adults, etc.) OR age not specified (as seen in conference abstracts, etc.).

