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Environmental Enteric Dysfunction, WASH, and Nutritional Status of Women, Infants, and Young Children:

Findings from Uganda, Sierra Leone, and Nepal

Christopher Duggan, MD, MPH; Jacqueline Lauer, PhD, MPH; Akriti Singh, PhD MPH; Shibani Ghosh, PhD

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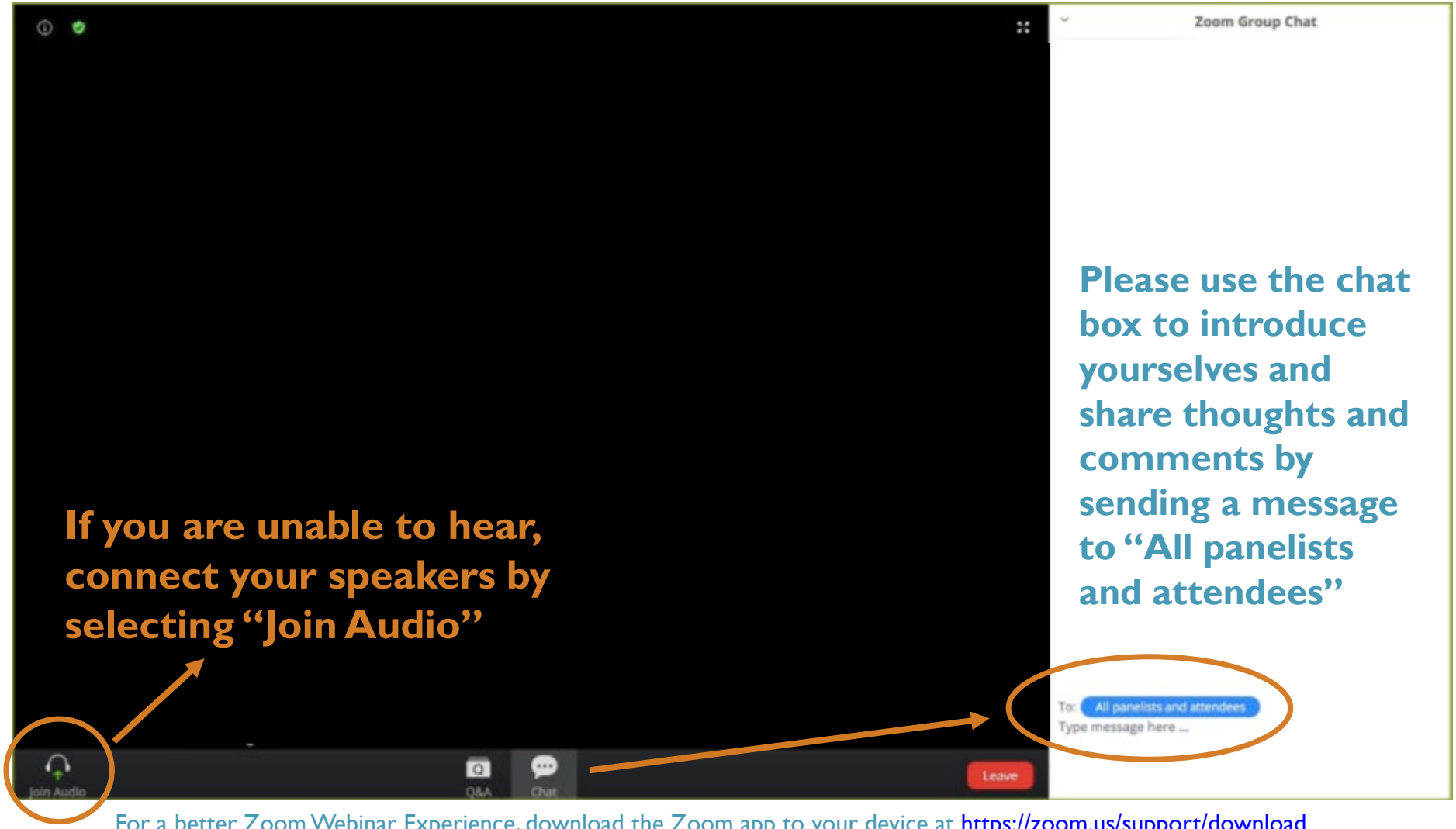

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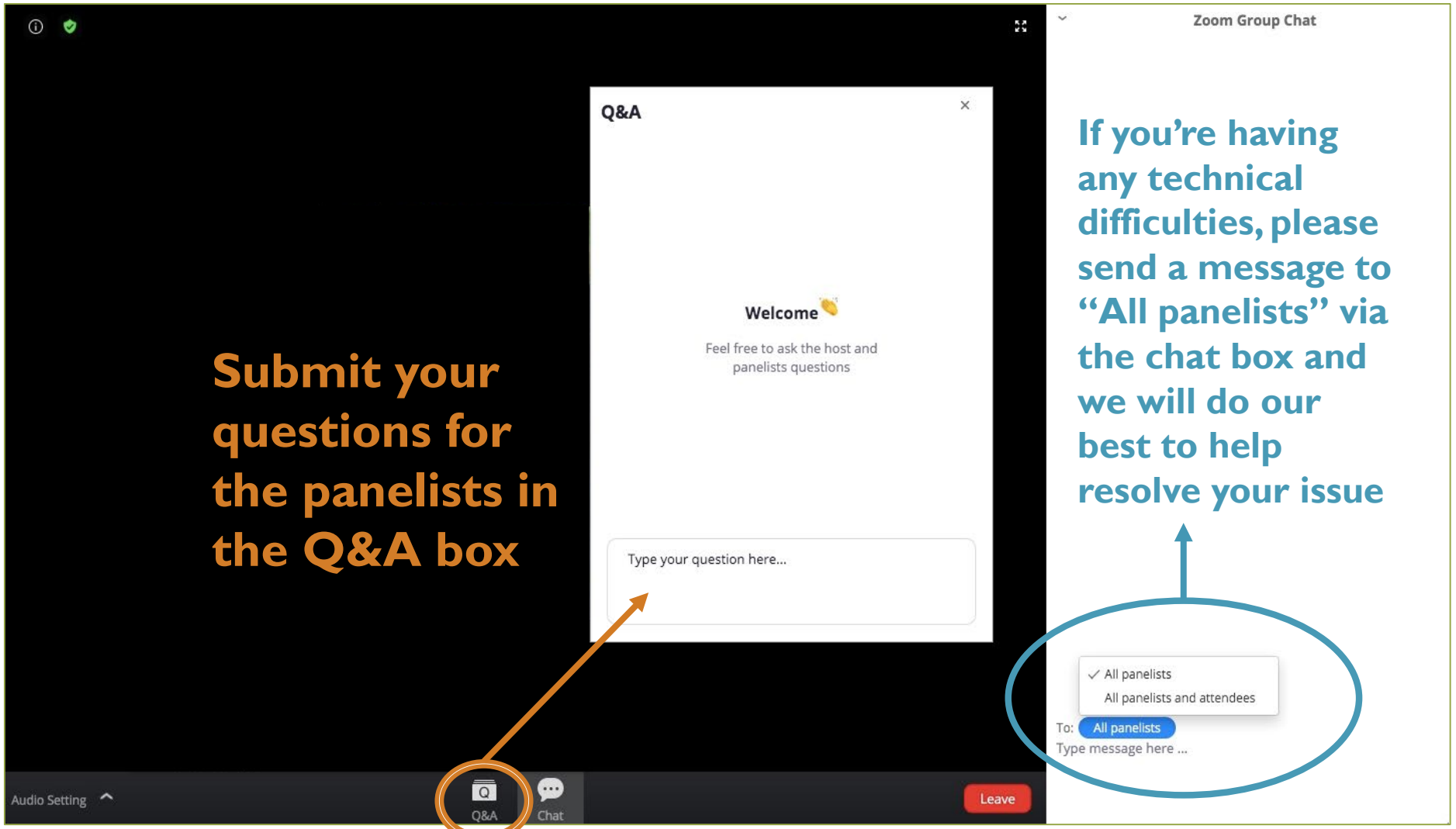
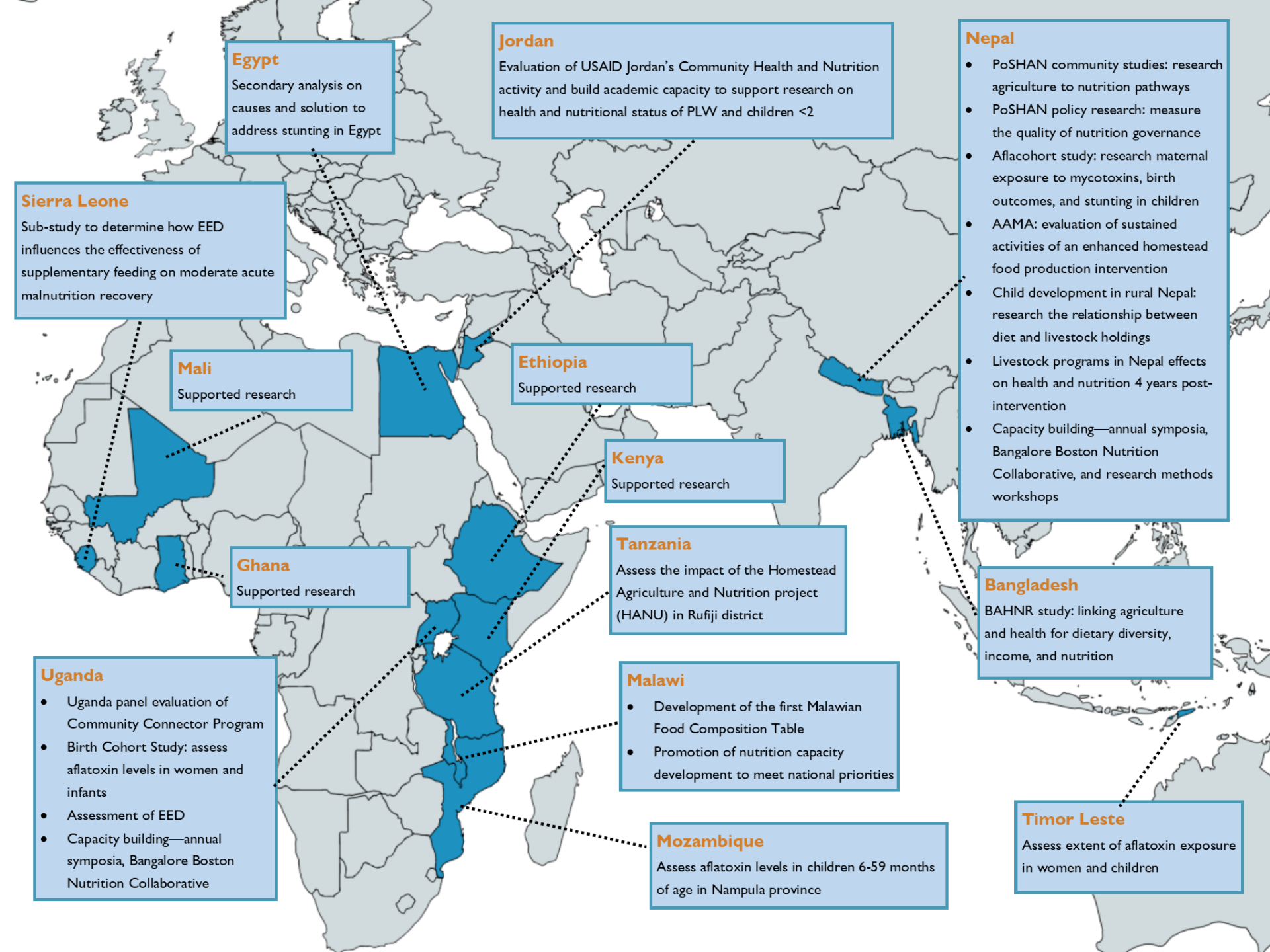
Q&A AND CHAT




Egypt
Secondary analysis on causes and solution to address stunting in Egypt
Jordan
Evaluation of USAID Jordan's Community Health and Nutrition activity and build academic capacity to support research on health and nutritional status of PLW and children <2
Nepal
PoSHAN community studies: research agriculture to nutrition pathways
PoSHAN policy research: measure the quality of nutrition governance
Aflacohort study: research maternal exposure to mycotoxins, birth outcomes, and stunting in children
AAMA: evaluation of sustained activities of an enhanced homestead food production intervention
Child development in rural Nepal: research the relationship between diet and livestock holdings
Livestock programs in Nepal effects on health and nutrition 4 years post-intervention
Capacity building—annual symposia, Bangalore Boston Nutrition Collaborative, and research methods workshops
Sierra Leone
Sub-study to determine how EED influences the effectiveness of supplementary feeding on moderate acute malnutrition recovery
Mali
Supported research
Ethiopia
Supported research
Kenya
Supported research
Tanzania
Assess the impact of the Homestead Agriculture and Nutrition project (HANU) in Rufiji district
Ghana
Supported research
Bangladesh
BAHNR study: linking agriculture and health for dietary diversity, income, and nutrition
Uganda
Uganda panel evaluation of Community Connector Program
Birth Cohort Study: assess aflatoxin levels in women and infants
Assessment of EED
Capacity building—annual symposia, Bangalore Boston Nutrition Collaborative
Malawi
Development of the first Malawian Food Composition Table
Promotion of nutrition capacity development to meet national priorities
Mozambique
Assess aflatoxin levels in children 6-59 months of age in Nampula province
Timor Leste
Assess extent of aflatoxin exposure in women and children

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RESEARCH THEME:
NEGLECTED BIOLOGICAL MECHANISMS

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INNOVATION LAB FOR NUTRITION
WEBINAR SERIES

Environmental Enteric Dysfunction, WASH, and Nutritional Status of Women, Infants, and Young Children:
Findings from Uganda, Sierra Leone, and Nepal

WEDNESDAY, AUGUST 19TH
9:00AM - 10:30AM (ET)

CHRISTOPHER DUGGAN
Boston Children's Hospital/Harvard

JACQUELINE LAUER
Boston University

AKRITI SINGH
Tufts University

SHIBANI GHOSH
Tufts University

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EED, WASH, AND NUTRITIONAL STATUS IN UGANDA

Jacqueline Lauer, PhD, MPH

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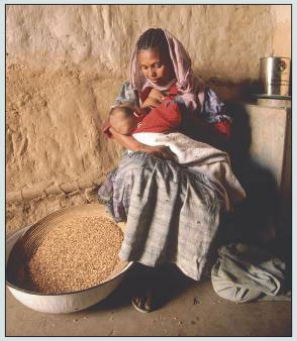
DISCLOSURES

I have no disclosures in relation to this presentation.

THE LANCET
Maternal and Child Nutrition - June, 2013 www.thelancet.com



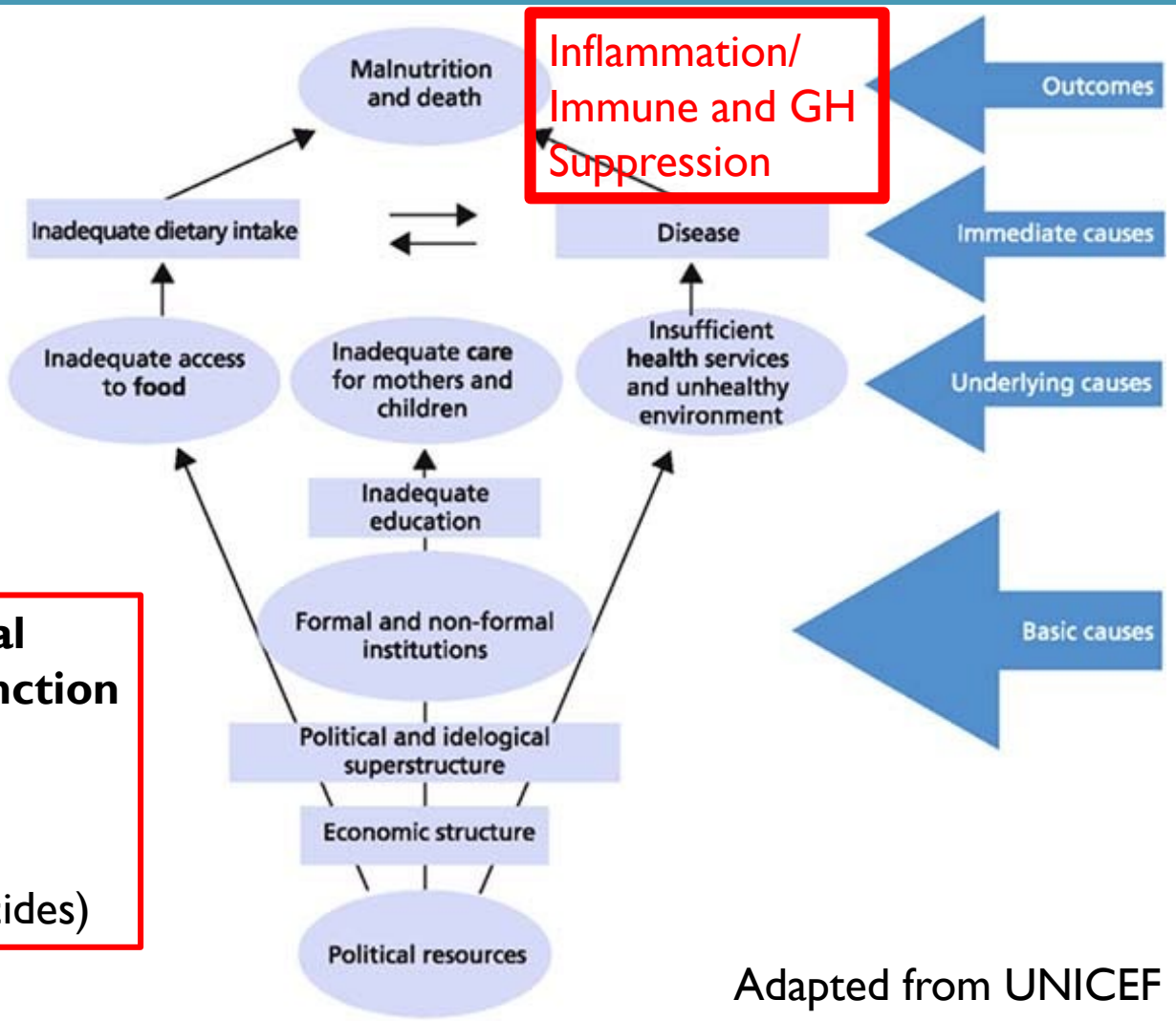
"The Series identifies a set of ten proven nutrition-specific interventions, which if scaled up from present population coverage to cover 90% of the need, would eliminate about 900 000 deaths of children younger than 5 years in the 34 high nutrition-burden countries —where 90% of the world's stunted children live."

Maternal and Child Nutrition

	Number of lives saved*	Cost per life-year saved†
Optimum maternal nutrition during pregnancy		
Maternal multiple micronutrient supplements to all Calcium supplementation to mothers at risk of low intake‡ Maternal balanced energy protein supplements as needed Universal salt iodisation‡	102 000 (49 000–146 000)	$571 (398–1191)
Infant and young child feeding		
Promotion of early and exclusive breastfeeding for 6 months and continued breastfeeding for up to 24 months Appropriate complementary feeding education in food secure populations and additional complementary food supplements in food insecure populations	221 000 (135 000–293 000)	$175 (132–286)
Micronutrient supplementation in children at risk		
Vitamin A supplementation between 6 and 59 months age Preventive zinc supplements between 12 and 59 months of age	145 000 (30 000–216 000)	$159 (106–766)
Management of acute malnutrition		
Management of moderate acute malnutrition Management of severe acute malnutrition	435 000 (285 000–482 000)	$125 (119–152)§

Data are number (95% CI) or cost in 2010 international dollars (95% CI). *Effect of each of package when all four packages are scaled up at once. †Cost per life-year saved assumes that a life saved of a child younger than 5 years saves on average 59 life-years, based on WHO data (2011[189]) that life expectancy at birth on average in low-income countries is 60, and that most deaths of children younger than 5 years occur in the first year of life. To convert to cost per discounted life-year saved multiply these estimates by 59/32 (ie, 1·84). ‡Intervention has effect on maternal or child morbidity, but no direct effect on lives saved. §Cost per life-year saved by management of severe acute malnutrition only, costs for supplementary feeding for moderate acute malnutrition are currently unavailable.

Table 5: **Effect of packages of nutrition interventions at 90% coverage**



- **Environmental enteric dysfunction**
- Aflatoxins
- Environmental pollutants (air pollution, pesticides)

Adapted from UNICEF (1990)

EED RESEARCH QUESTIONS

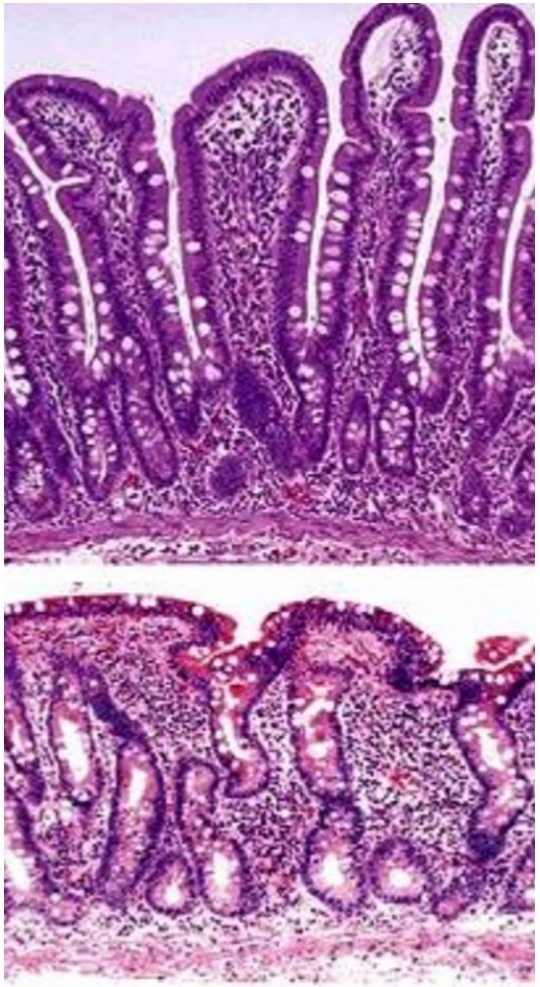
- How should EED be assessed (i.e., what biomarker(s) should we be using)?
- What are the underlying contributors to EED?
- What is the relationship between infant/child EED and poor growth outcomes/micronutrient deficiencies?
- What is the relationship between maternal EED during pregnancy and poor birth outcomes?

WHAT IS EED AND HOW IS ASSESSED?

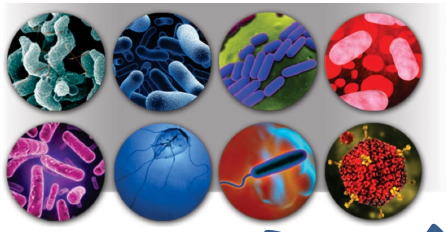
Environmental Enteric Dysfunction

- EED has no universally accepted case definition or diagnostic criteria but is characterized by **changes in the structure and function of the small intestine:**
  - Blunting of the villi
  - Reduced epithelial surface area and absorptive capacity
  - Altered mucosal barrier integrity
  - Intestinal and systemic Inflammation

- It is postulated that EED develops throughout infancy as the result of **chronic exposure to enteropathogens** due to living in poor water, hygiene, and sanitation (WASH) conditions.

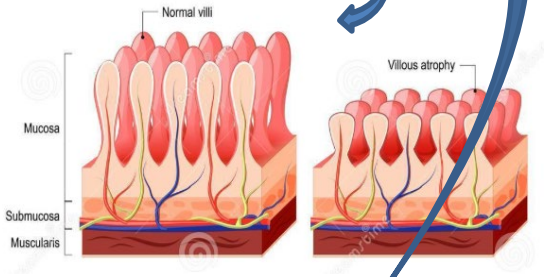


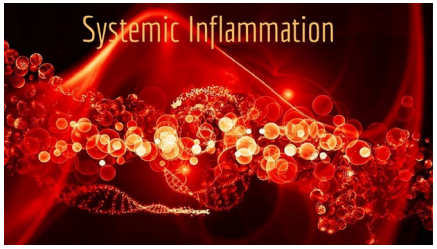
Mbuya MN & Humphrey JH, 2016

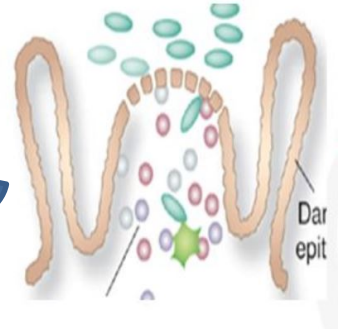



STUNTING
Low height
for age

EED


Normal villi
Villous atrophy
Mucosa
Submucosa
Muscularis


Systemic Inflammation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The American Journal of Clinical Nutrition
Vol. 21, No. 9, September, 1968, pp. 1023-1029
Printed in U.S.A.

Small Intestine Dysfunction in Pakistanis and Americans Resident in Pakistan[1,2]

John Lindenbaum, M.D.[3]

Recovery of Small-Intestinal Structure and Function After Residence in the Tropics

II. Studies in Indians and Pakistanis Living in New York City

CHARLES D. GERSON, M.D., THOMAS H. KENT, M.D., JNAN R. SAHA, M.Sc.,
NAVEED SIDDIQI, M.B.B.S., and JOHN LINDENBAUM, M.D.,
New York, New York; and Iowa City, Iowa

THE VILLUS ARCHITECTURE OF THE SMALL INTESTINE IN THE TROPICS: A NECROPSY STUDY

C. J. G. Chacko, K. A. Paulson, V. I. Mathan and S. J. Baker
Wellcome Research Unit and Departments of Pathology and Medicine, Christian Medical College Hospital, Vellore, India

Plates LX and LXI

Intestinal permeability, mucosal injury, and growth faltering in Gambian infants

P. G. LUNN C. A. NORTHROP-CLEWES R. M. DOWNES

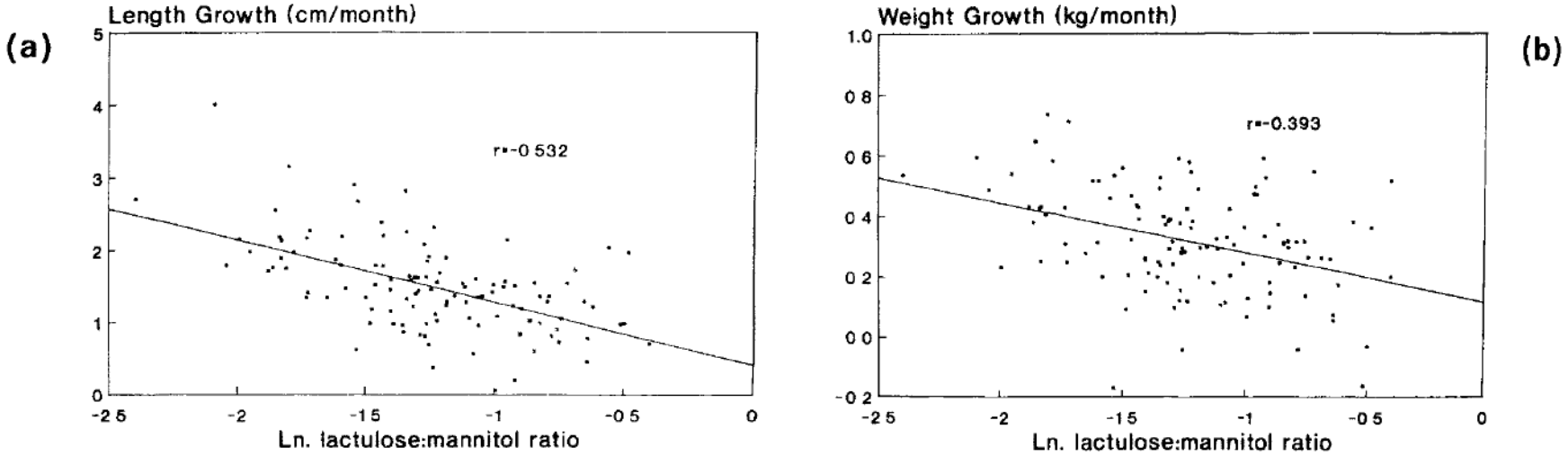


Fig 2—The relation between intestinal permeability (expressed as $\log_e$ lactulose:mannitol ratio) and mean monthly (a) length and (b) weight growth of 119 rural Gambian infants.

Significance of regression coefficients, $p < 0{\cdot}001$.

L:M TEST

- **Lactulose sugar**
  - Too large to be absorbed by healthy intestine
  - L is a measure of barrier efficacy
  - EE ↑ lactulose absorption
- **Mannitol sugar**
  - Small and moves across intestine in quantities proportional to absorptive surface area
  - M is a measure of absorptive capacity
  - EE ↓ mannitol absorption

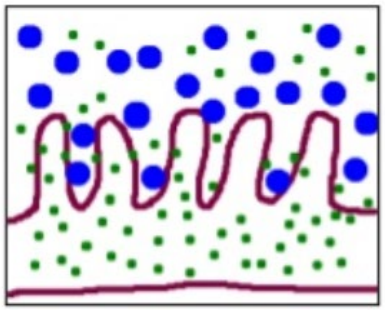
LM Dose

↓

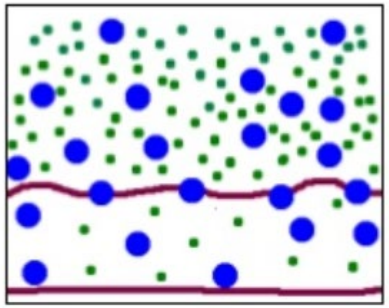
5-Hour Urine Collection

↓

Measure L:M in Urine



Healthy Intestine = Low L:M ratio



EE = High L:M ratio

Courtesy of Audrie Lin and Steve Luby
http://www.slideshare.net/aashishysg/audrie-2013-0731-delhi-conference-ee-pilot-final

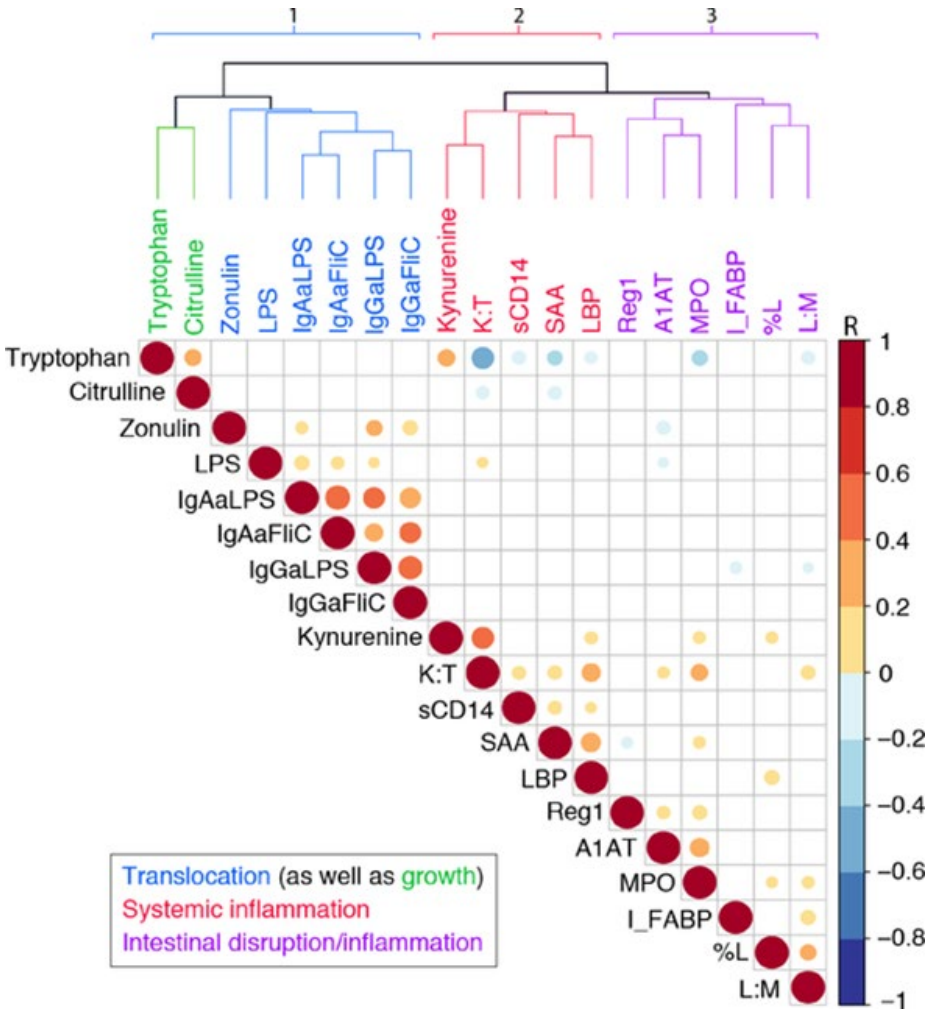
L:M TEST LIMITATIONS

- Time-consuming (5+ hours)
- Burdensome
- Expensive
- High rate of test failure
  - E.g. Spilled/leaked urine or stool contamination
- Lacks formal evaluation studies
- Measures absorptive capacity and permeability, but not necessarily other domains of EED
- Inconsistently correlated with EED symptoms and growth outcomes in young children

Biomarkers of environmental enteric dysfunction (EED)				
Intestinal permeability	Epithelial damage/repair	Microbial translocation	Gut inflammation	Host response to EED
• L:M ratio • L:R ratio • %L excretion • %M, %R excretion • Serum zonulin	• Fecal AAT • Fecal Reg1β • Plasma I-FABP	• LPS • LPS IgA, IgG, EndoCAb • LBP • Flic IgA, IgG • sCD14 • Bacterial DNA	• Fecal MPO • Fecal CAL • Fecal NEO	• Fecal mRNA transcripts

Microbiome dysfunction	Systemic inflammation	Growth hormone resistance
• Microbiome immaturity score (MAZ) • Hydrogen glucose breath test (SIBO)	• Plasma CRP • Plasma AGP • Plasma Kyn, Trp, K:T ratio • Plasma IgG and IgA	• GH • IGF-1 • FGF-21 • SIRT1

Tickell, K.D., Atlas, H.E. and Walson, J.L., 2019. Environmental enteric dysfunction: a review of potential mechanisms, consequences and management strategies. *BMC medicine*, *17*(1), p.181.

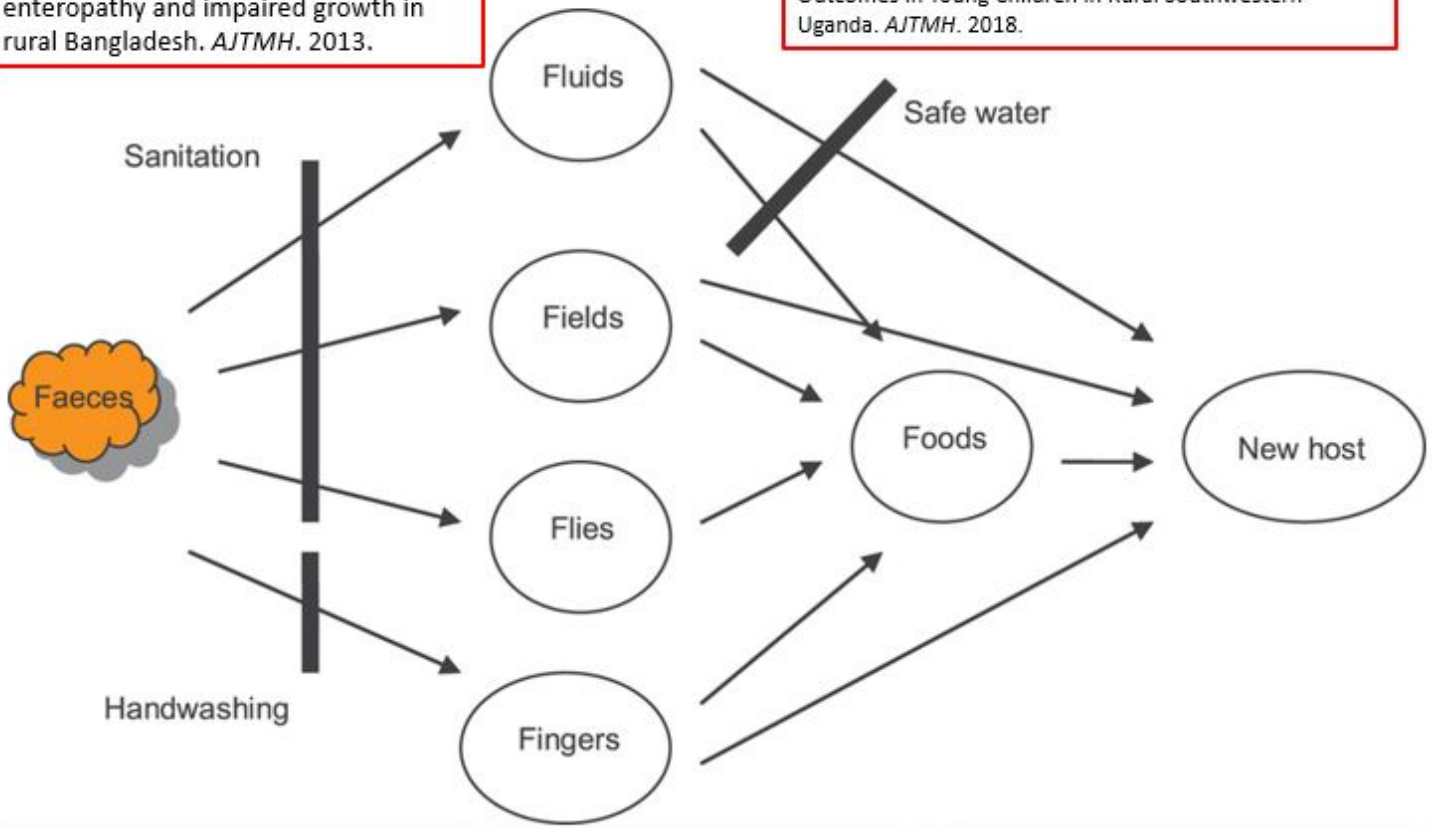


Guerrant RL et al. PLOS ONE 2016: 11(9): e0158772

EED AND WASH

Lin A, et al. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. *AJTMH*. 2013.

Lauer JM, et al. Unsafe Drinking Water Is Associated with Environmental Enteric Dysfunction and Poor Growth Outcomes in Young Children in Rural Southwestern Uganda. *AJTMH*. 2018.



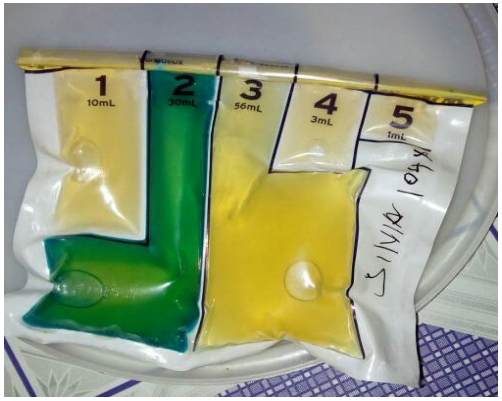
Morita, T, et al. "Mouthing of soil contaminated objects is associated with environmental enteropathy in young children." *TMIH*. 2017.

George CM, et al. Geophagy is associated with environmental enteropathy and stunting in children in rural Bangladesh. *AJTMH. 2015.*

George CM, et al. Fecal markers of environmental enteropathy are associated with animal exposure and caregiver hygiene in Bangladesh. *AJTMH*. 2015.

STUDY DESIGN

- Cross-sectional, observational sub-study in 7 sub-counties in rural southwestern Uganda, nested within an existing longitudinal birth cohort study (UBCS, NCT04233944).
- EED was assessed at 12-16 months using the 4-5 hr L:M test (n=385)
- Anthropometry/ covariate data were abstracted from the birth cohort study, with visits every 3 months
- Water quality was assessed at 6 months using a portable water quality test.



The Aquagenx Compartment Bag Test (CBT) detects and quantifies (MPN) *E. coli* bacteria in a 100 mL water sample.

WATER QUALITY BY SOURCE

TABLE 2

Comparison of water quality (safe vs. unsafe)* by main water source among 377 households in southwestern Uganda

Main water source	Total	Safe, *n* (%)	Unsafe, *n* (%)
Piped	8	4 (50.0)	4 (50.0)
Public tap	45	26 (57.8)	19 (42.2)
Tube well/borehole	57	17 (29.8)	40 (70.2)
Protected well/spring	85	35 (41.2)	50 (58.8)
Unprotected well/spring	110	54 (49.1)	56 (50.9)
Rain water	15	11 (73.3)	4 (26.7)
Surface water	54	17 (31.5)	37 (68.5)
Other	3	1 (33.3)	2 (66.7)
Total	377	165 (43.8)	212 (56.2)

According to the World Health Organization, improved drinking water sources are piped water, public taps, tube wells/boreholes, protected wells/springs, and rainwater. Unimproved sources are unprotected wells/springs and surface water.

*Safe water is defined as the lack of the presence of *Escherichia coli* contamination according to the results of a compartment bag test. Unsafe water is defined as any *E. coli* contamination detected.

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WATER QUALITY AND EED (L:M)

TABLE 3

Association between water quality (safe vs. unsafe)† and L:M test results in unadjusted and adjusted linear regression models‡

	Unadjusted linear regression model	Adjusted linear regression model
Ln L:M ratio	−0.23 (−0.47, 0.00)*	−0.22 (−0.44, 0.00)*
Urinary lactulose, % dose excreted	−0.09 (−0.16, −0.02)*	−0.08 (−0.14, −0.01)*
Urinary mannitol, % dose excreted	−0.26 (−1.13, 0.60)	−0.09 (−1.05, 0.87)
LMER	−0.02 (−0.04. 0.003)	−0.02 (−0.04, 0.01)

L:M = lactulose:mannitol; LMER = L:M excretion ratio. Cells present β coefficient and 95% confidence interval, * *P*-value < 0.05.

† Safe water is defined as the lack of the presence of *Escherichia coli* contamination according to the results of a compartment bag test. Unsafe water is defined as any *E. coli* contamination detected.

‡ Unadjusted and adjusted regression models adjusted for subcounty clustering. Adjusted regression model controls for gender of child, gender of household head, mother's height, caregiver education level, family size, and asset score.

Am. J. Trop. Med. Hyg., 99(6), 2018, pp. 1606–1612
doi:10.4269/ajtmh.18-0143

Unsafe Drinking Water Is Associated with Environmental Enteric Dysfunction and Poor Growth Outcomes in Young Children in Rural Southwestern Uganda

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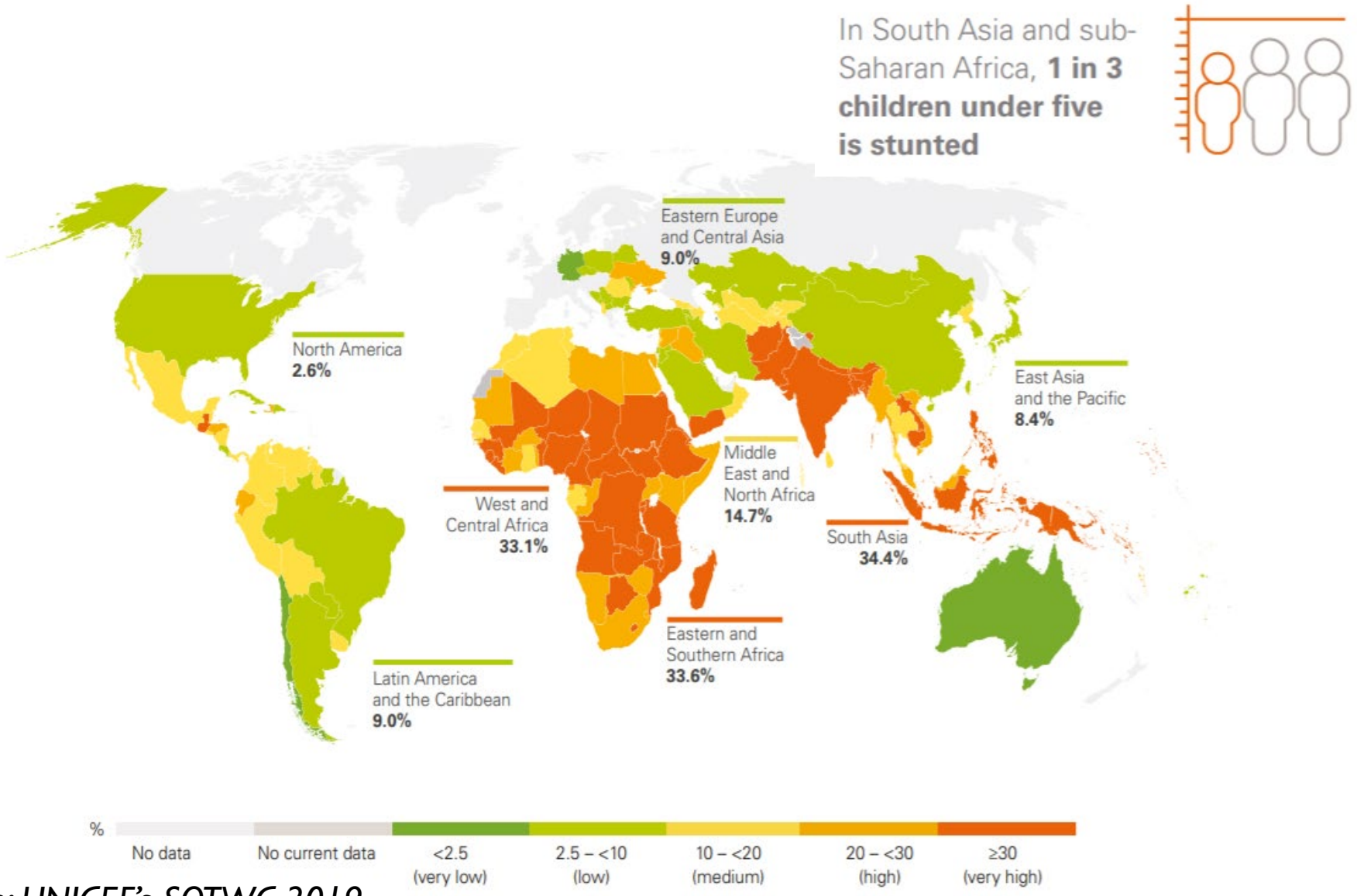
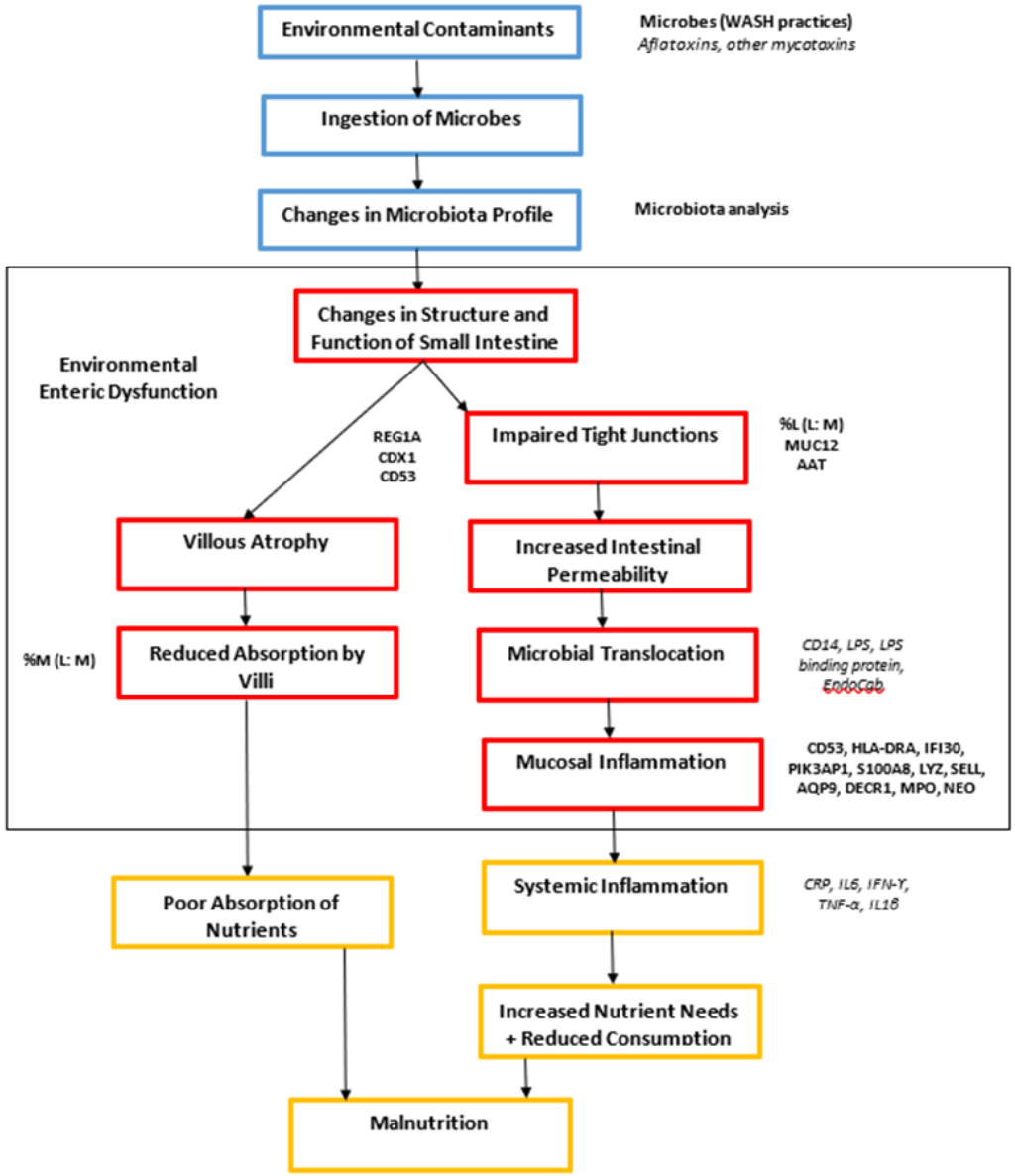
[1]*Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy, Tufts University, Boston, Massachusetts;* [2]*United States Agency for International Development (USAID) Feed the Future Innovation Lab for Nutrition, Tufts University, Boston, Massachusetts;* [3]*Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, Massachusetts;* [4]*Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts;* [5]*Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts;* [6]*Tufts University Cummings School of Veterinary Medicine, Tufts University School of Engineering, Medford, Massachusetts;* [7]*Department of Agribusiness and Natural Resource Economics, Makerere University, Kampala, Uganda;* [8]*School of Food Technology and Nutrition, Makerere University, Kampala, Uganda*

EED AND LINEAR GROWTH GROWTH



Source: UNICEF's SOTWC 2019


Environmental Contaminants
Microbes (WASH practices)
Aflatoxins, other mycotoxins
Ingestion of Microbes
Changes in Microbiota Profile
Microbiota analysis
Changes in Structure and Function of Small Intestine
Environmental Enteric Dysfunction
REG1A
CDX1
CD53
Impaired Tight Junctions
%L (L: M)
MUC12
AAT
Villous Atrophy
Increased Intestinal Permeability
%M (L: M)
Reduced Absorption by Villi
Microbial Translocation
CD14, LPS, LPS binding protein, EndoCab
Mucosal Inflammation
CD53, HLA-DRA, IFI30, PIK3AP1, S100A8, LYZ, SELL, AQP9, DECR1, MPO, NEO
Poor Absorption of Nutrients
Systemic Inflammation
CRP, IL6, IFN-Y, TNF-α, IL1ß
Increased Nutrient Needs + Reduced Consumption
Malnutrition

STUDY DESIGN

- Cross-sectional analysis of 6-mo-old infants (n = 548) enrolled in the UBCS
- study

- EED was assessed via serum concentrations of anti-flagellin and anti- LPS immunoglobulins (Igs) (Gewirtz Lab, UGA)

- SI was assessed via serum concentrations of α1-acid glycoprotein (AGP) and C-reactive protein (CRP) (VitMin Lab, Willstaett, Germany)

- Iron status was assessed via serum concentrations of hemoglobin (Hb), soluble transferrin receptor (sTfR), and ferritin (VitMin Lab, Willstaett, Germany)

- Associations were assessed using adjusted linear regression analysis (STATA 15)

TABLE 4 Associations between EED (anti-flagellin and anti-LPS Igs) and SI (AGP and CRP) biomarkers and anthropometric measures for 548 Ugandan infants aged 6 mo old[1]

	LAZ		WAZ		WLZ	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
EED, OD						
Anti-flagellin IgA	−0.21 (−0.41, 0.00)	0.048*	0.00 (−0.21, 0.22)	0.98	0.18 (−0.07, 0.43)	0.14
Anti-flagellin IgG	−0.29 (−0.87, 0.28)	0.30	0.04 (−0.44, 0.53)	0.85	0.40 (−0.05, 0.85)	0.08
Anti-LPS IgA	−0.23 (−0.44, −0.03)	0.029*	−0.02 (−0.23, 0.18)	0.84	0.18 (−0.10, 0.45)	0.19
Anti-LPS IgG	−0.33 (−0.58, −0.09)	0.011*	0.02 (−0.43, 0.47)	0.92	0.38 (−0.15, 0.92)	0.15
SI						
AGP, g/L	−0.29 (−0.47, −0.11)	0.004*	−0.03 (−0.26, 0.19)	0.52	0.14 (−0.17, 0.45)	0.35
CRP, mg/L	−0.11 (−0.16, −0.06)	0.000*	−0.06 (−0.14, 0.02)	0.13	0.01 (−0.08, 0.10)	0.83

[1] Values are β-coefficients (95% CIs) and *P* values from linear regression models with a continuous biomarker term. All biomarkers were ln-transformed before analysis. Adjusted models controlled for maternal age, maternal height, household head educational level, infant sex, infant birth weight, household food security status (HFIAS), improved water source (yes/no), and subcounty clustering. EED models also controlled for inflammation (i.e., AGP).* $P < 0.05$. AGP, α1-acid glycoprotein; CRP, C-reactive protein; EED, environmental enteric dysfunction; HFIAS, Household Food Insecurity Access Scale; Ig, immunoglobulin; LAZ, length-for-age *z* score; OD, optical density; SI, systemic inflammation; WAZ, weight-for-age *z* score; WLZ, weight-for-length *z* score.

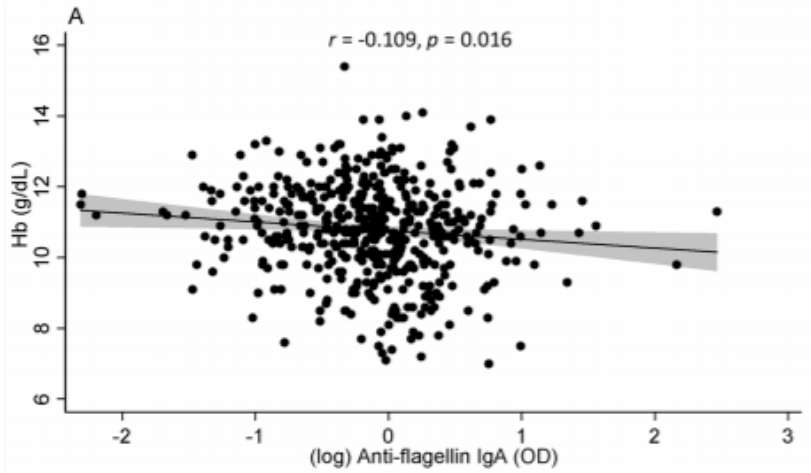
TABLE 5 Associations between EED biomarkers (anti-flagellin and anti-LPS Igs) and iron status (Hb, sTfR, and ferritin) for 548 Ugandan infants aged 6 mo old[1]

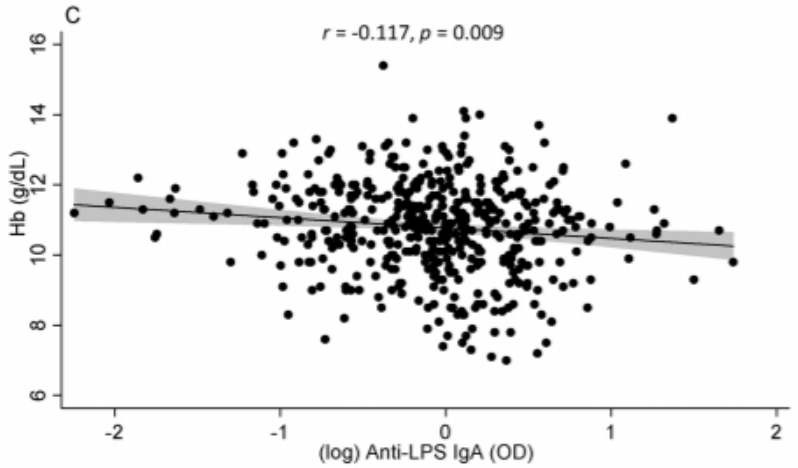
	Hb,[2] g/dL		sTfR,[3] mg/L (adj)		Ferritin,[3] μg/L (adj)	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Anti-flagellin IgA, OD	−0.24 (−0.45, −0.02)	0.034*	0.31 (−0.72, 1.34)	0.53	1.94 (−0.87, 4.47)	0.16
Anti-flagellin IgG, OD	−0.58 (−1.13, 0.00)	0.049*	2.31 (0.34, 4.28)	0.025*	7.65 (0.28, 15.58)	0.06
Anti-LPS IgA, OD	−0.26 (−0.51, 0.00)	0.047*	0.53 (−0.39, 1.45)	0.24	2.74 (0.36, 5.12)	0.027*
Anti-LPS IgG, OD	−0.60 (−1.28, 0.09)	0.08	3.13 (0.75, 5.51)	0.013*	4.87 (−1.07, 10.80)	0.10

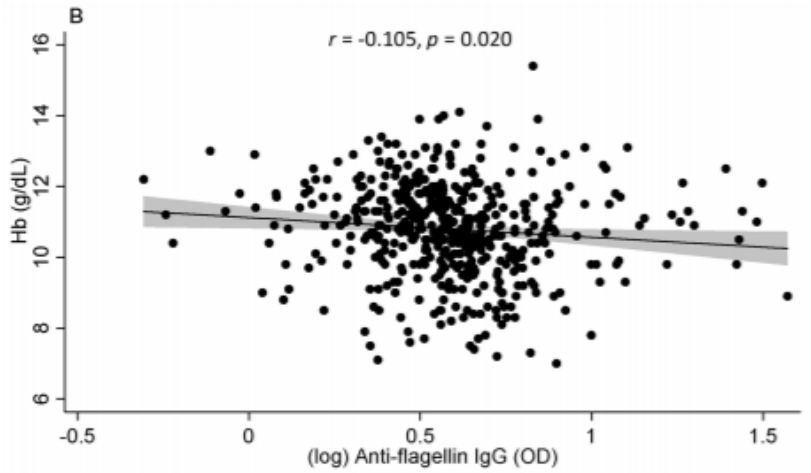
[1] Values are β-coefficients (95% CIs) and *P* values from linear regression models with a continuous biomarker term. EED biomarkers were ln-transformed before analysis. Models controlled for infant sex, age, and subcounty clustering. *$P < 0.05$. adj, adjusted; BRINDA, Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia; EED, environmental enteric dysfunction; Hb, hemoglobin; Ig, immunoglobulin; OD, optical density; sTfR, soluble transferrin receptor.

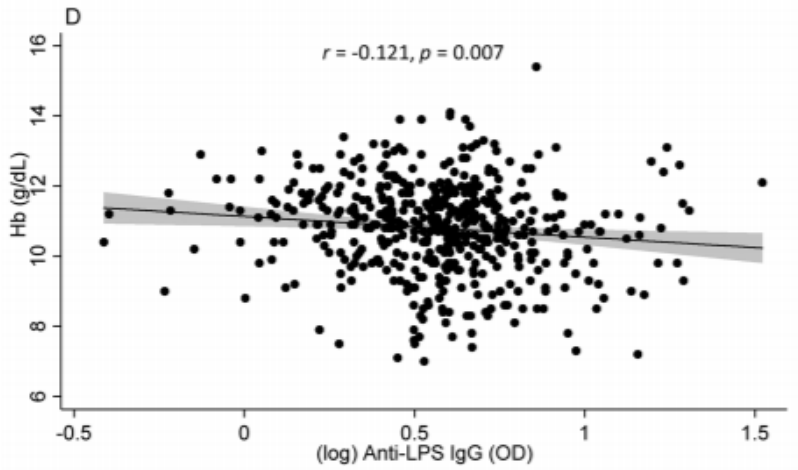
[2] $n = 488$.

[3] sTfR and ferritin adjusted for inflammation using the BRINDA method (36).


A
r = -0.109, p = 0.016
Hb (g/dL)
(log) Anti-flagellin IgA (OD)


C
r = -0.117, p = 0.009
Hb (g/dL)
(log) Anti-LPS IgA (OD)


B
r = -0.105, p = 0.020
Hb (g/dL)
(log) Anti-flagellin IgG (OD)


D
r = -0.121, p = 0.007
Hb (g/dL)
(log) Anti-LPS IgG (OD)

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The Journal of Nutrition
Community and International Nutrition

Markers of Environmental Enteric Dysfunction Are Associated with Poor Growth and Iron Status in Rural Ugandan Infants

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MATERNAL EED AND BIRTH OUTCOMES

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STUDY DESIGN

Objective

To examine the relation between maternal EED and adverse birth outcomes in a sample of 258 pregnant Ugandan women and their newborn infants.

Methods

Prospective cohort study in Mukono, Uganda.

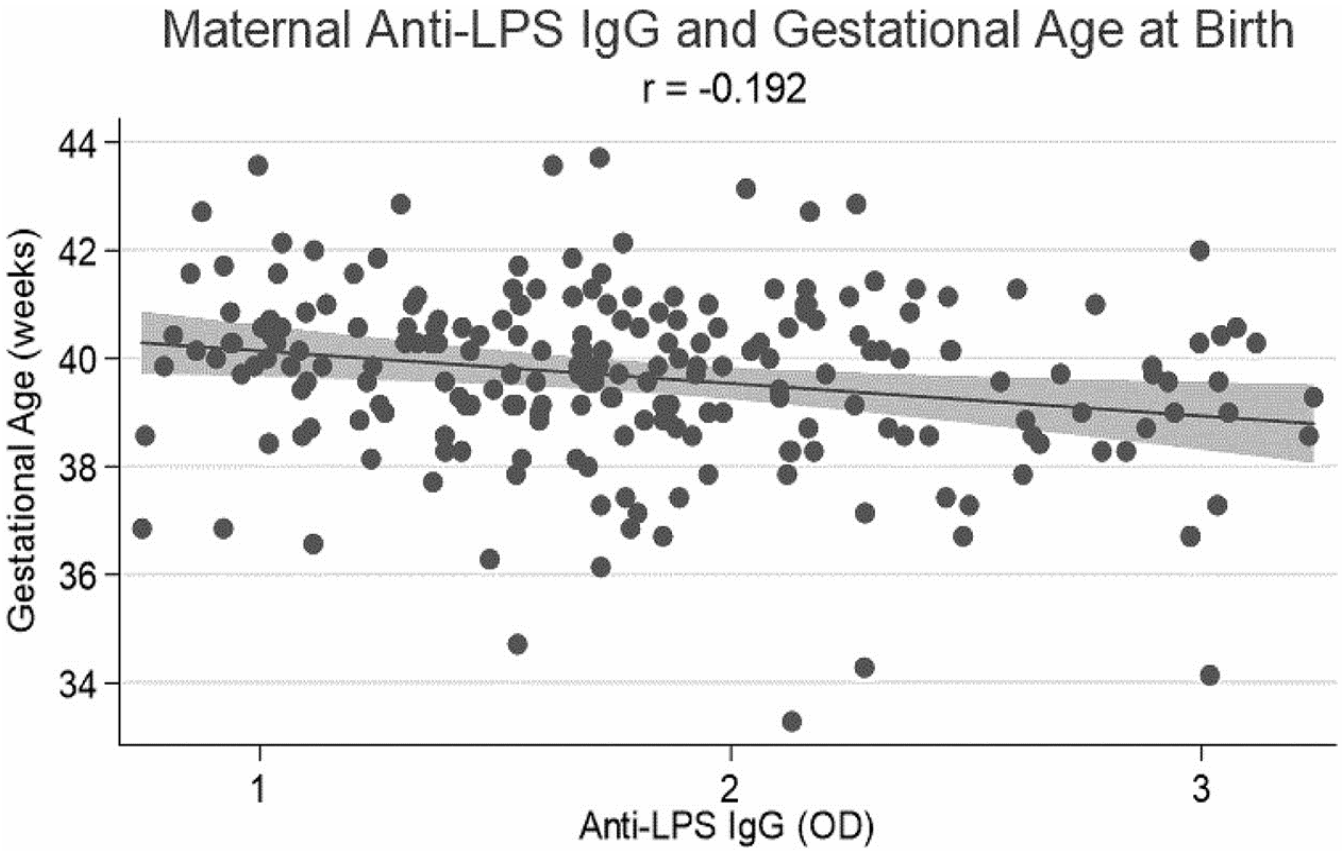
EED was measured **by urinary L:M ratio and serum anti-flagellin/anti-LPS biomarkers.**

Covariates were obtained from **survey data collected at 2 time points** during pregnancy.

Associations were assessed through the use of unadjusted and adjusted **linear regression models**.

VISIT SCHEDULE

Visit	Time	Location	Description
#1: Enrollment visit (n=254)	After first prenatal visit (9-27 weeks gestation)	MHC IV	• Ultrasound scan • Hb test/blood pressure tests • Venous blood draw • Anthropometry (height, weight, MUAC) • Questionnaire
#2: L:M test (n=247)	< 1 week after enrollment visit	Participants' residence	• Solution containing 5 grams of lactulose and 2 grams of mannitol • 4-hour timed urine collection
#3: Follow-up visit (n=236)	3 weeks prior to participants' EDD	Participants' residence	• Anthropometry (weight, MUAC) • Questionnaire • Water quality test
#4: Delivery visit (n=232 total, 220 born alive)	Within 48 hours of delivery	Participants' residence or health facility	• Infant anthropometry (length, weight, head circumference)



The American Journal of Clinical Nutrition, Volume 108, Issue 4, October 2018, Pages 889–896, https://doi.org/10.1093/ajcn/nqy176

Higher concentrations of anti-flagellin IgG and anti-LPS IgG were **significantly associated with shorter length of infant gestational age at birth, lower length at birth, and lower LAZ at birth**

TABLE 3

Biomarkers of maternal EED as predictors of infant gestational age (weeks), length (centimeters), and LAZ at birth ($n = 220$) in unadjusted and adjusted linear regression models[1]

	Gestational age, wk		Length, cm		LAZ	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
L:M	0.04 (−0.22, 0.30) $P = 0.761$	0.02 (−0.24, 0.29) $P = 0.858$	0.04 (−0.21, 0.30) $P = 0.746$	0.01 (−0.22, 0.24) $P = 0.901$	0.03 (−0.11, 0.16) $P = 0.712$	0.01 (−0.11, 0.13) $P = 0.842$
%LE	0.02 (−0.25, 0.29) $P = 0.897$	0.006 (−0.27, 0.28) $P = 0.968$	−0.03 (−0.29, 0.24) $P = 0.850$	−0.03 (−0.27, 0.20) $P = 0.776$	−0.008 (−0.15, 0.13) $P = 0.915$	−0.009 (−0.13, 0.11) $P = 0.881$
Anti-flagellin IgA	−0.26 (−0.96, 0.44) $P = 0.463$	−0.37 (−1.10, 0.36) $P = 0.322$	0.11 (−0.57, 0.79) $P = 0.743$	−0.15 (−0.79, 0.49) $P = 0.643$	0.05 (−0.31, 0.41) $P = 0.785$	−0.11 (−0.44, 0.23) $P = 0.533$
Anti-LPS IgA	−0.24 (−1.06, 0.58) $P = 0.566$	−0.25 (−1.10, 0.60) $P = 0.564$	−0.36 (−1.15, 0.43) $P = 0.372$	−0.48 (−1.22, 0.25) $P = 0.195$	−0.21 (−0.63, 0.21) $P = 0.323$	−0.28 (−0.67, 0.10) $P = 0.152$
Anti-flagellin IgG	−0.79 (−1.66, 0.08) $P = 0.075$	−0.89 (−1.77, −0.01) $P = 0.047^*$	−0.68 (−1.52, 0.16) $P = 0.110$	−0.80 (−1.55, −0.05) $P = 0.036^*$	−0.38 (−0.83, 0.06) $P = 0.089$	−0.44 (−0.83, −0.05) $P = 0.029^*$
Anti-LPS IgG	−0.98 (−1.82, −0.15) $P = 0.021^*$	−1.01 (−1.87, −0.17) $P = 0.019^*$	−0.50 (−1.32, 0.32) $P = 0.234$	−0.79 (−1.54, −0.04) $P = 0.039^*$	−0.29 (−0.72, 0.15) $P = 0.197$	−0.40 (−0.79, −0.01) $P = 0.043^*$

[1] Values are β-coefficients (95% CIs) and P values; all EED biomarkers were natural log transformed before analysis. Adjusted model controls for maternal age, height, diastolic blood pressure, years of education, first pregnancy (yes/no), $^*P < 0.05$. Household Food Insecurity Access Scale score, safe water (yes/no), and infant birth weight. EED; environmental enteric dysfunction; LAZ, length-for-age z score; L:M, lactulose:mannitol; %LE, percentage lactulose excretion.

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Article Contents

Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda

Jacqueline M Lauer ✉, Christopher P Duggan, Lynne M Ausman, Jeffrey K Griffiths, Patrick Webb, Edgar Agaba, Nathan Nshakira, Hao Q Tran, Andrew T Gewirtz, Shibani Ghosh

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CONCLUSIONS

- Key challenges persist, including a lack of agreed-upon case-definition and diagnostic criteria for EED
  - Given that EED has multiple domains, a multi-plex panel of biomarkers may be a promising path forward.

- The connection between poor WASH and EED is still hypothesized but has strong biological plausibility.
  - However, WASH interventions often do not provide sufficient protection from environmental contamination to prevent or ameliorate EED and improve growth outcomes (WASH Benefits).

- There is mounting evidence that EED impairs linear growth in infants and young children in LMICs.
  - More research is needed on the role of EED in birth outcomes, micronutrient deficiencies, and other forms of undernutrition.

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Environmental Enteric Dysfunction during Moderate Acute Malnutrition in Sierra Leone

Akriti Singh, PhD, MPH

Tufts University

USAID
FROM THE AMERICAN PEOPLE

Tufts UNIVERSITY
GERALD J. AND DOROTHY R.
Friedman School of
Nutrition Science and Policy

EED AND ACUTE MALNUTRITION

Chronic T Cell–Mediated Enteropathy in Rural West African Children: Relationship with Nutritional Status and Small Bowel Function

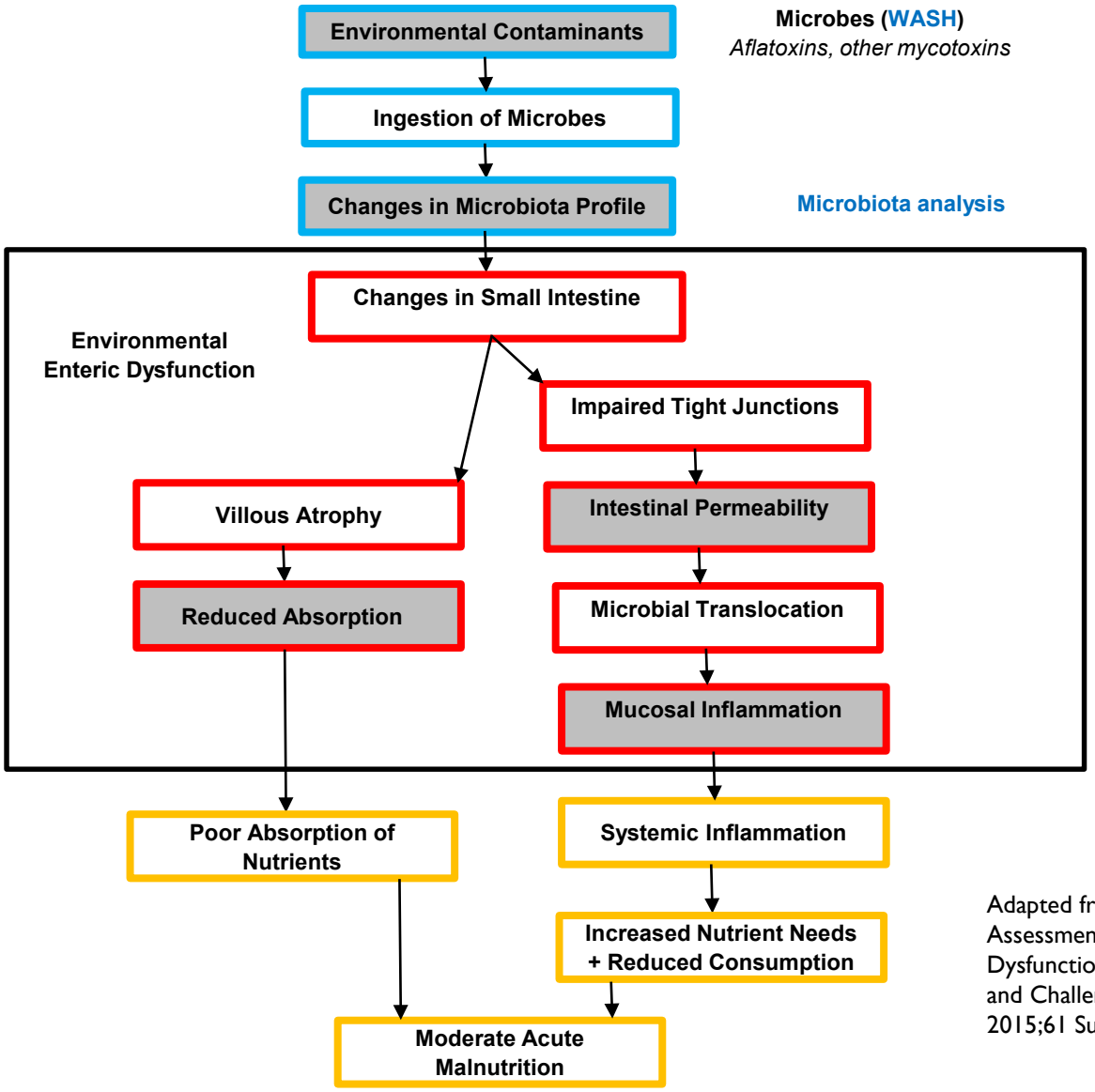
DAVID I. CAMPBELL, SIMON H. MURCH, MARINOS ELIA, PETER B. SULLIVAN, MUSTAPHA S. SANYANG, BABA JOBARTEH, AND PETER G. LUNN

Characterizing the metabolic phenotype of intestinal villus blunting in Zambian children with severe acute malnutrition and persistent diarrhea

Marta Farràs[1,2*], Kanta Chandwe[3], Jordi Mayneris-Perxachs[1], Beatrice Amadi[3], John Louis-Auguste[3,4], Ellen Besa[3], Kanekwa Zyambo[3], Richard Guerrant[5], Paul Kelly[3,4], Jonathan Richard Swann[1*]

ALTERNATIVE EED BIOMARKERS

Characteristics	Permeability	Absorption	Inflammation	Gut Defense
L:M markers				
L:M ratio				
Lactulose recovery				
Mannitol recovery				
Proteins				
Alpha-1-Antitrypsin				
Neopterin				
Myeloperoxidase				
mRNA transcripts				
Gut Inflammation Score				
Gut Permeability Score				
Gut Defense Score				



Adapted from Prendergast AJ et al. Assessment of Environmental Enteric Dysfunction in the SHINE Trial: Methods and Challenges. *Clinical Infectious Diseases.* 2015;61 Suppl 7:S726-32.

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EED AND GUT MICROBIOTA

Duodenal Microbiota in Stunted Undernourished Children with Enteropathy

R.Y. Chen, V.L. Kung, S. Das, M.S. Hossain, M.C. Hibberd, J. Guruge, M. Mahfuz, S.M.K.N. Begum, M.M. Rahman, S.M. Fahim, M.A. Gazi, R. Haque, S.A. Sarker, R.N. Mazumder, B. Di Luccia, K. Ahsan, E. Kennedy, J. Santiago-Borges, D.A. Rodionov, S.A. Leyn, A.L. Osterman, M.J. Barratt, T. Ahmed, and J.I. Gordon

Growth velocity in children with Environmental Enteric Dysfunction is associated with specific bacterial and viral taxa of the gastrointestinal tract in Malawian children

Chandni Desai[1,2], Scott A. Handley[1,2], Rachel Rodgers[3], Cynthia Rodriguez[3], Maria I. Ordiz[3], Mark J. Manary[3,4], Lori R. Holtz[3]*

Effects of microbiota-directed foods in gnotobiotic animals and undernourished children

Jeanette L. Gehrig*, Siddarth Venkatesh*, Hao-Wei Chang*, Matthew C. Hibberd, Vanderlene L. Kung, Jiye Cheng, Robert Y. Chen, Sathish Subramanian, Carrie A. Cowardin, Martin F. Meier, David O'Donnell, Michael Talcott, Larry D. Spears, Clay F. Semenkovich, Bernard Henrissat, Richard J. Giannone, Robert L. Hettich, Olga Ilkayeva, Michael Muehlbauer, Christopher B. Newgard, Christopher Sawyer, Richard D. Head, Dmitry A. Rodionov, Aleksandr A. Arzamasov, Semen A. Leyn, Andrei L. Osterman, Md Iqbal Hossain, Munirul Islam, Nuzhat Choudhury, Shafiqul Alam Sarker, Sayeeda Huq, Imteaz Mahmud, Ishita Mostafa, Mustafa Mahfuz, Michael J. Barratt, Tahmeed Ahmed, Jeffrey I. Gordon†

OBJECTIVES

- Examine the association between EED and growth during, and recovery from moderate acute malnutrition (MAM).
- Compare the microbiota profile of children with MAM, and different levels of EED during MAM.
- Examine the relationship among WASH condition, EED, and microbiota profile of children with MAM.

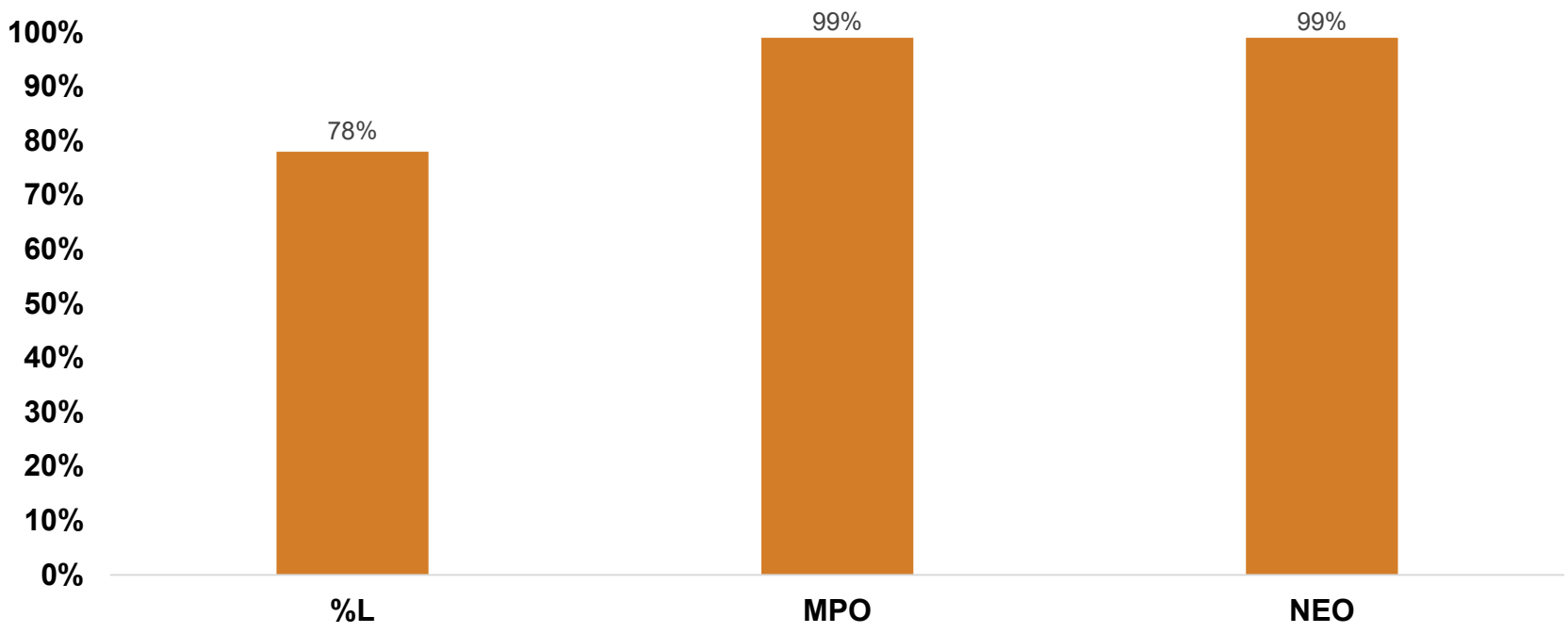
METHOD

- In collaboration with Food Aid Quality Review, Four Foods MAM Treatment Study in Pujehun district of Sierra Leone.
- Children 6-59 months of age were identified as MAM if they had mid-upper-arm circumference (MUAC) ≥ 11.5cm and <12.5cm and no bipedal edema.
- Given one of four foods: Super Cereal Plus with Amylase, Corn Soy Blend Plus, Corn Soy Whey Blend, and Ready to Use Supplementary Food.
- Assessed EED at enrollment into the supplemental feeding program.

RESULTS

Examine the association between EED and growth during, and recovery from moderate acute malnutrition (MAM).

HIGH BURDEN OF EED DURING MAM



High gut defense and low intestinal permeability predict recovery from MAM

	Recovery	
	Unadjusted	Adjusted
	β(95%CI)	β(95%CI)
L: M test		
LMER	0.43(-2.43,3.29)	-1.03(-4.02,1.95)
%L	0.81(-0.13,1.75)	-0.01(-1.02,1.01)
%M	**0.44(0.02,0.86)***	0.24(-0.20,0.69)
Fecal host mRNAs		
GI score	-0.11(-0.32,0.10)	-0.16(-0.38,0.06)
GS score	-0.09(-0.29,0.11)	-0.10(-0.31,0.10)
GD score	**0.39(0.12,0.66)****	**0.36(0.08,0.64)***
Fecal proteins		
AAT	**-1.05(-1.80,-0.29)****	**-1.35(-2.35,-0.36)****
MPO	-0.18(-0.46,0.11)	-0.28(-0.60,0.04)
NEO	0.26(-0.06,0.58)	0.34(-0.05,0.72)
Protein score	-0.14(-0.30,0.01)	-0.16(-0.32,0.01)

Results based on mixed effects regression models. Adjusted model controlled for age, gender, previous severe acute malnutrition status, and study food.

Recovery from MAM defined as achieving MUAC≥ 12.5cm within 12 weeks of supplemental feeding

High inflammation and permeability are associated with growth during MAM

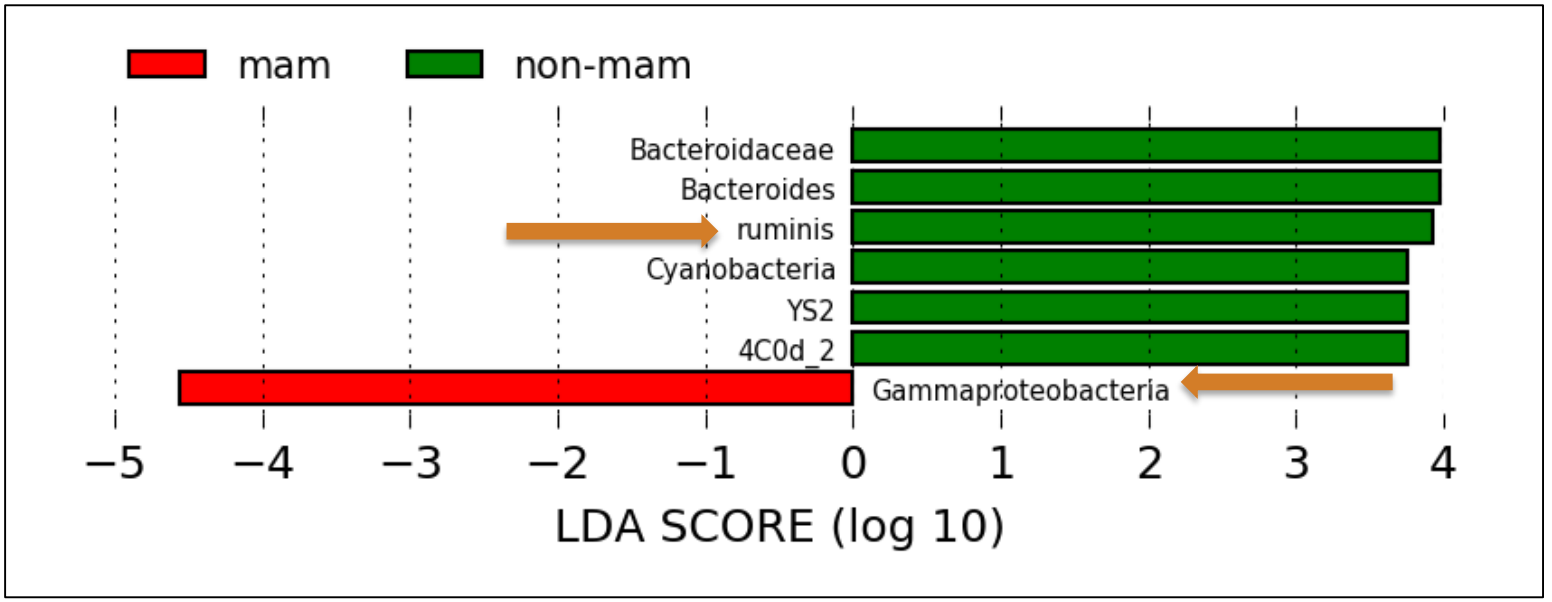
	LAZ at Enrollment		WLZ at Enrollment	
	Unadjusted	Adjusted	Unadjusted	Adjusted
	β(95%CI)	β(95%CI)	β(95%CI)	β(95%CI)
L: M test				
LMER	0.83(-0.26,1.92)	0.39(-0.68,1.46)	0.31(-0.57,1.18)	0.41(-0.11,0.94)
%L	-0.32(-0.76,0.13)	-0.04(-0.57,0.50)	-0.16(-0.48,0.17)	0.16(-0.09,0.42)
%M	-0.12(-0.32,0.08)	0.06(-0.16,0.28)	-0.13(-0.28,0.02)	0.01(-0.14,0.16)
Fecal host mRNAs				
GI score	-0.01(-0.09,0.07)	**-0.08(-0.14,-0.02)***	-0.00(-0.04,0.03)	**-0.03(-0.06,-0.01)***
GS score	0.02(-0.06,0.09)	0.03(-0.01,0.07)	**-0.05(-0.09,-0.01)***	**-0.06(-0.09,-0.02)****
GD score	-0.02(-0.12,0.08)	0.02(-0.10,0.13)	-0.01(-0.10,0.08)	0.04(-0.05,0.12)
Fecal proteins				
AAT	**-0.48(-0.86,-0.10)***	0.16(-0.19,0.51)	**-0.40(-0.59,-0.20)*****	0.02(-0.27,0.31)
MPO	0.14(0.00,0.28)	0.04(-0.15,0.23)	**0.08(0.03,0.14)****	**0.06(0.00,0.12)***
NEO	**0.21(0.02,0.40)***	0.00(-0.17,0.17)	**0.19(0.08,0.29)****	0.03(-0.06,0.11)
Protein score	0.04(-0.05,0.13)	0.02(-0.06,0.10)	0.03(-0.00,0.07)	0.04(-0.01,0.09)

Results based on mixed effects regression models. Adjusted model controlled for age, gender, previous severe acute malnutrition status.

RESULTS

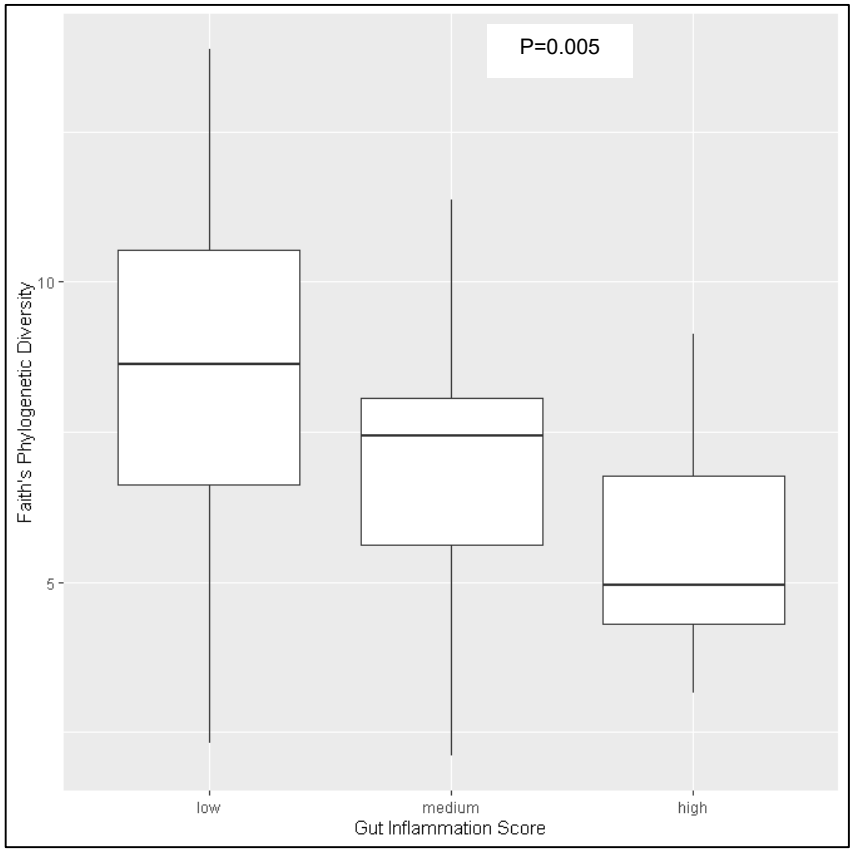
Compare the microbiota profile of children with MAM, and different levels of EED during MAM.

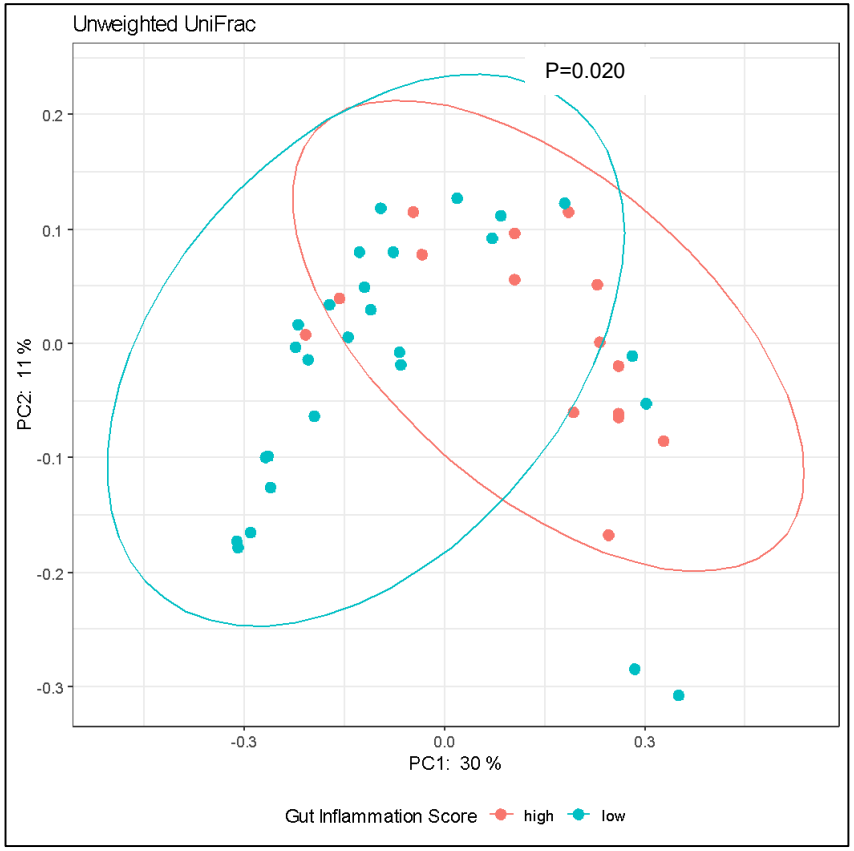
Gut microbiota is enriched in inflammogenic taxa during MAM



Result based on 16S rRNA V4 amplicon sequencing, followed by computational analysis in Quantitative Insights Into Microbial Ecology 2, and examination of differentially abundant taxa using Linear Discriminant Analysis Effect Size algorithm.

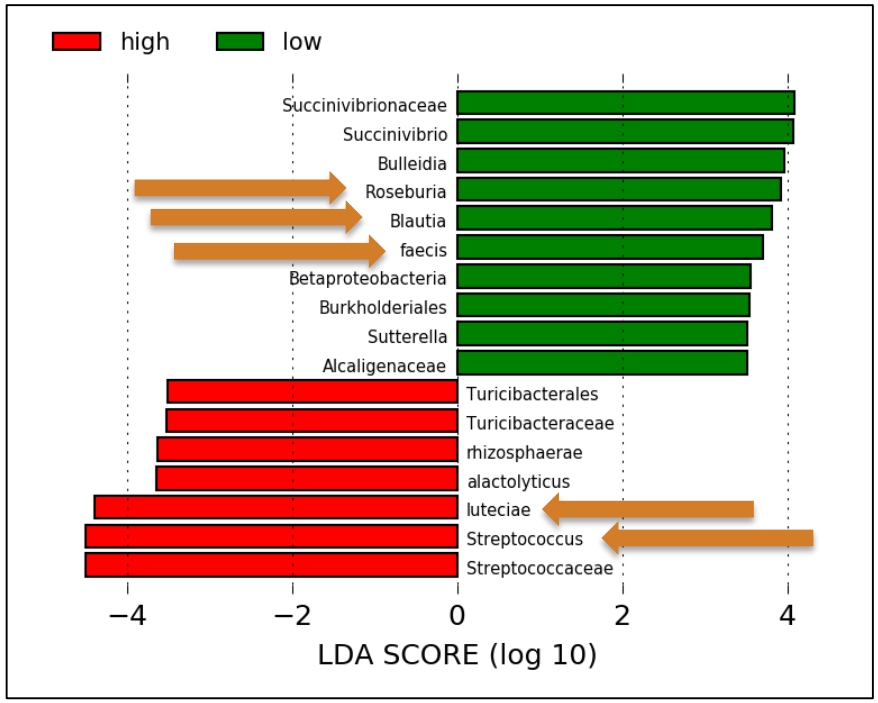
Gut microbial structure is altered during EED





Results based on 16S rRNA V4 amplicon sequencing, followed by computational analysis conducted in Quantitative Insights Into Microbial Ecology 2.

Gut microbiota is enriched in beneficial taxa during low EED



Result based on 16S rRNA V4 amplicon sequencing, followed by computational analysis in Quantitative Insights Into Microbial Ecology 2, and examination of differentially abundant taxa using Linear Discriminant Analysis Effect Size algorithm.

RESULTS

Examine the relationship among WASH condition, EED, and microbiota profile of children with MAM.

Lower intestinal permeability is associated with improved drinking water source

	Unadjusted	Adjusted
	β(95%CI)	β(95%CI)
L:M test		
LMER	**-0.02(-0.03,-0.01)*** **	**-0.02(-0.02,-0.01)*** **
%L	-0.06(-0.12,0.01)	-0.05(-0.10,0.01)
%M	0.05(-0.08,0.17)	0.05(-0.06,0.15)
Host fecal protein		
AAT	**-0.14(-0.27,-0.01)***	**-0.12(-0.22,-0.02)***
MPO	-0.12(-0.43,0.20)	-0.15(-0.44,0.13)
NEO	-0.01(-0.43,0.40)	-0.06(-0.45,0.34)
Host fecal mRNA transcripts		
GI socre	-0.00(-0.26,0.26)	-0.02(-0.25,0.21)
GS score	**-0.21(-0.38,-0.05)***	**-0.17(-0.33,-0.02)***
GD score	0.13(-0.13,0.39)	0.12(-0.11,0.34)

Drinking water source defined as improved vs. unimproved based on UNICEF/WHO Joint Monitoring Program definitions.

Lower intestinal inflammation is associated with improved sanitation facility

	Unadjusted	Adjusted
	β(95%CI)	β(95%CI)
L:M test		
LMER	-0.00(-0.02,0.01)	0.00(-0.01,0.02)
%L	-0.01(-0.05,0.04)	0.01(-0.04,0.05)
%M	0.01(-0.05,0.08)	-0.01(-0.07,0.06)
Host fecal protein		
AAT	0.00(-0.06,0.06)	0.04(-0.04,0.12)
MPO	0.22(-0.11,0.54)	0.21(-0.09,0.51)
NEO	-0.10(-0.30,0.10)	**-0.19(-0.35,-0.02)***
Host fecal mRNA transcripts		
GI score	-0.01(-0.12,0.10)	0.04(-0.07,0.15)
GS score	-0.13(-0.30,0.03)	-0.10(-0.27,0.07)
GD score	-0.13(-0.29,0.04)	-0.16(-0.37,0.05)

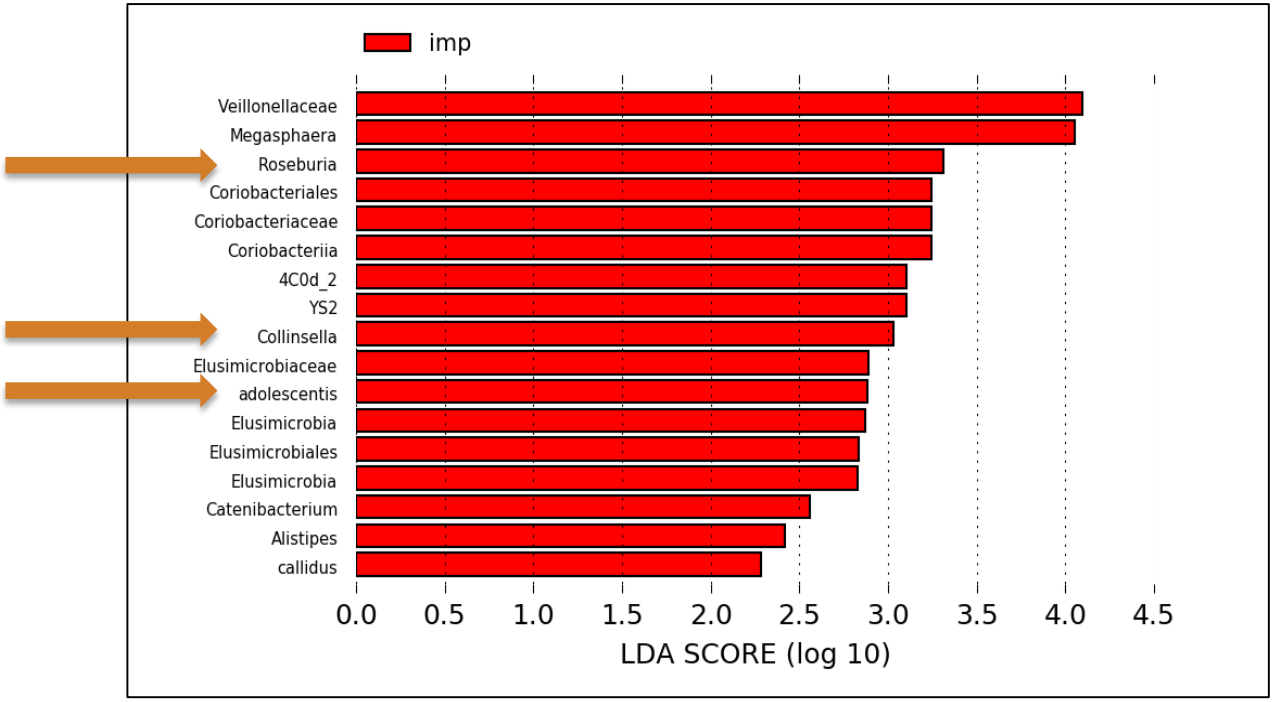
Sanitation facility defined as improved vs. unimproved based on UNICEF/WHO Joint Monitoring Program definitions.

Geophagy observed among more children living with unimproved sanitation facility

	Improved (n=40)	Unimproved (n=27)	P-value
	n(%)		
Child			
Clean hands*	7(18%)	2(7%)	0.235
Put soil/animal feces in mouth	**20(50%)**	**20(74%)**	**0.049**
Washed hands before eating	14(35%)	9(33%)	0.408
Washed hands after eating	12(30%)	9(33%)	0.238
Caregiver			
Clean hands*	9(23%)	4(15%)	0.435
Washed hands before feeding	21(53%)	14(52%)	0.090
Washed hands after feeding	22(55%)	13(48%)	0.238
Washed hands after diaper change	14(35%)	8(30%)	0.646
Household			
Clean compound**	9(23%)	2(7%)	0.102
Drinking water storage container has lid	31(78%)	20(74%)	0.747
Drinking water storage container is clean†	7(18%)	1(4%)	0.088
Drinking water looks clean‡	13(33%)	9(33%)	0.943
Animals observed drinking from drinking water	7(18%)	7(26%)	0.405

Sanitation facility defined as improved vs. unimproved based on WHO/UNICEF Joint Monitoring Program definitions.

Gut microbiota is enriched in beneficial taxa when living in improved sanitation conditions



Result based on 16S rRNA V4 amplicon sequencing, followed by computational analysis in Quantitative Insights Into Microbial Ecology 2, and examination of differentially abundant taxa using Linear Discriminant Analysis Effect Size algorithm.

CONCLUSIONS

- Gut microbiota of children with MAM were enriched in inflammogenic taxa.
- Children with MAM living in households with improved WASH conditions had lower risk of EED, and beneficial microbes.
- Alterations of the gut microbiota were associated with MAM, and gut inflammation during EED.
- This raises the possibility of microbiota-directed interventions using nutritional therapy and WASH in the treatment of MAM and EED.

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EED markers and Water Hygiene and Sanitation in Nepal: Findings from the Aflacohort Study

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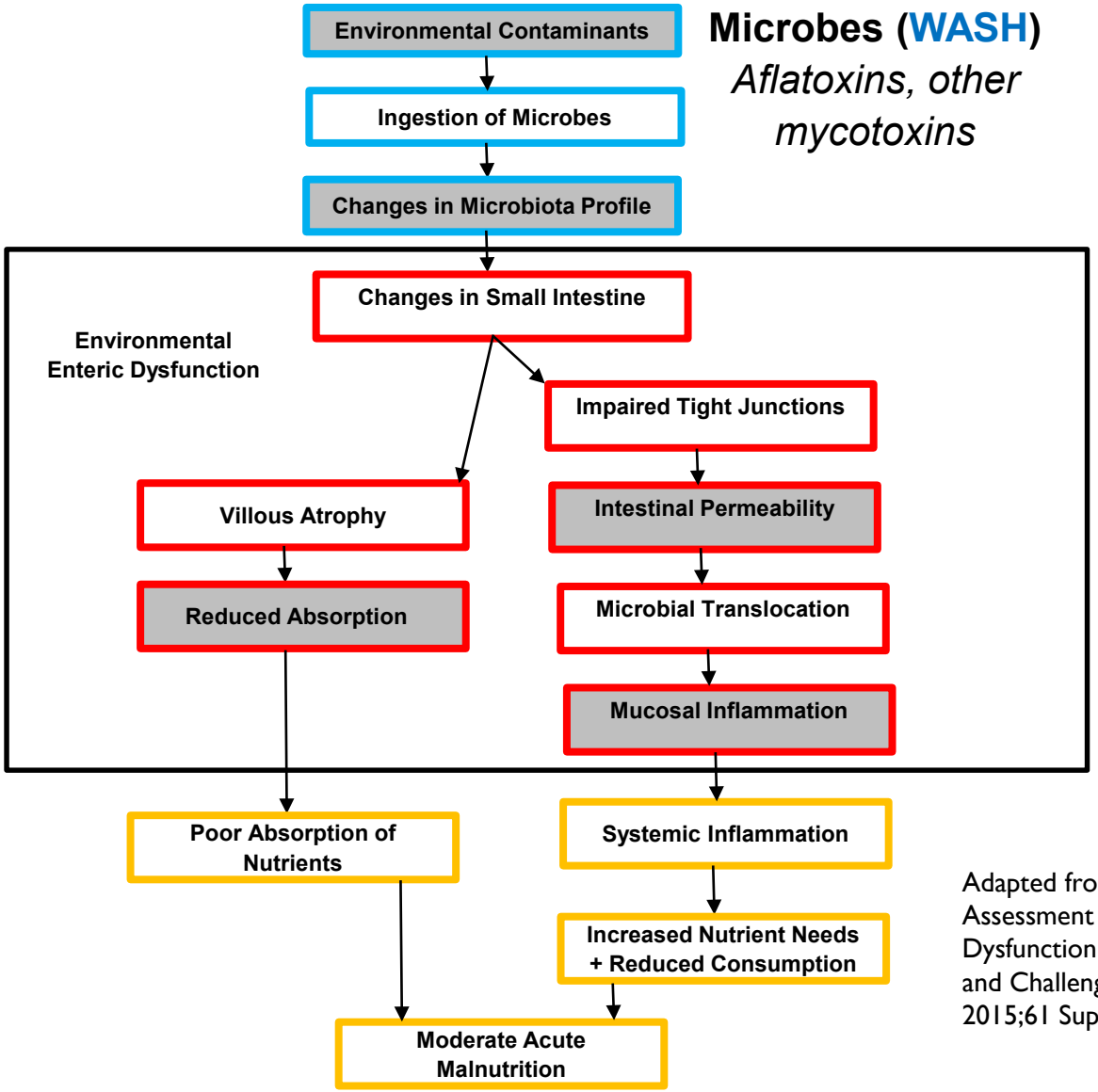
BACKGROUND

- Stunting rates are still high in Nepal and Timor Leste – 36% (2016) and 51% (2013) respectively (https://data.worldbank.org)
- Environmental enteric dysfunction has been implicated in the development of the stunting syndrome
- Poor WASH practices have been found to be associated with EED
- In addition, it is postulated that toxins such as aflatoxin may induce EED thereby adding to the risk burden (6–8).



Adapted from Prendergast AJ et al. Assessment of Environmental Enteric Dysfunction in the SHINE Trial: Methods and Challenges. *Clinical Infectious Diseases*. 2015;61 Suppl 7:S726-32.

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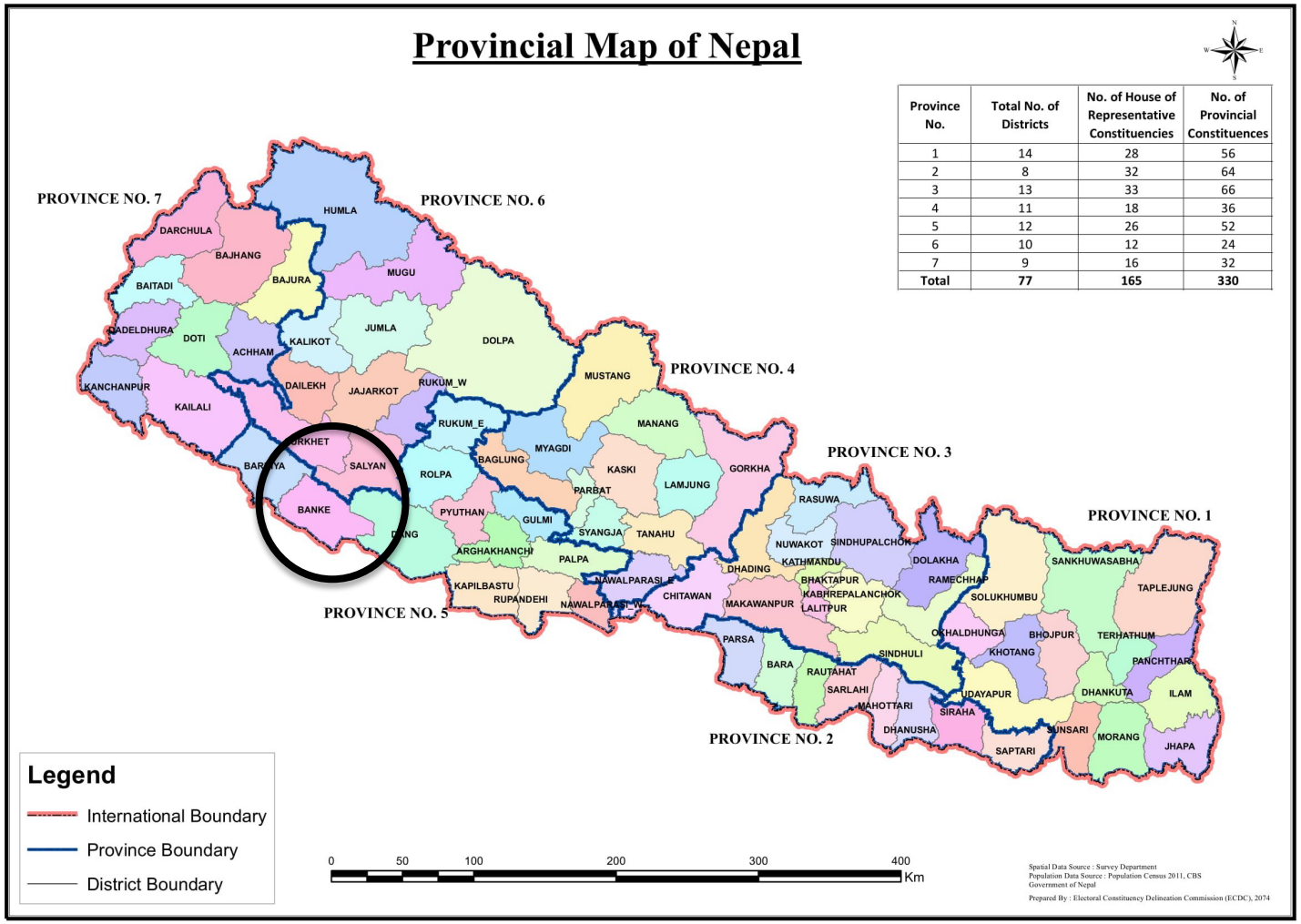
AFLACOHORT STUDY

- Observational Birth Cohort Study
- Location: Banke District of Nepal
- n=1,675 mother-infant dyads



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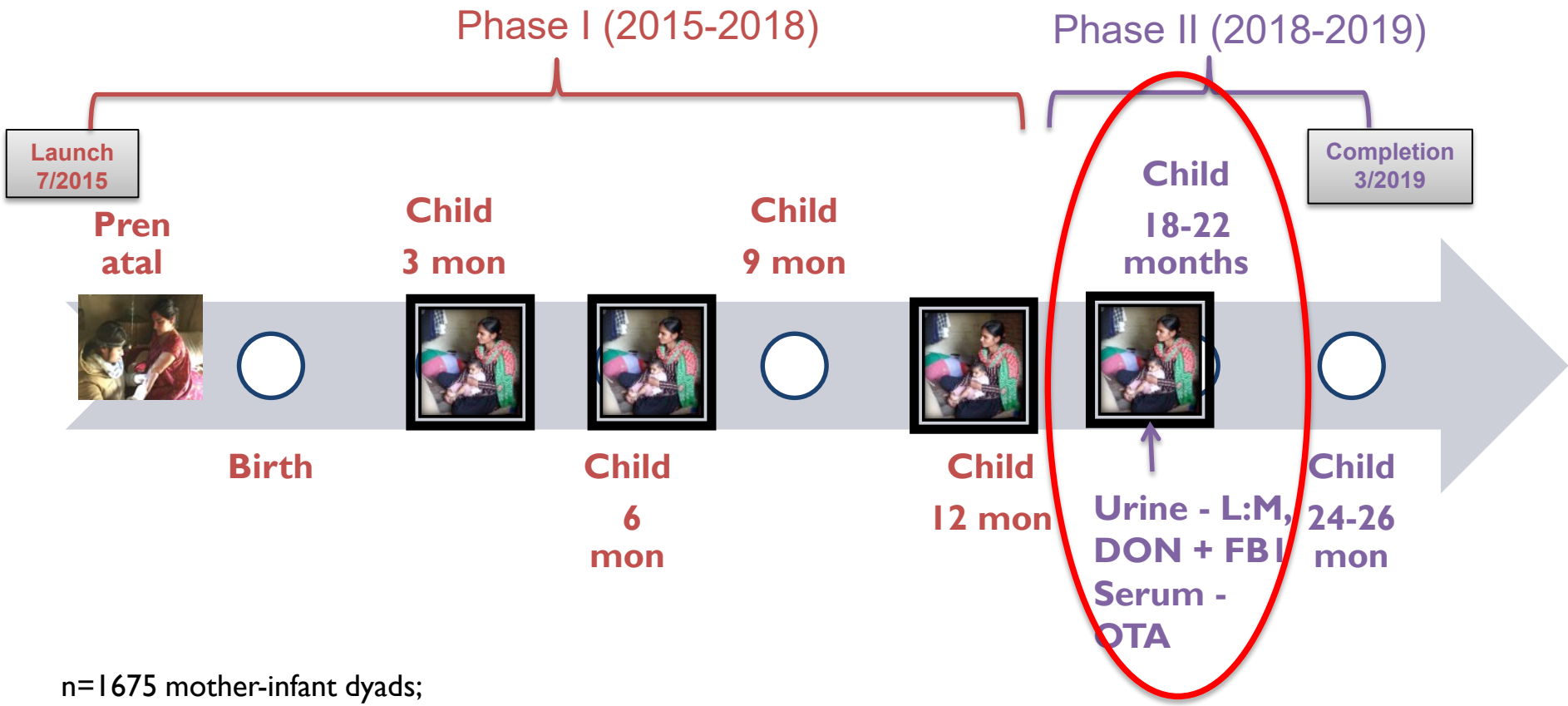
AflaCohort Study (2015-2019)



n=1675 mother-infant dyads;

L:M: lactulose:mannitol; DON: Deoxynivalenol; FB1: Fumonisin B1; OTA: Ochratoxin A

DESCRIPTIVES

CHILD (18-22 months)	% (n)
Sex, female	52.7 (368)
Low birth weight (% <2500 g)	20.6 (142)
Diarrhea 2 weeks prior (%)	7.0 (46)
Minimum dietary diversity (%) [1]	70 (487)
Stunted, LAZ <−2 SD	41.5 (289)
Underweight, WAZ<−2 SD	33.9 (236)
Wasted, WLZ<−2 SD	13.5 (94)
Low head circumference, HCZ<−2 SD	24.2 (169)
Household Improved Water source (%)	96% (653)
Household Improved Toilet Facility (%)	64% (431)

[1] Minimum dietary diversity was defined as the proportion of children who received foods made from four or more food groups out of the seven food groups during the previous day.

EED MARKERS DESCRIPTIVES

EED Marker	n	Mean ± SD
L:M ratio	675	0.29 ± 0.53
Percent lactulose excreted (% L)	675	0.24 ± 0.20
Percent mannitol excreted (%M)	675	5.05 ± 3.16
LMER	675	0.06 ± 0.11

L:M: lactulose:mannitol ratio; LMER: Lactulose Mannitol Excretion Ratio

MYCOTOXIN EXPOSURE, CHILD 18-22 MO

	n	Detectable (%)	Min	Max	Average mean (SD)	Geometric mean (CI)
Aflatoxin B1, (pg/mg albumin)	699	595 (85)	0.40	128.1	2.4 (7.88)	1.3 (1.2, 1.4)
Ochratoxin A, ng/mL	699	699 (100)	0.02	44.5	0.48 (1.82)	0.31 (0.29, 0.33)
Fumonisin B1, pg/mg creatinine	683	683 (100)	6.57	132,373	2,594 (9,756.7)	192.1 (163.7, 225.3)
DON ng/mg creatinine	685	596 (87)	0.04	129.9	0.78 (5.42)	0.31 (0.28, 0.33)

EED, WASH AND MYCOTOXINS

	LMER	%L	%M
Improved toilet	-0.195** (-0.331, -0.058)	-0.075 (-0.259, 0.108)	0.119 (-0.045, 0.284)
AFB1	0.025 (-0.028, 0.078)	0.021 (-0.050, 0.094)	-0.003 (-0.068, 0.061)
FB1	0.017 (-0.008, 0.043)	0.003 (-0.031, 0.037)	-0.014 (-0.045, 0.017)

Adjusted for child gender, number of household members, mother's education level and VDC

CONCLUSIONS

- We find a significant association between markers of intestinal permeability and absorption and access to an improved toilet facility
- We do not find an association with improved water source
- Markers of intestinal permeability are not associated with either aflatoxin or fumonisins
- Further analysis of the associations with growth and development are underway

RESEARCH AND POLICY IMPLICATIONS

- Work linking WASH, the microbiota, infection, health and nutritional status (stunting and moderate acute malnutrition)
- Advances the thinking in nutrition science and applied nutrition at the intersection of environmental contamination (whether household, individual or community level)
- Need for longitudinal studies and randomized interventions that address some specific areas highlighted
- Interventions focused on reducing environmental contamination (household, individual, community/institutional) need to consider the source, extent and intensity of contamination when planning responses.

Q&A

THANK YOU

- To register for any of these events, you can visit **NutritionInnovationLab.org** or **AdvancingNutrition.org**.
- Recordings and slides for each webinar will also be posted on our websites.

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