FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

EED as a cause of stunting

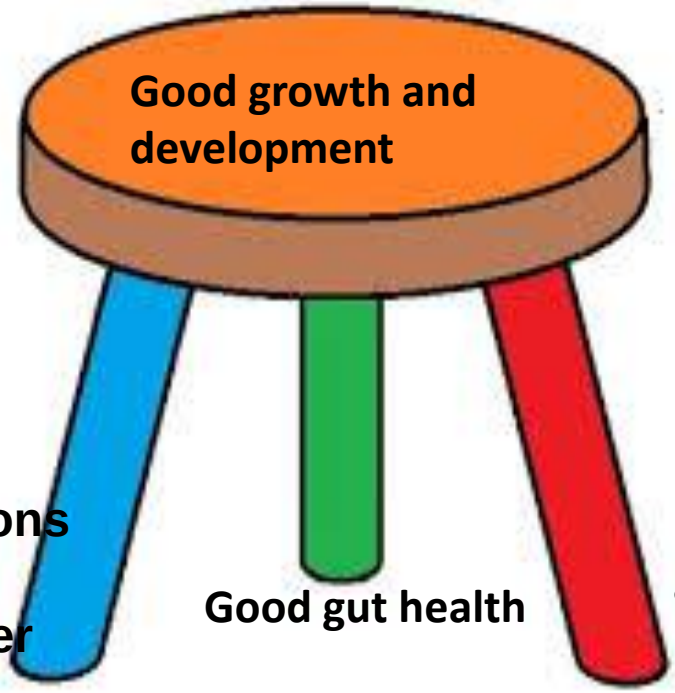
Mark J. Manary, MD
Washington University School of Medicine.
St. Louis, Missouri, USA.

Gainesville, March 2018

[Name presenter here]
Feed the Future Innovation Lab for Livestock Systems, University of Florida
Photo credits: University of Florida

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

FOR NORMAL GROWTH AND DEVELOPMENT 3 CONDITIONS MUST BE MET



No excess of symptomatic common infections such as malaria, diarrhea, or lower respiratory tract infections

Diet provides adequate macro- and micronutrients in bioavailable forms

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

STUNTING

- Affects 25% of children globally, 35% in Africa, 38% in Ethiopia.
- Stunting is associated with:
  - Increased mortality from diarrhea, pneumonia, other infectious diseases.
  - Impaired cognitive development.
  - Reduced income (by up to 22%).
  - Reduced life expectancy by up to 17%.
  - A significant portion of stunting comes from EED which comes from marginal diet + microbial imbalance.
- Need for interventions to reduce this cause of morbidity and mortality.

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

STUNTING IN AFRICA HAS MANY CAUSES

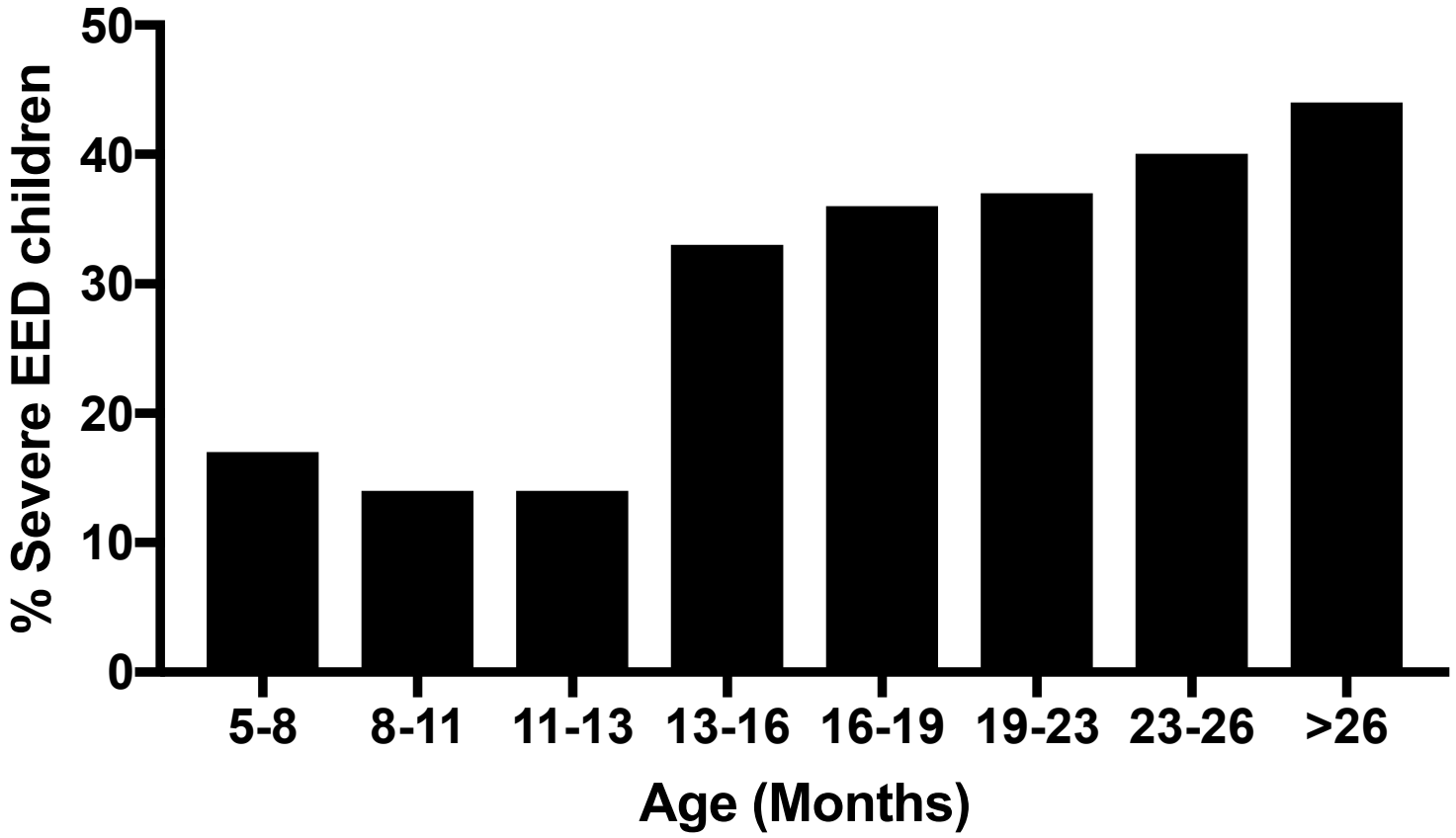
- About 33% of stunting occurs in utero, evidence suggest this is mostly a result of maternal inflammation
- About 50% of stunting occurs from 6-12 mo of age, and this thought to be the result of inadequate diet
- About 15% of stunting occurs after 1 year of age and this is thought to be the result of poor gut health.

ENVIRONMENTAL ENTERIC DYSFUNCTION

- Develops in the first three years of a child in developing countries.
- It is characterized by a chronic inflammation of the small intestine, abnormal villous architecture and reduced intestinal mucosal surface area.
- Etiology of the disease is unknown, it is associated with unsanitary living conditions, colonization by intestinal pathogens and malnutrition.

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

CHILDREN WITH SEVERE EED IN LEGUME STUDY



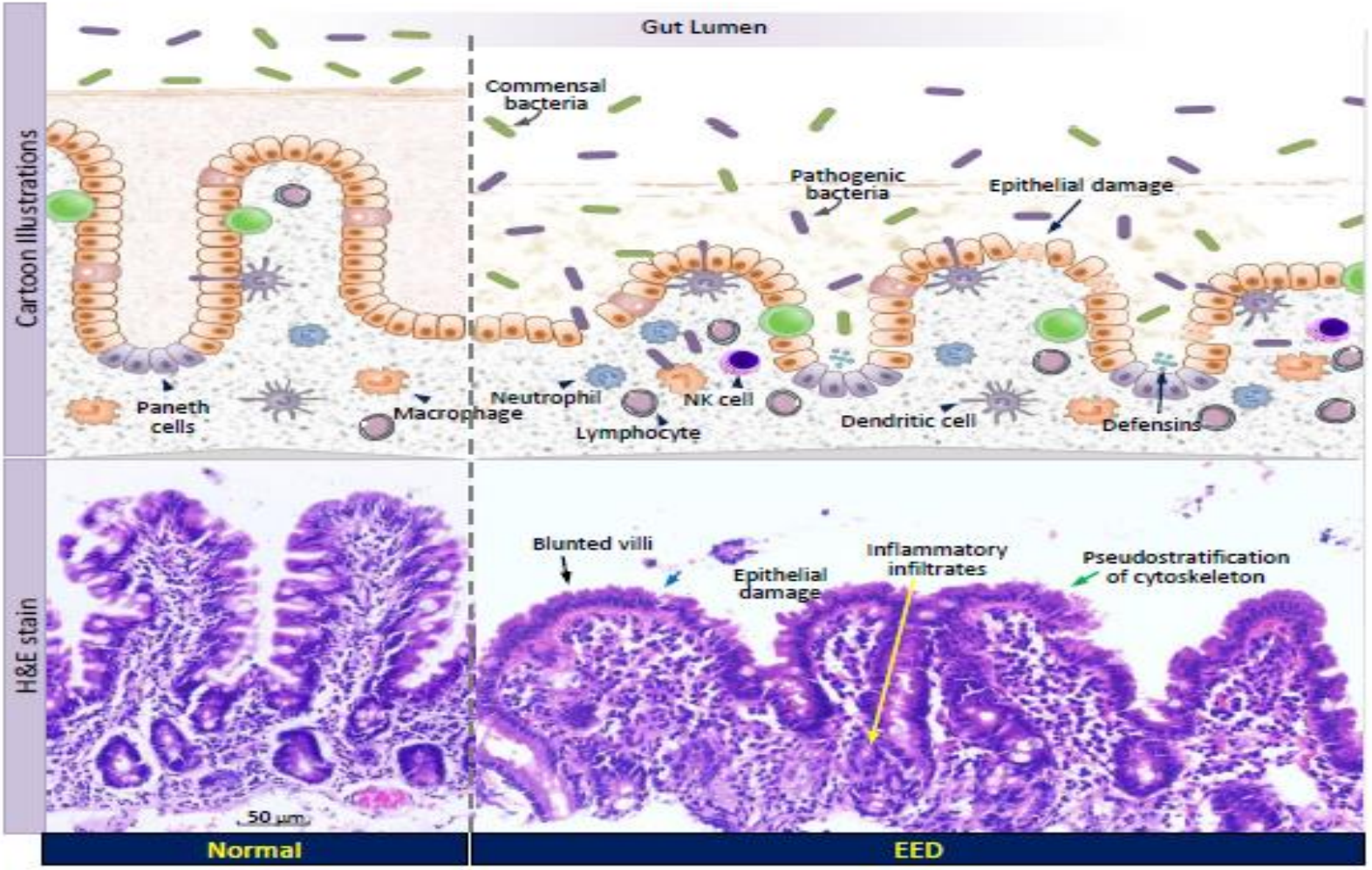
USAID FROM THE AMERICAN PEOPLE

BILL & MELINDA GATES foundation

ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE

CGIAR

UF IFAS UNIVERSITY of FLORIDA

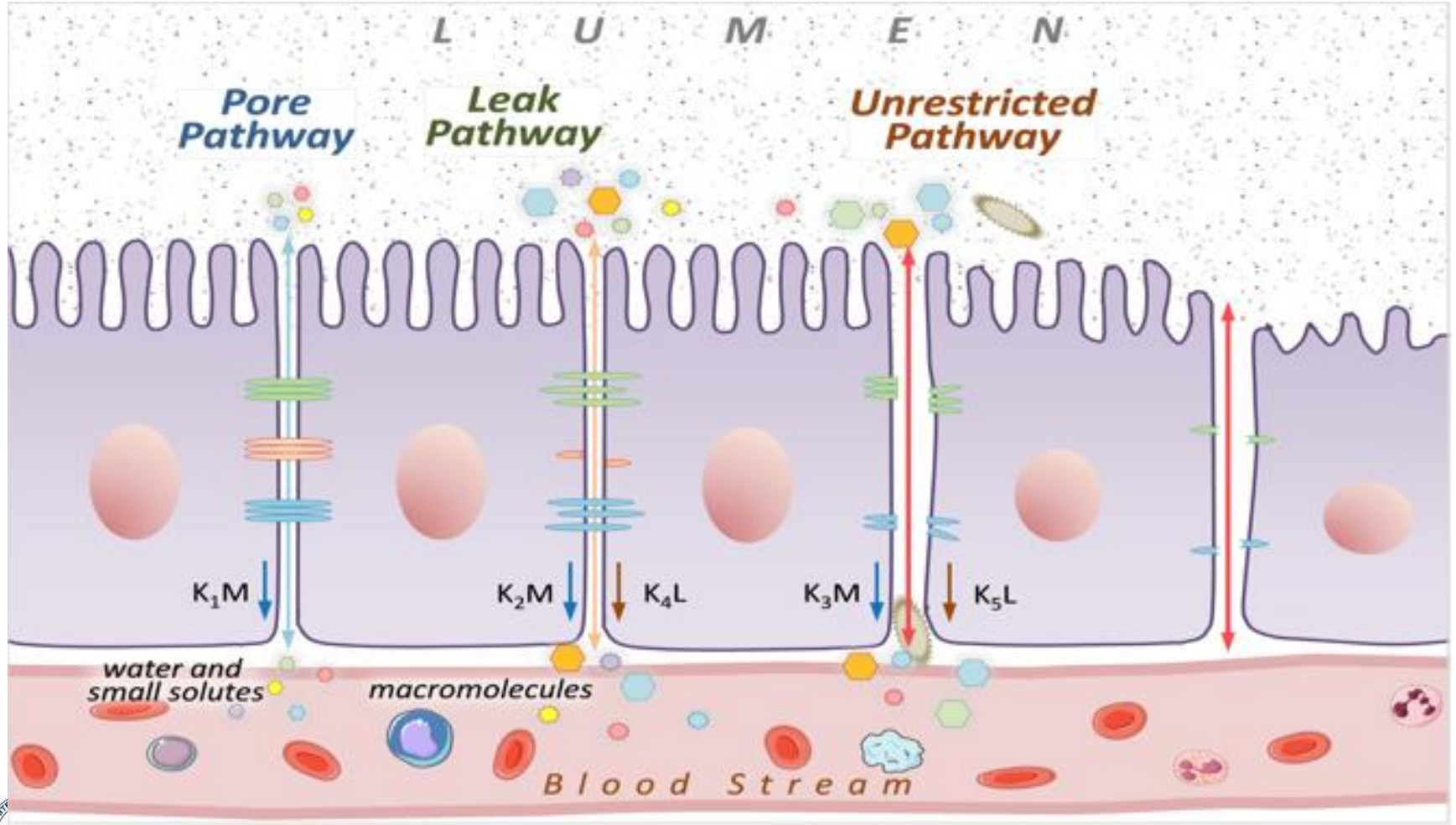

Cartoon Illustrations
Gut Lumen
Commensal bacteria
Pathogenic bacteria
Epithelial damage
Paneth cells
Macrophage
Neutrophil
Lymphocyte
NK cell
Dendritic cell
Defensins
H&E stain
Blunted villi
Epithelial damage
Inflammatory infiltrates
Pseudostratification of cytoskeleton
50 µm
Normal
EED

DIAGNOSIS OF EED

- Because the collection of routine biopsy specimens is impractical and unethical, enteropathy is most commonly identified using site specific sugar absorption test
- This test involves the ingestion of sugars that are not metabolized, some fraction of the monosaccharides are absorbed and then excreted in the urine, disaccharides are absorbed in lessor. Most common is

Lactulose:Mannitol test

INTERPRETATION OF DUAL SUGAR ABSORPTION TEST

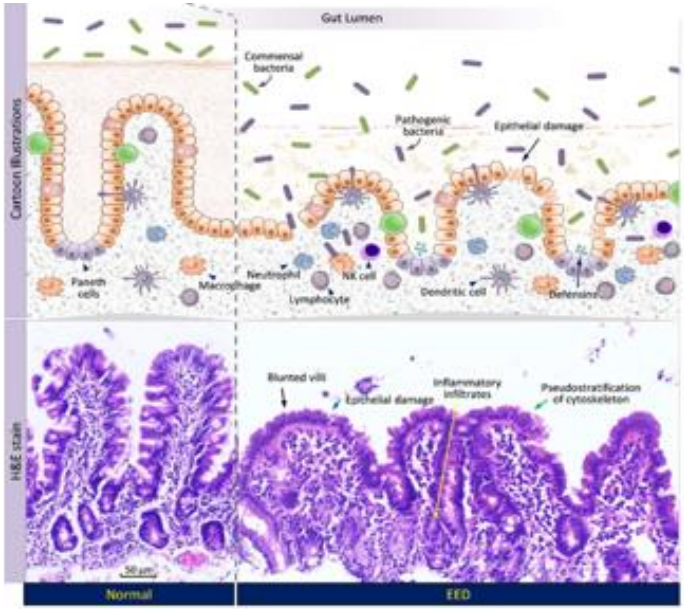


INTERPRETATION OF DUAL SUGAR ABSORPTION TEST

- Simplistic interpretation is that lactulose enters the body through damaged pathways, and more lactulose represents more damage.
- Mannitol is normalizing factor for transit time and bowel length, and also more mannitol is absorbed from healthy guts.
- Test result is expressed as a ratio L:M
- But Mannitol is **not** absorbed transcellularly, whereever lactulose can enter so can and does mannitol. In reality mannitol is a composite measure of normal and damaged epithelial surfaces, which reduces its utility as a normalizing factor.
- It is better just to use lactulose absorption alone to determine amount of gut damage and extend the urine collection time to reduce variations in gut transit time.

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

BIOLOGICAL PERTURBATIONS IN EED



SERUM METABOLITES

Low circulating

- *Phosphatidylcholines*
- *Sphingomyelins*
- *Tryptophan*
- *Ornithine*
- *Citrulline*
- *Carnitine*

High circulating

- *Glutamate*
- *Taurine*
- *Serotonin*

BACTERIA

Low abundance

- *Succinivibrio*
- *Klebsiella*
- *Clostridium_XI*

High abundance

- *Megasphaera*
- *Mitsuokella*
- *Suterella*

STOOL

KEGG Signalling Pathways

- *NF-kappa B signaling pathway*
- *Toll-like receptor signaling pathway*
- *NOD-like receptor signaling pathway*
- *Chemokine signaling pathway*
- *TNF signaling pathway*
- *Osteoclast differentiation*
- *B-cell receptor signalling pathway*
- *FC gamma R-mediated phagocytosis*
- *NK cell mediated cytotoxicity*
- *T-cell receptor signalling pathway*

GeneGO Canonical Pathways

- *Inegrin inside-out signalling in neutrophils*
- *Inhibition of neutrophil migration by proresolving lipid mediators in COPD*
- *Transcription regulation of granulocyte development*
- *Lipoxin inhibitory action on fMLF induced neutrophil chemotaxis*
- *G-CSF induced myeloid differentiation*
- *Chemokines and adhesion*

Transcripts

ARRB2
CXCR2
LYN, CLEC7A
NCF2, FCGR2A
FCGR3B, BCL2A1
SOCS3, IFITM1
FCER1G,
PIK3AP1

Host Response

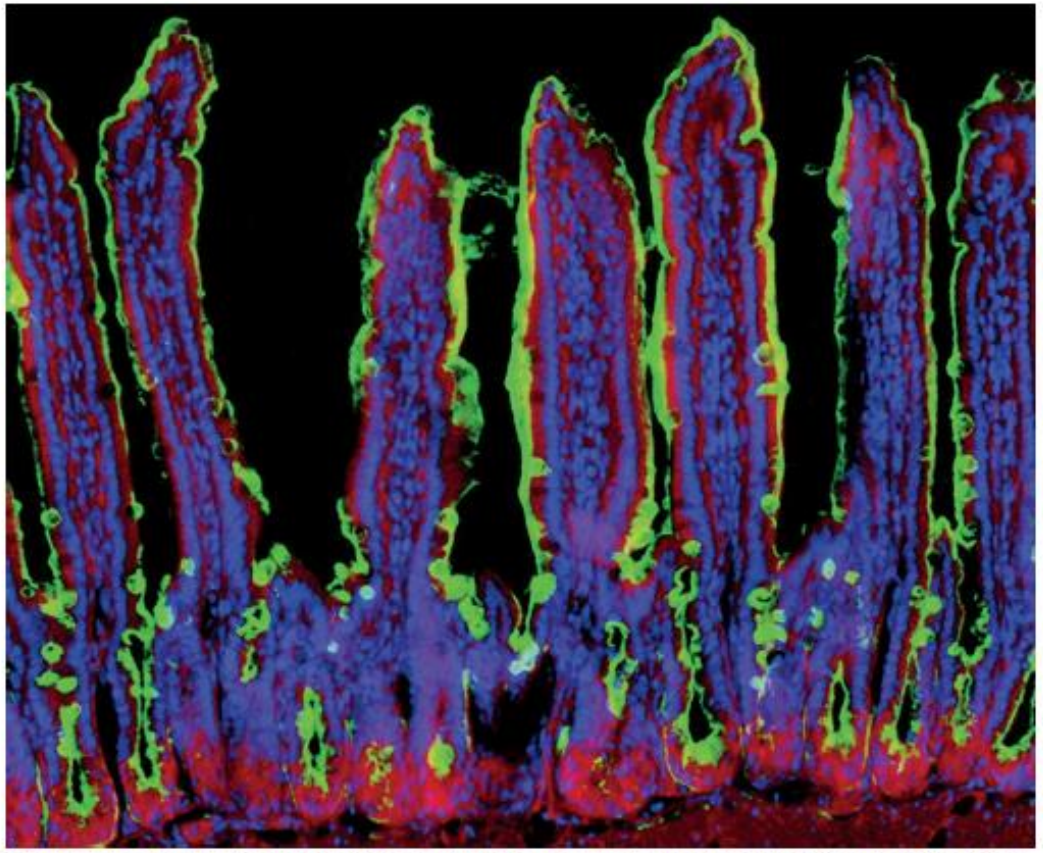
- *Recruitment of diverse immunologically active cells*
- *Enhanced anti-viral defenses*
- *Chronic inflammation*
- *Compromised Mucus layer*
- *Compromised cell adhesion and increased permeability*
- *Apoptosis*

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

Recurrent infection progressively disables host protection against intestinal inflammation

(Based on *Salmonella* study in mice, 2017)



Gut reaction: Food poisoning triggers chronic inflammation. Recurrent *Salmonella* infections progressively induce host Neuraminidase 3 (green) on the surface of enterocytes among duodenal epithelial cells of the small intestine. Epithelial cells are counterstained to also visualize DNA among cell nuclei (blue) and the cytoskeleton component α-tubulin (red). Elevated neuraminidase activity accelerates the molecular aging and clearance of IAP in triggering colitis.

USAID FROM THE AMERICAN PEOPLE

BILL & MELINDA GATES foundation

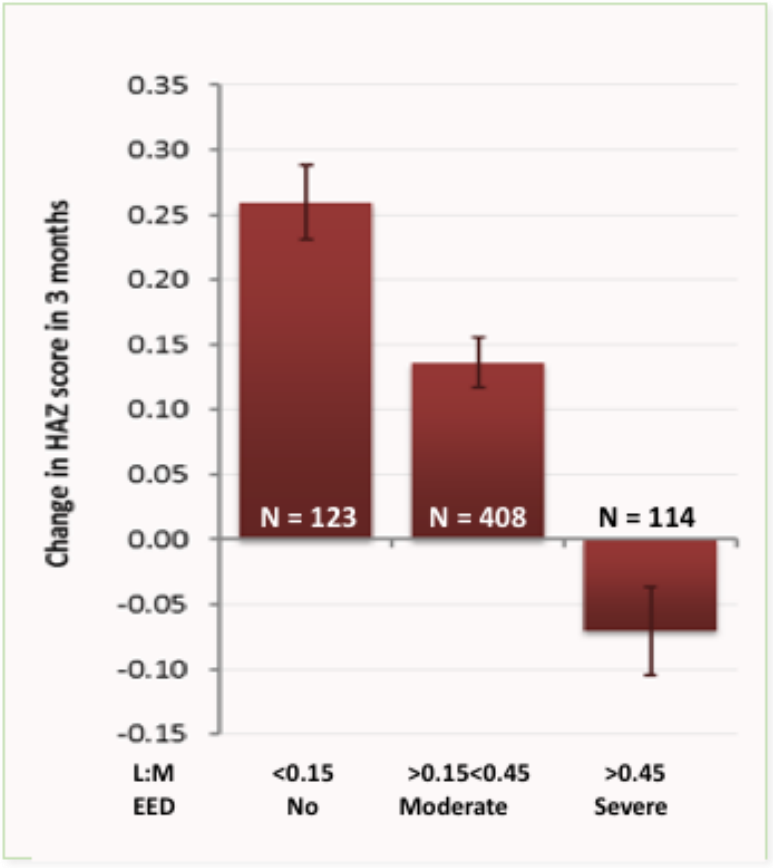
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE

CGIAR

UF IFAS UNIVERSITY of FLORIDA

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

STUNTING IS PREDICTED BY THE LACTULOSE:MANNITOL TEST



L:M is correlated with change in HAZ.

Pearson's correlation coefficient = -0.27 (P<0.001).

Spearman's correlation coefficient = -0.32 (P<0.001).

Linear regression modeling of change in HAZ over subsequent 3 months identified the following predictive factors:

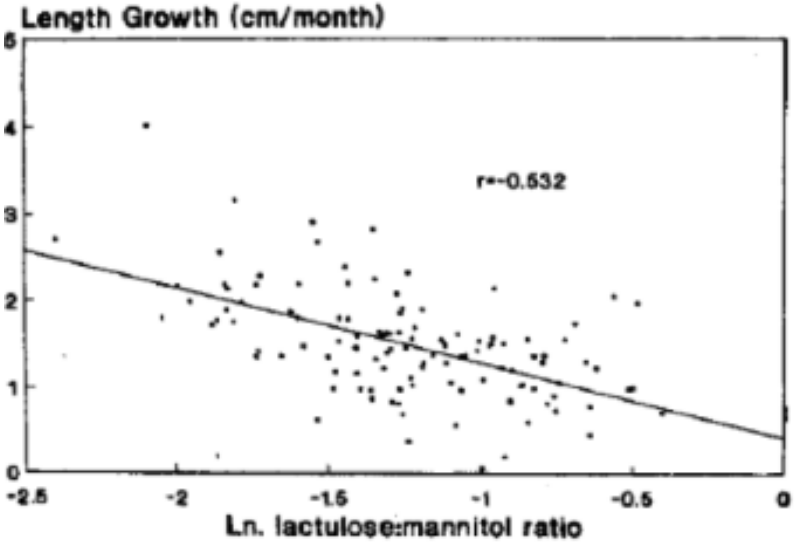
Coefficients[a]

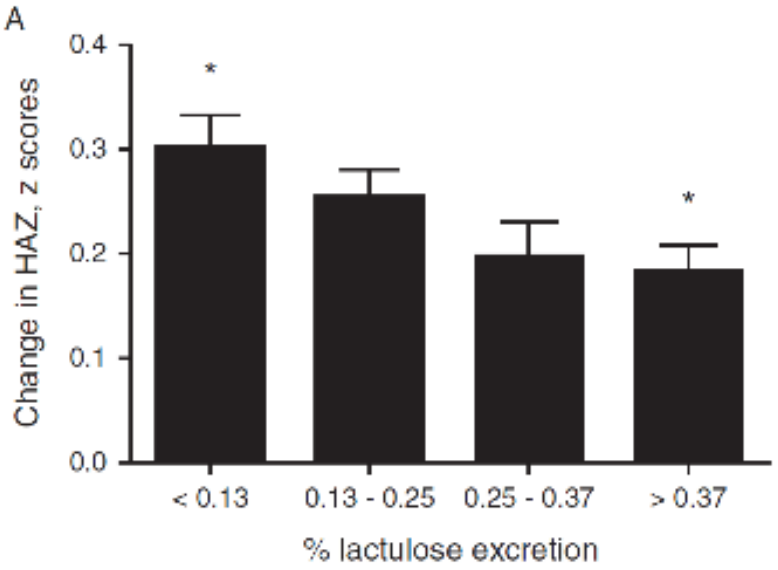
Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.
1	(Constant)	-0.352	0.109		-3.226	0.001
	L:M	-0.214	0.054	-0.140	-3.971	0.000
	sex	-0.008	0.026	-0.010	-0.309	0.758
	age	0.005	0.001	0.147	3.913	0.000
	HAZ	-0.117	0.011	-0.352	-10.429	0.000
	WHZ	0.081	0.014	0.197	5.705	0.000
	HFIAS	-0.011	0.004	-0.106	-3.009	0.003
	Dietdivers	0.012	0.012	0.038	1.055	0.292
	Momcare	0.059	0.073	0.028	0.806	0.420
	Dadhome	-0.006	0.032	-0.007	-0.193	0.847

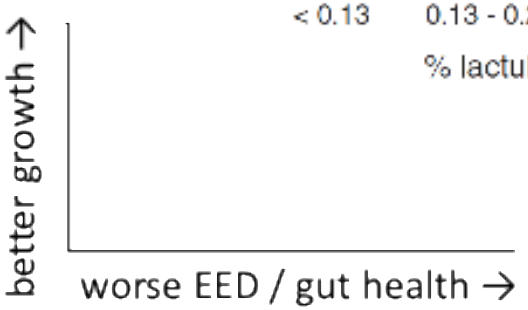
a. Dependent Variable: ΔHAZ, r = 0.564

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

EED IS ASSOCIATED WITH STUNTING







PREVIOUS INTERVENTIONS ATTEMPTED HEAL EED AND REDUCE STUNTING

- Probiotic: Lactobacillus GG
- Antibiotic intervention: rifaximin
- Deworming with albendazole
- High-dose zinc.
- Prebiotic intervention: dietary resistant starch type 2.
- Poly-unsaturated fatty acid supplementation.
- Complementary feeding with legumes: common bean and cowpea.
- Lactoferrin and Lysozyme supplementation.

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

WASH BENEFIT STUDY

- Focus on: Water quality, sanitation, hand washing and nutritional intervention during the first years of life.
- Rural Bangladesh and Kenya – cluster-randomized controlled trials
- >6400 newborns per country
- Measure primary outcomes after two years of intervention:
  1. Length for age Z scores (LAZ) and caregiver report diarrhea
  2. Stunting prevalence, markers EED and child development scores (verbal, motor and personal/social)

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

WASH BENEFIT STUDIES IN KENYA - FINDINGS

- None of the interventions reduced diarrhea prevalence compared with the active control.
- The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.
- Among the children receiving nutrition intervention (feeding counseling + lipid nutrient supplements) LAZ was about 0.15 z-scores greater.

FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

WASH BENEFIT STUDY BANGLADESH

- Sanitation, handwashing and nutrition interventions (or combinations) reduced diarrhea prevalence by 40%.
- The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.
- Among the children receiving nutrition intervention (feeding counseling + lipid nutrient supplements) LAZ was about 0.19 z-scores greater.

USAID FROM THE AMERICAN PEOPLE
BILL & MELINDA GATES foundation
ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE
CGIAR
UF IFAS UNIVERSITY of FLORIDA

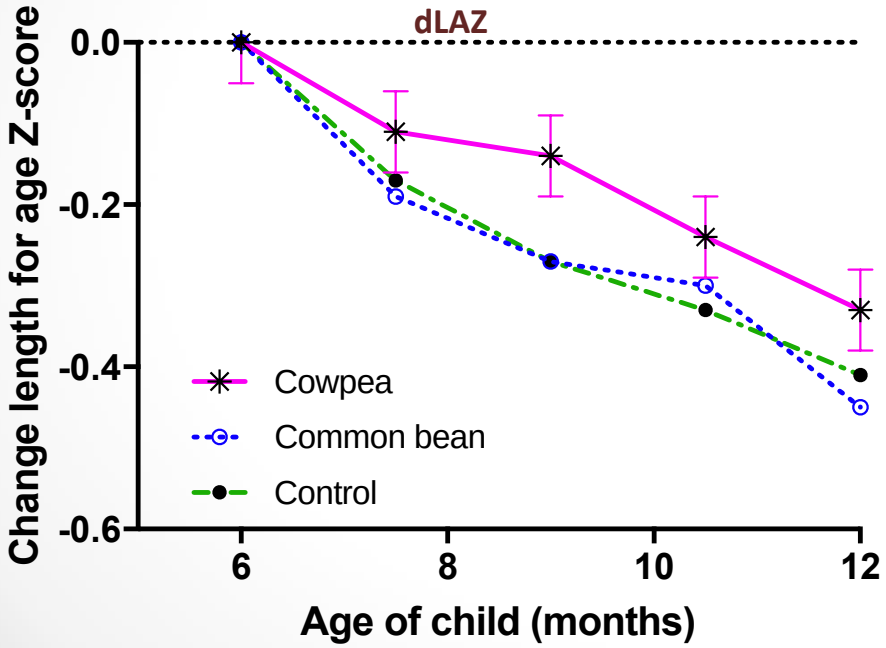
SHINE study

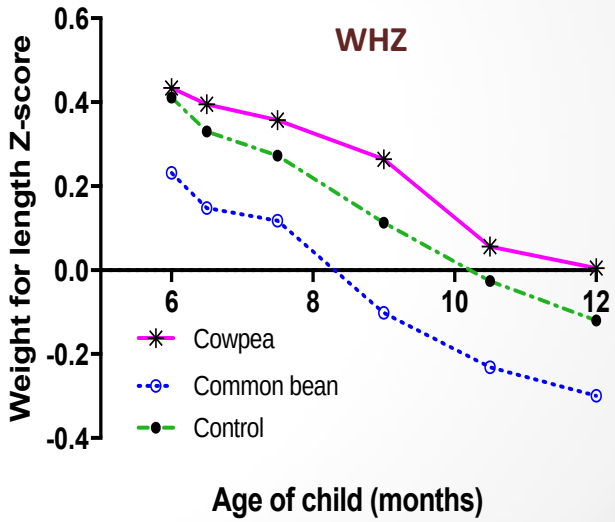
- Focus on: Effect of improved water, sanitation and hygiene and/or improved infant feeding on child stunting and anemia at 18 months age.
- Rural Zimbabwe - randomized control trial
- 5280 participants
- Measure primary outcomes after two years of intervention:
  1. Length and hemoglobin at 18 months.
  2. Infant EED, anthropometric measurements, program impact pathways, breastfeeding, maternal/infant HIV effect, diarrhea prevalence, child neurodevelopment, mycotoxin exposure, maternal and child microbiota, rotavirus an polio vaccination and adverse birth outcomes.

Legumes and growth

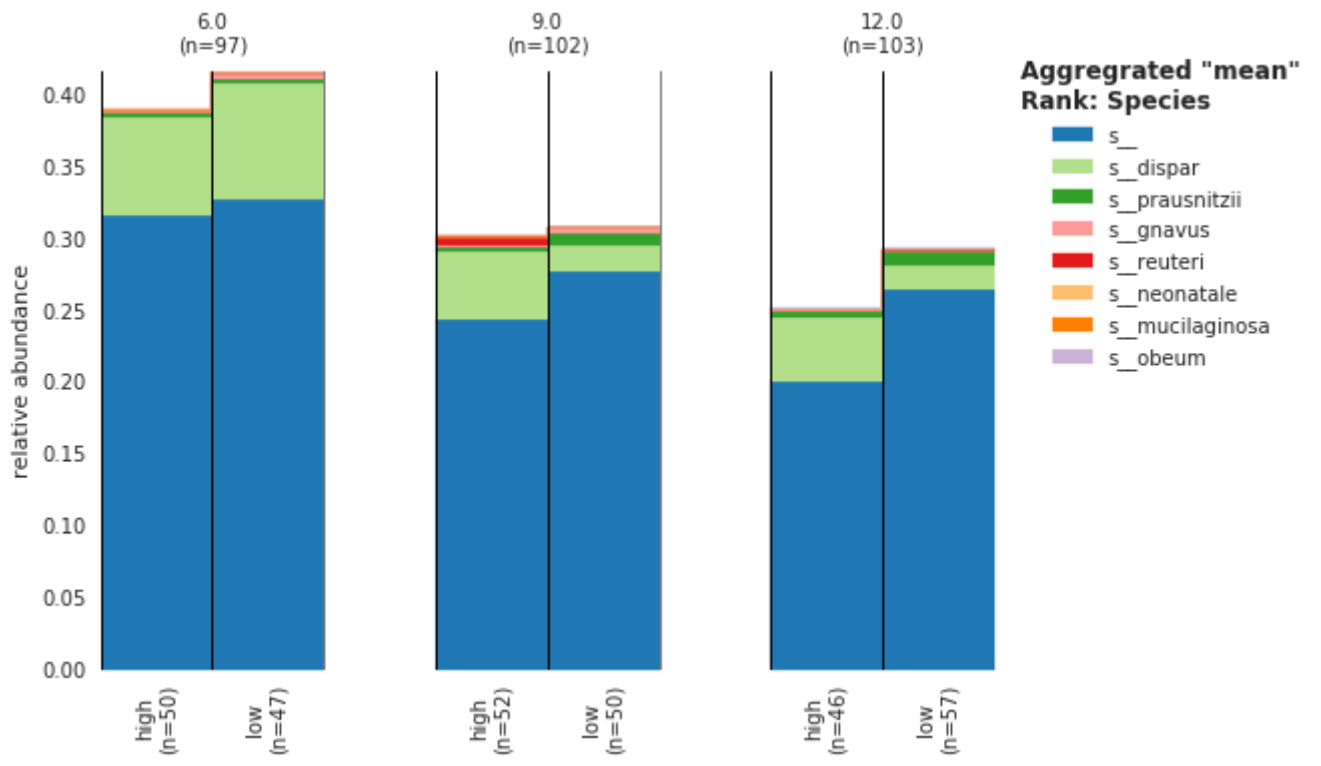
- Randomized, double-blind controlled clinical complementary feeding trial were conducted in Malawi with common bean and cowpea.
- Local legumes were chosen for their nutrient and fiber content; nutrients to provide protein and indigestible carbohydrate to nurture the microbiota, provided about 40% of complementary food requirement.
- Goal to improve gut health & reduce stunting.

Change in LAZ and WHZ in 6-12 mo old





EED and microbiota signature - Species



FEED THE FUTURE
The U.S. Government's Global Hunger & Food Security Initiative

Thank you

USAID FROM THE AMERICAN PEOPLE

BILL & MELINDA GATES foundation

ILRI INTERNATIONAL LIVESTOCK RESEARCH INSTITUTE

CGIAR

UF IFAS UNIVERSITY of FLORIDA