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# EED INTERVENTIONS: ONGOING LITERATURE

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**START  
CENTER**

STRATEGIC ANALYSIS,  
RESEARCH & TRAINING CENTER

Department of Global Health | University of Washington

# Agenda

- Introduction
- Project Background and Objectives
- Timeline
- Methods
- Results

## Work Order to the UW START Team

### Background

- Environmental enteric dysfunction (EED) is a condition in which repeated enteropathogen infection leads to chronic gut inflammation and the increase of gut permeability. The result is malabsorption of nutrients linked to slowed linear growth (i.e. stunting) and decreased cognitive development.
- The Enteric and Diarrheal Diseases (EDD) and Discovery and Translational Sciences (DT&S) teams are investing in studies to define EED and understand the causal pathways of pathology and EED's association with morbidity and to build a case for an intervention.
- No current BMGF intervention trials for EED, the goal is to start funding interventional trials by 2016.

### Objectives

- Conduct a landscape analysis of the **current** and past intervention trials that have outcomes related to EED
- Summarize applicable trials including: rationale, design & inclusion criteria, intervention(s), geography, size/power, endpoints, & outcomes

# Timeline



## Scoping



- Confirm work plan and scope
- Strategize approach



= Check-In Point



= Biomarkers Consortium Meeting

## Phase 1a



- Review relevant literature & extract data
- Relay initial findings & finalize results

## Phase 1b



- Extract from ClinicalTrials.gov
- Interview experts
- Compile interviews & finalize results

# ClinicalTrials.gov

## ClinicalTrials.gov

A service of the U.S. National Institutes of Health

*ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more [about clinical studies](#) and [about this site](#), including relevant [history, policies, and laws](#).*

ClinicalTrials.gov currently lists **202,210 studies** with locations in all 50 States and in **190 countries**.

### Search for Studies

Example: "Heart attack" AND "Los Angeles"

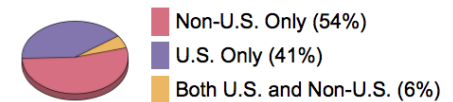
environmental enteric dysfunction (  )

[Advanced Search](#) | [See Studies by Topic](#)  
[See Studies on Map](#)

### Search Help

- [How to search](#)
- [How to find results of studies](#)
- [How to read a study record](#)

### Locations of Recruiting Studies



Total N = 36,975 studies

## □ Search terms

□ (environmental enteric dysfunction OR environmental enteropathy OR EED OR tropical enteropathy OR enteric dysfunction) OR ("growth faltering" OR "stunting")

□ Filter: "Interventional"

## □ Results

□ n=154

## Key Informant Interviews

### WASH Benefits:

Stephen Luby, Stanford University

### SHINE:

Jean Humphrey, Johns Hopkins University;  
Andrew Prendergast, Queen Mary University of London

### IMAGINE:

Sean Moore, Cincinnati Children's Hospital Medical Center

### *Lactobacillus reuteri* in Healthy Children:\*

Margaret Kosek, Johns Hopkins University

### Impact of Legumes vs Corn- soy Flour on EED, Zinc Resistant Starch Project, etc.:

Mark Manary, Washington University in St. Louis

### BEED:

Tahmeed Ahmed, ICDDR, Bangladesh

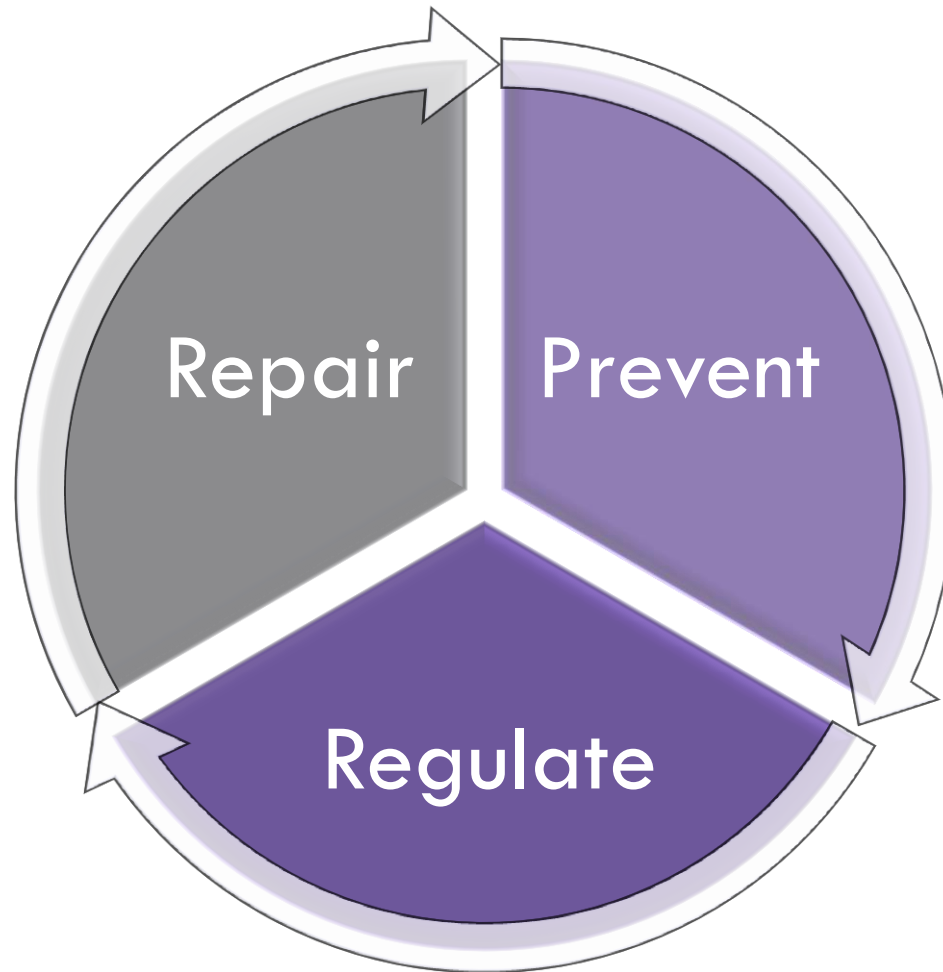
### ABCD, Toto Bora:

Judd Walson, University of Washington

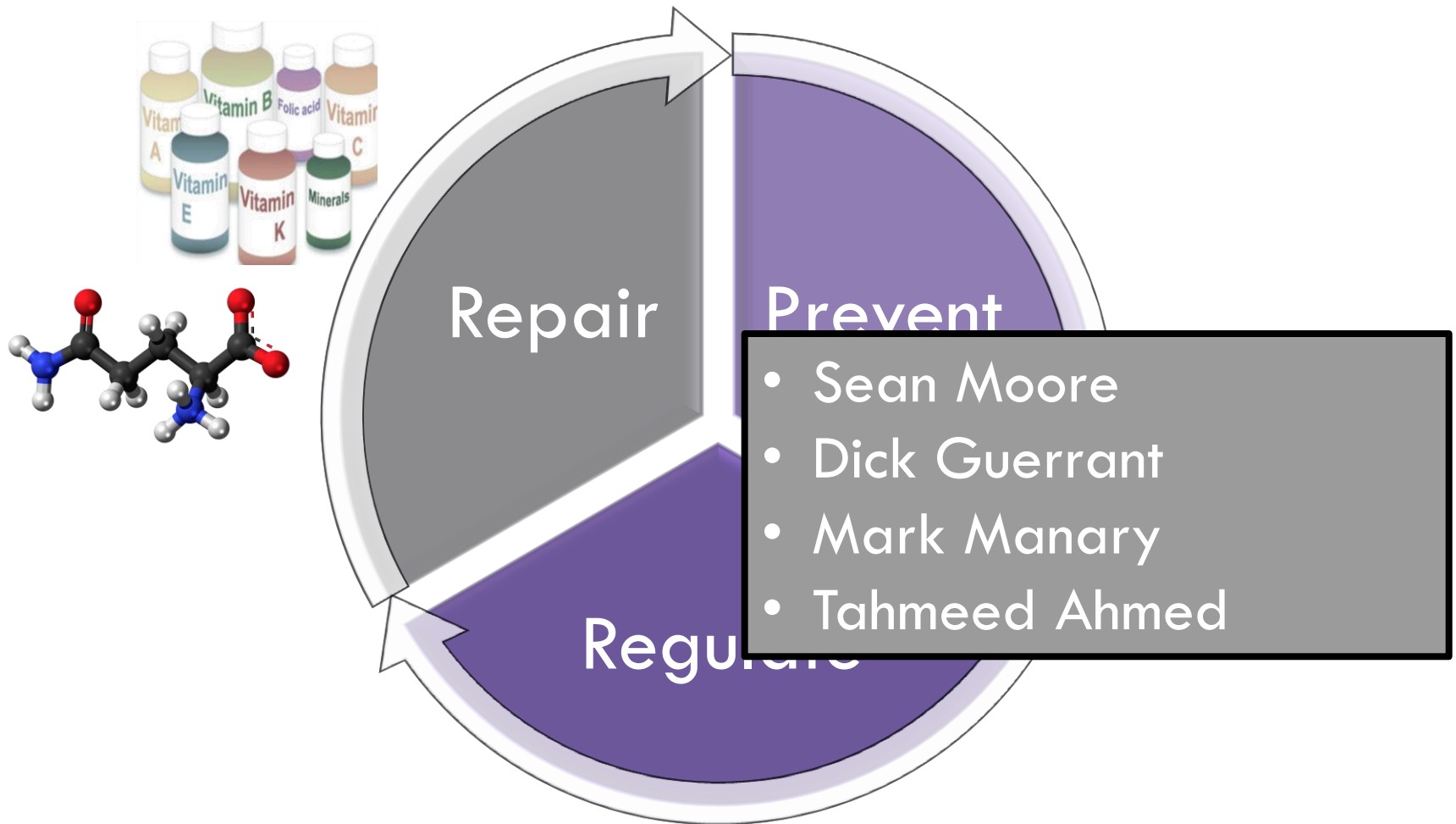
### Other Subject Matter Experts

- Jay Berkley, KEMRI Wellcome Trust
- Bill Petri, University of Virginia
- Dick Guerrant, , University of Virginia

## Key Informant Interviews: Perspectives

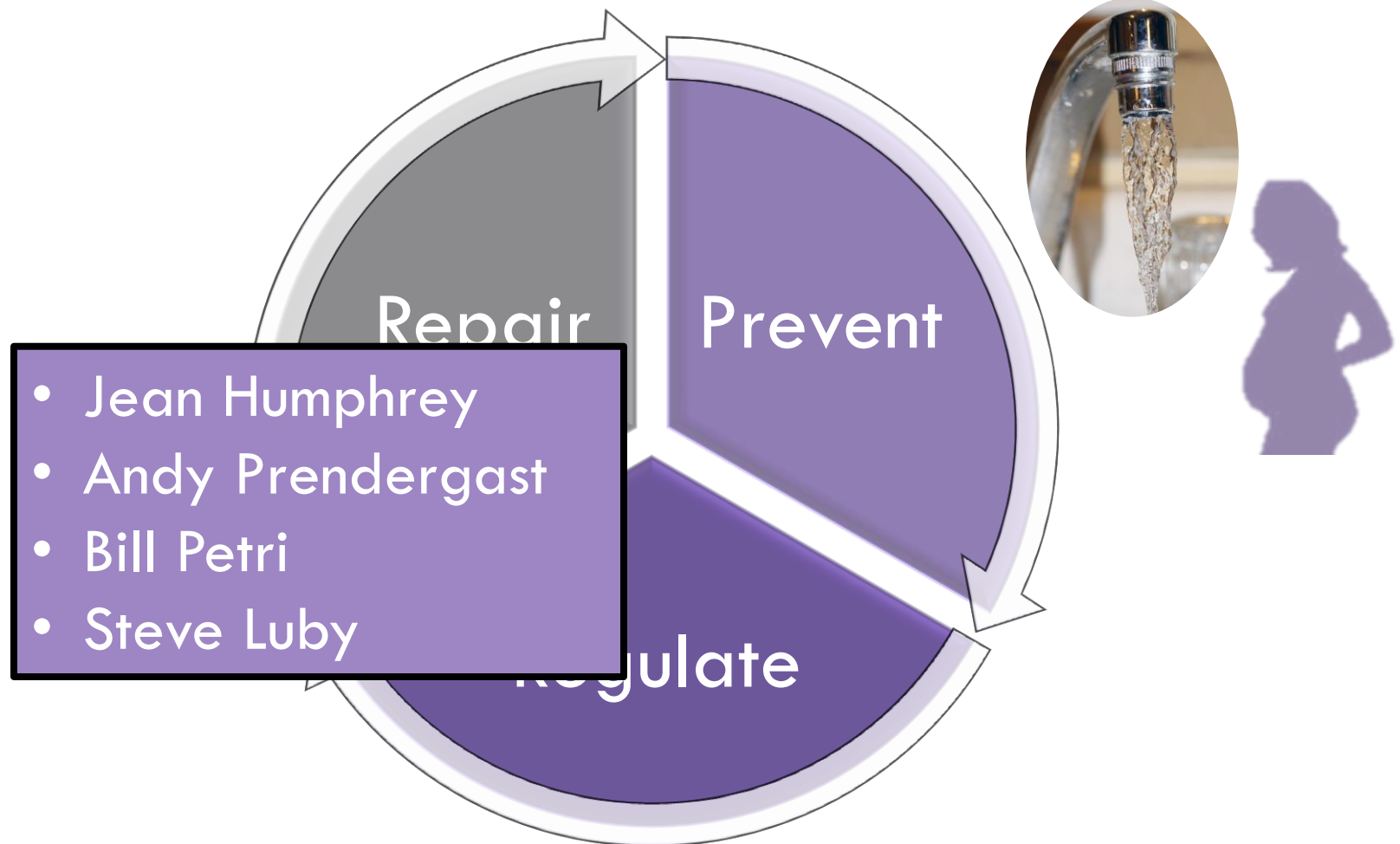


## Key Informant Interviews: Perspectives

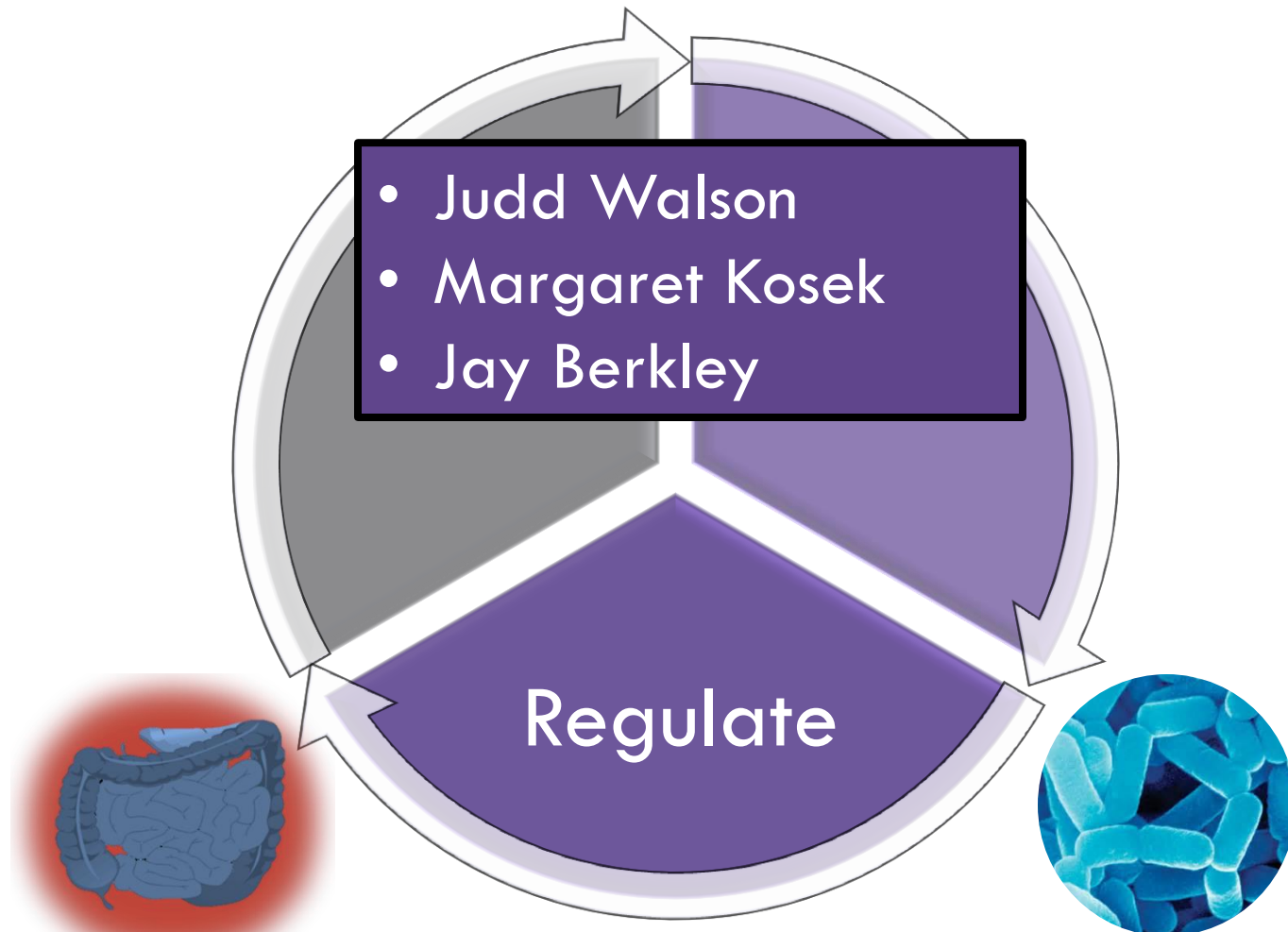




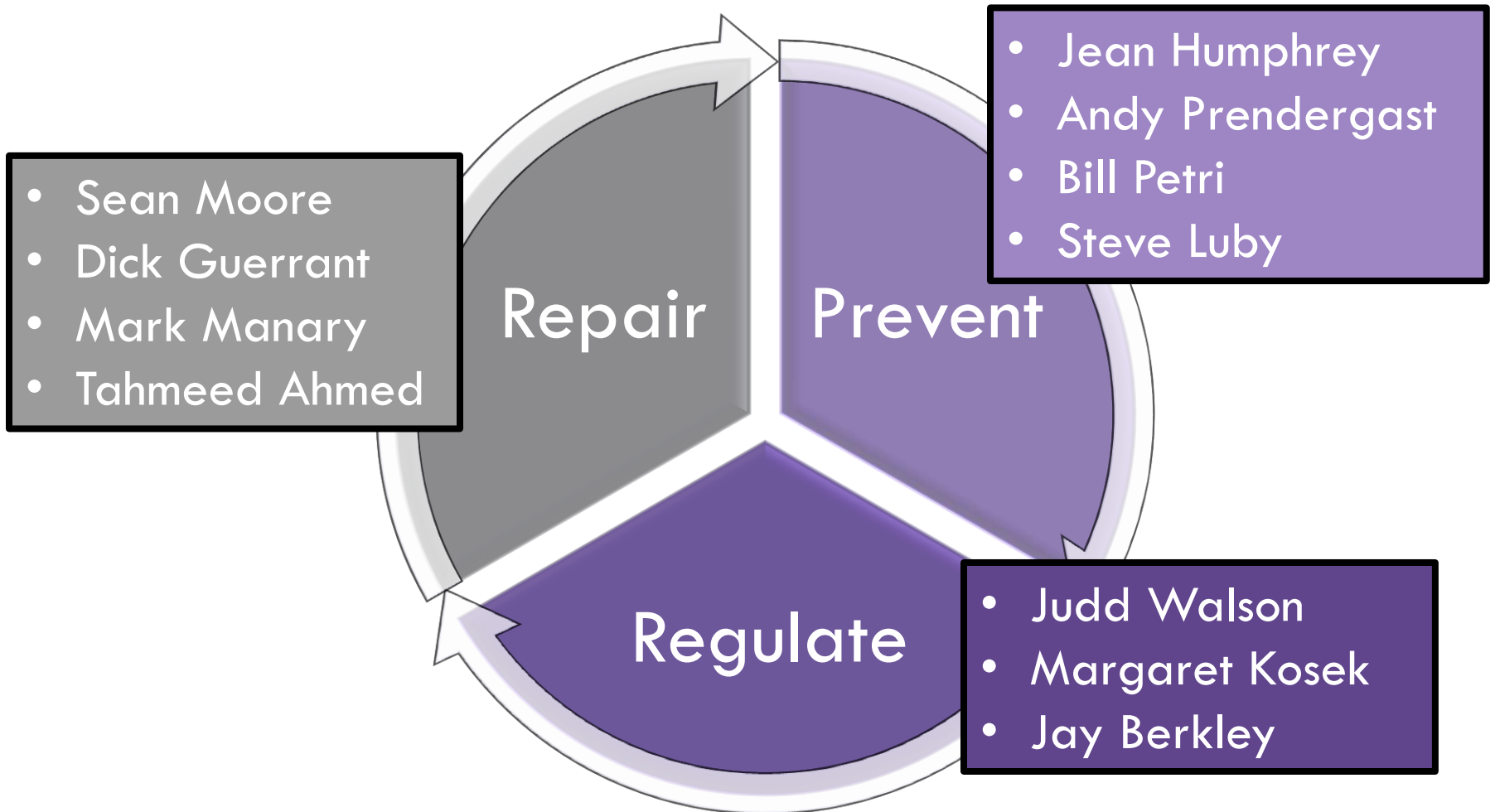
## Key Informant Interviews: Perspectives



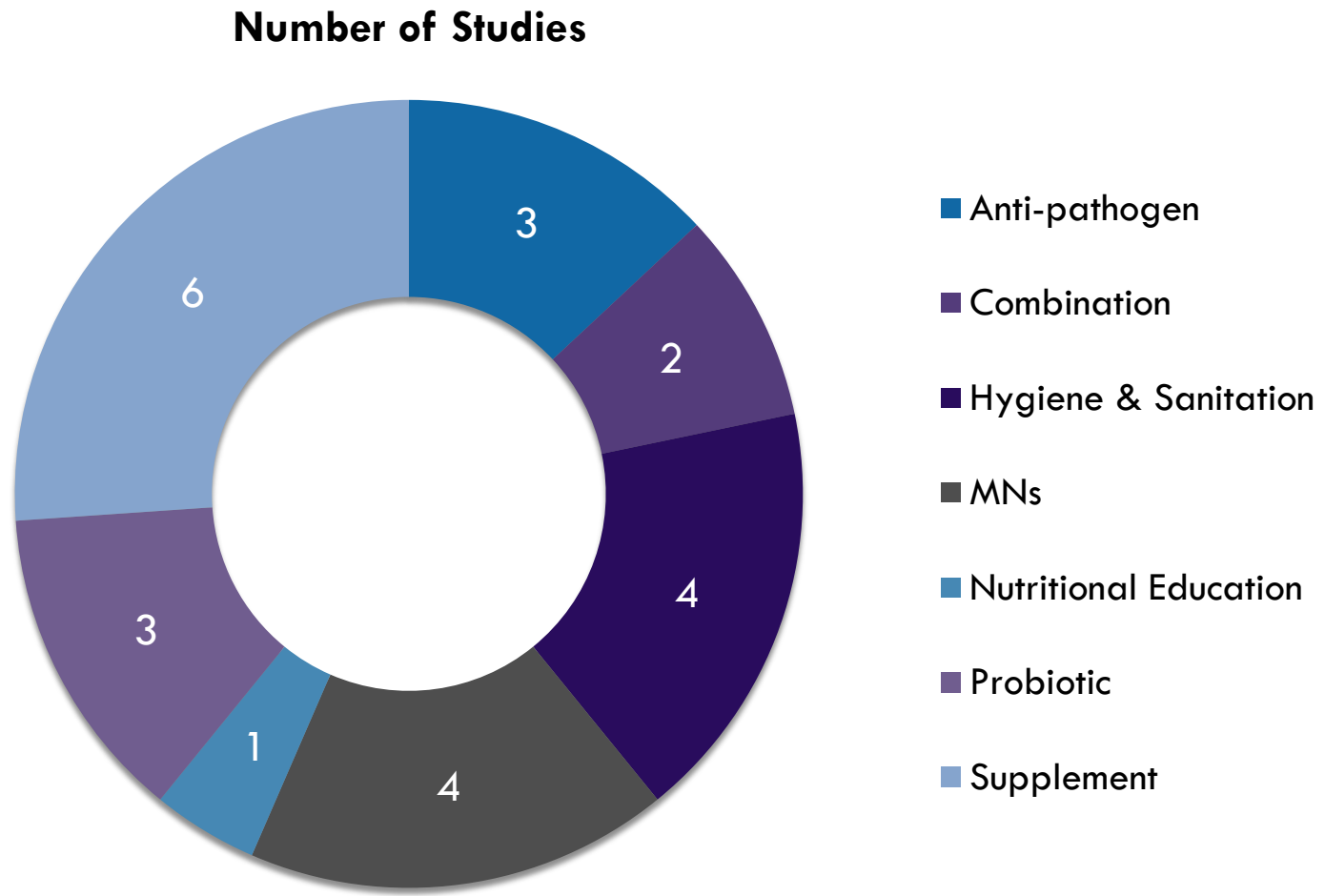
## Key Informant Interviews: Perspectives



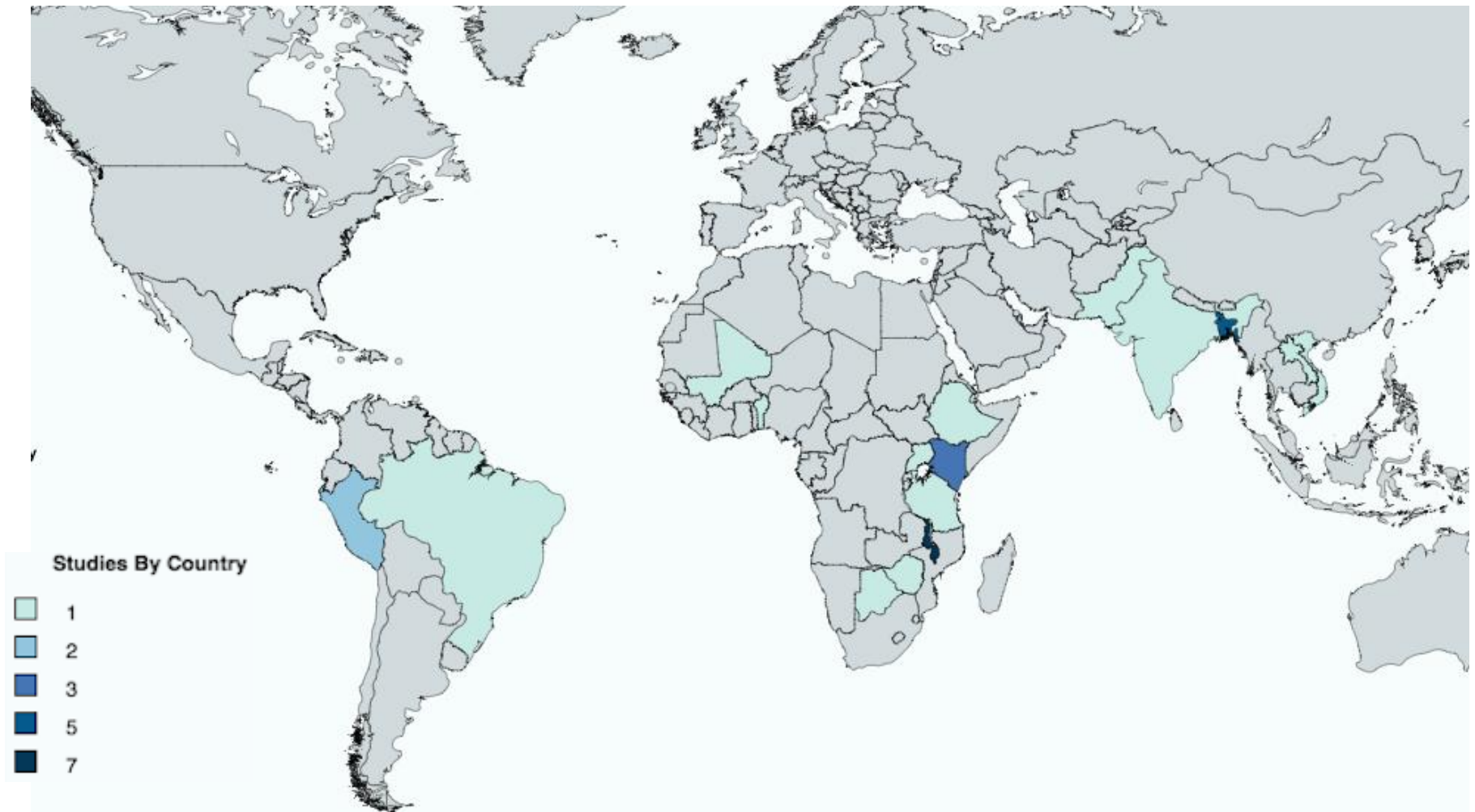
## Key Informant Interviews: Perspectives



## Number of Studies by Intervention Type

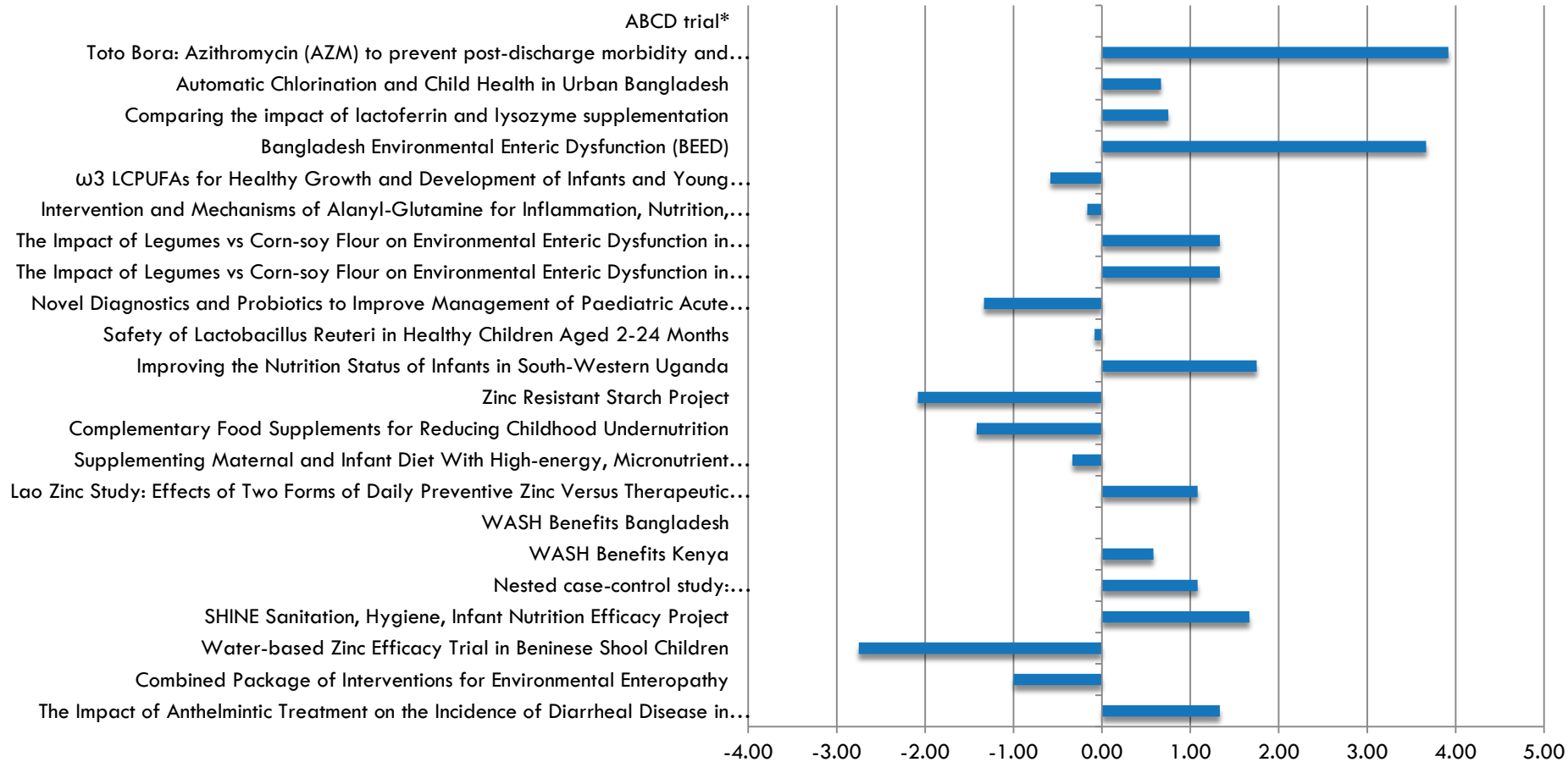


## Studies by Geography



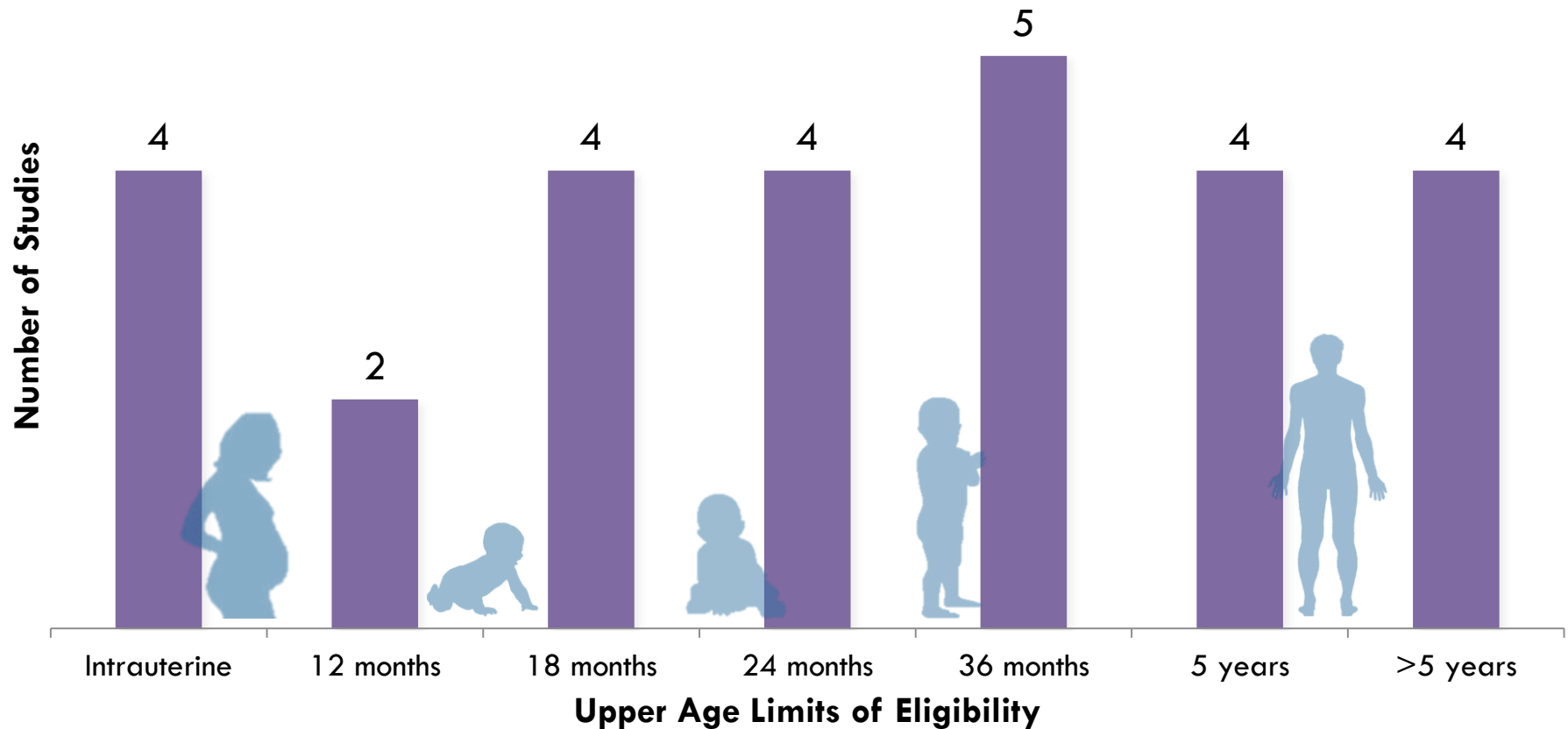
# Milestones

## Years to Completion



## Upper Ages of Eligibility

## Upper Age of Eligibility in Ongoing Studies



## Future Directions

*"If there is a window when these therapies will improve growth and cognitive ability then it may be worth a short course of an expensive drug."*

- GLP2, analogue tegduglutide – conceptual

*"Try other SIBO treatments and give in a short course and see if it works and is safe. Longer way down the line is steroids but need safer drugs."*

*"Maternal health is so important. You know these children are all living side by side in this certain slum in Dhaka. There's no discernible difference in their living conditions, yet only half the children end up stunted and the other don't. One thing that determines if you are stunted or not is how healthy your mother is."*



*"Growth may be an imperfect proxy for cognitive development"*

- *"Fruits in a minute"*



## Innovative Ideas

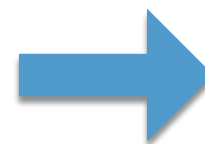
- Perform a natural experiment in individuals in mass migration from the Middle East and Asia to Europe
- Vaccinate women of childbearing age against *Shigella* and *Campylobacter*
- Investigate further ApoE mimetic peptides in children and their role in cognitive development



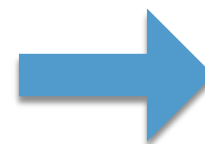
## Search Terms for Pubmed

### Terms

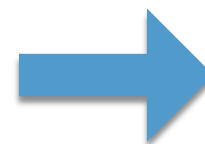
- (Intestinal or gut) AND (inflamm\* OR absorp\* OR permea\* OR leaky)
- **AND** ((D-xylose OR mannitol OR rhamnose) OR "lactulose paracellular uptake" OR "L:M ratio" OR (α1-anti-trypsin OR alpha\*anti-trypsin) OR "alanyl-glutamine" OR "plasma cytokines" or "plasma citrulline" OR calprotectin OR lactoferrin OR "lactose tolerance test" OR myeloperoxidase OR MPO OR "REG 1B" OR neopterin OR "plasma LPS core antibody" OR "LPS binding protein" OR "soluble CD14" OR (kynurenine AND tryptophan) OR "K:T ratio" OR "KT ratio" OR "dual sugar absorption test" OR "serum flagellin IgG" OR "serum flagellin IgA" OR "serum ferritin" OR "serum GLP" OR "serum CRP" OR EndoCab OR "Endogenous endotoxin-core antibody")
- **OR** ("EED" OR "Environmental Enteric Dysfunction" OR "Enteric Dysfunction" OR "Tropical Enteric Dysfunction" OR "Tropical Sprue")



Clinical  
Characteristics

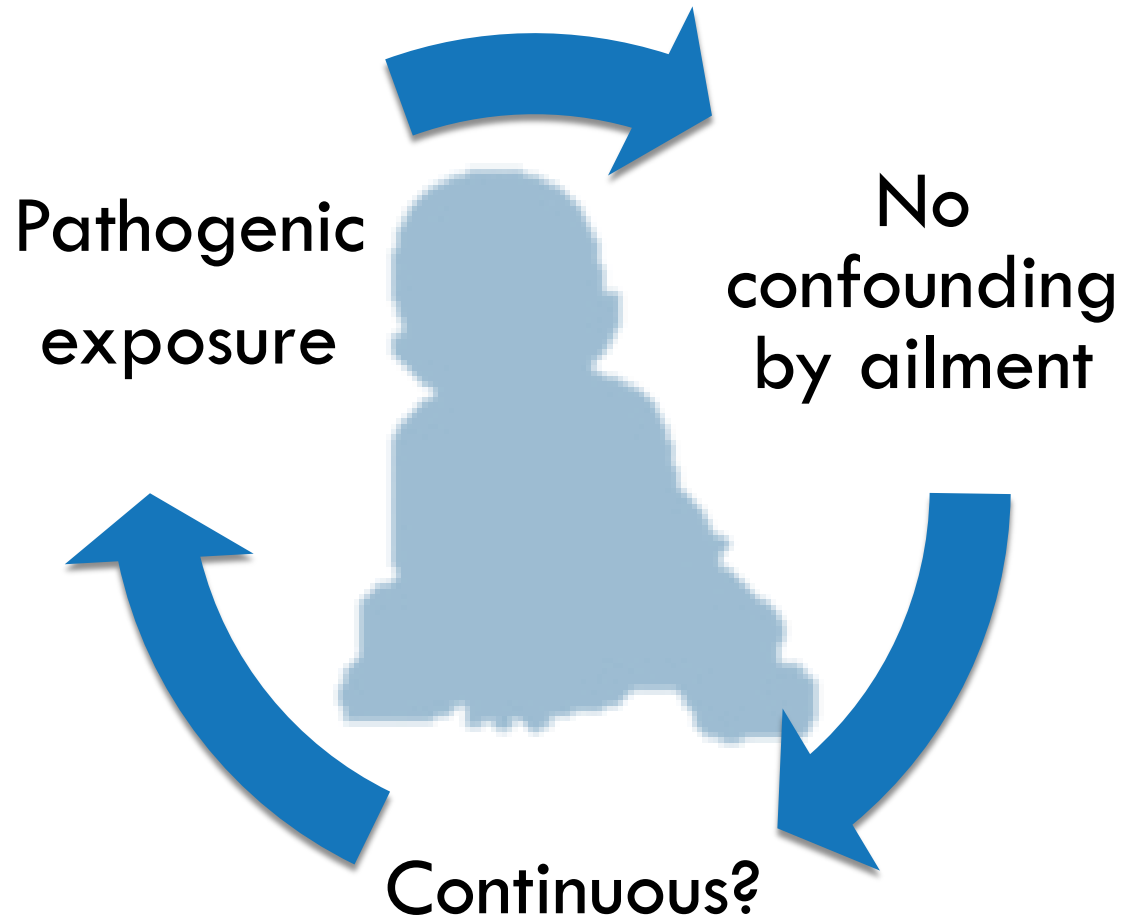


All possible  
biomarkers



Initial EED-  
specific terms

# Environmental Enteric Dysfunction?



## Interventions

**Nutritional**

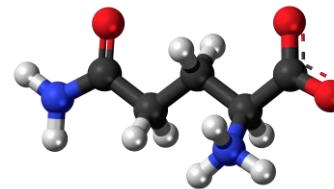
- Micronutrients
  - Zinc
  - Vit A
  - Multi-
- Functional Foods
- Breastfeeding

**\*Biotics**

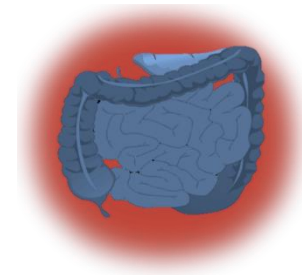
- Prebiotic
- Probiotics
- Anti-biotics
  - Albendazole
  - Azithro
  - Co-trim
  - Rifaximin

**Hygiene & Sanitation**

- WASH
  - Tx & safe storage of H<sub>2</sub>O
  - Hand washing
  - Sanitary disposal of feces

**Other supplements**

- n-3 LC-PUFA
- Alanyl-glutamine
- Glutamine-tryptophan

**Anti-inflammatory**

- Mesalazine
- Budesonide

## Intervention Themes

## Categories of Intervention Analyses, 2005-2015

