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Mycotoxins, Environmental Enteric Dysfunction, and Inflammation: Implications for Research and Programming on Child Growth and Nutrition

April 28, 2021

Ahmed Kablan Christopher Duggan Shibani Ghosh Patrick Webb

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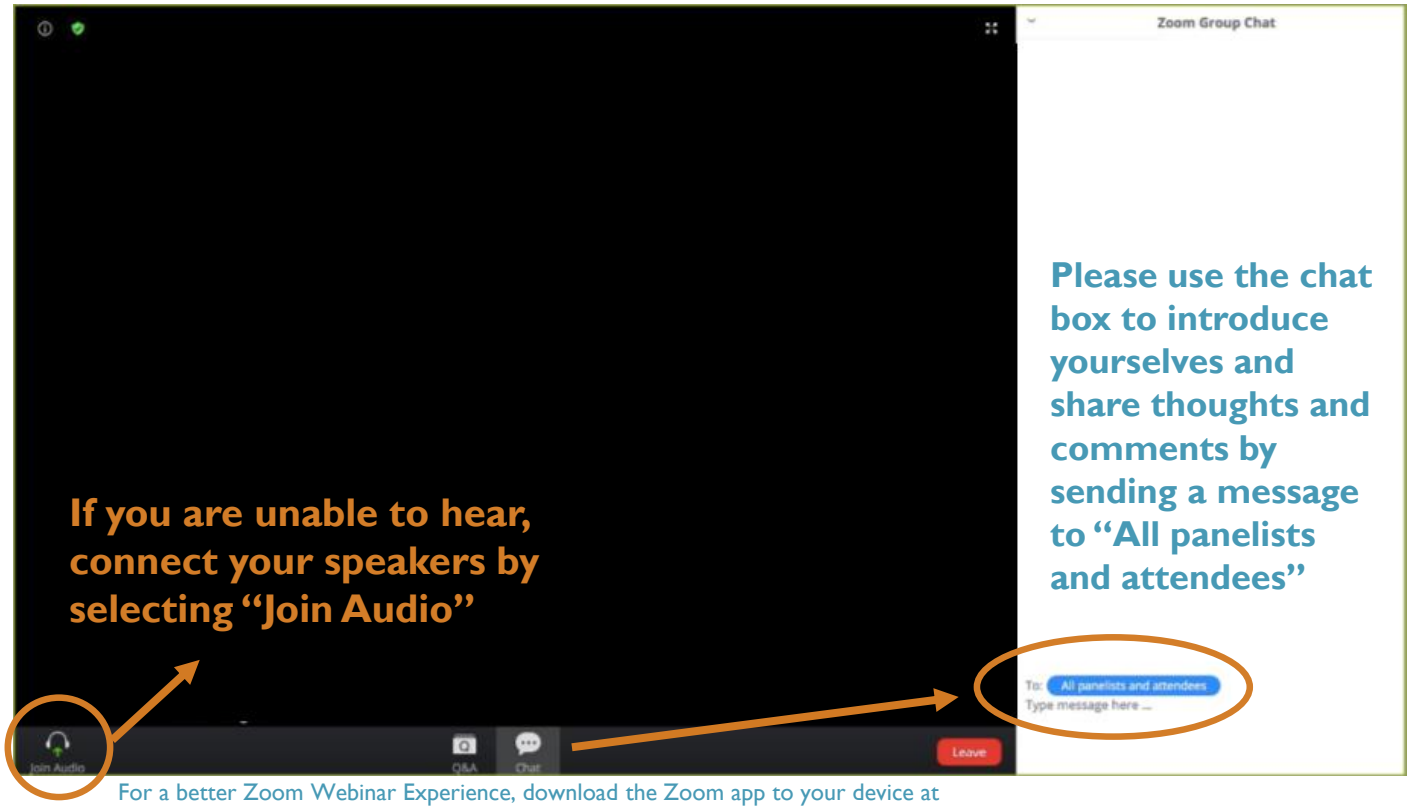

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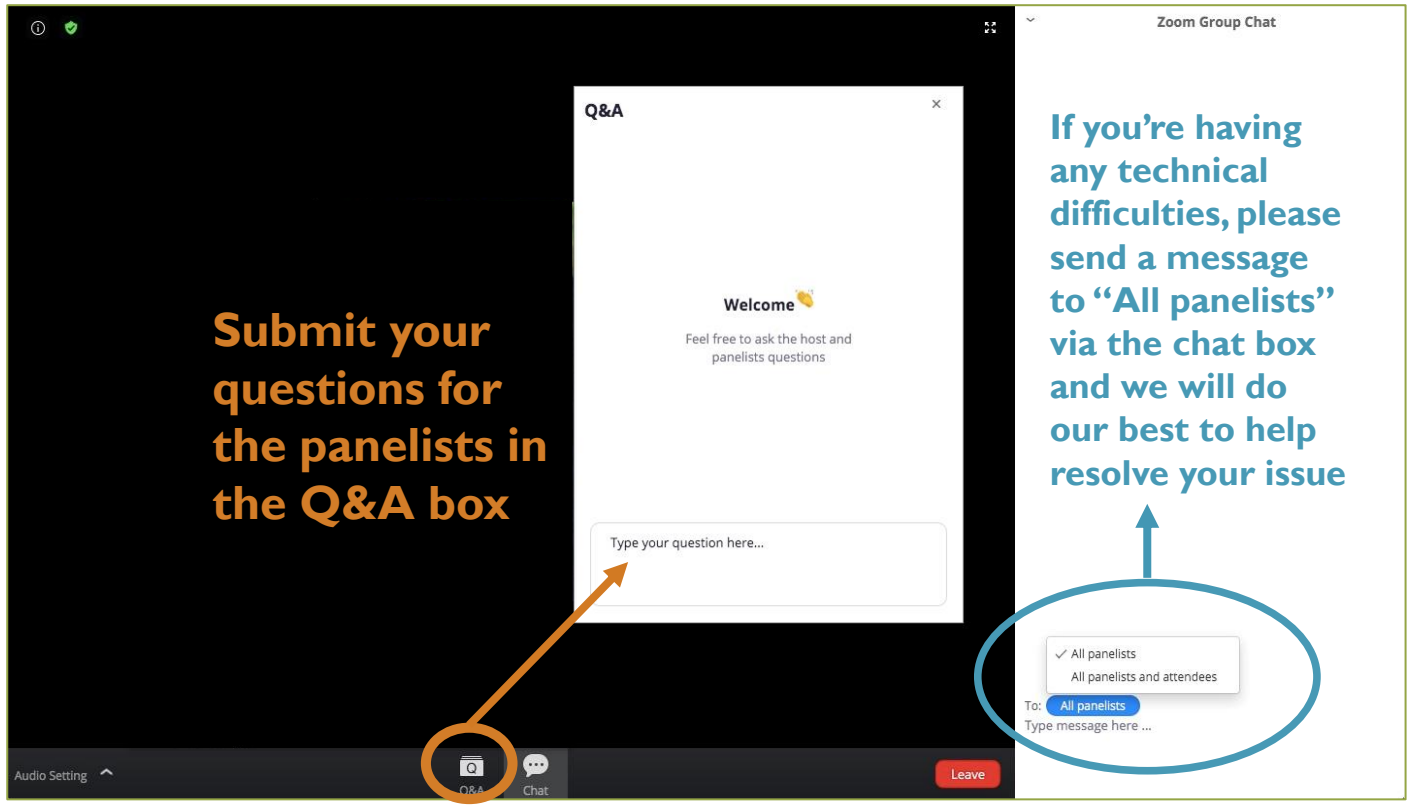
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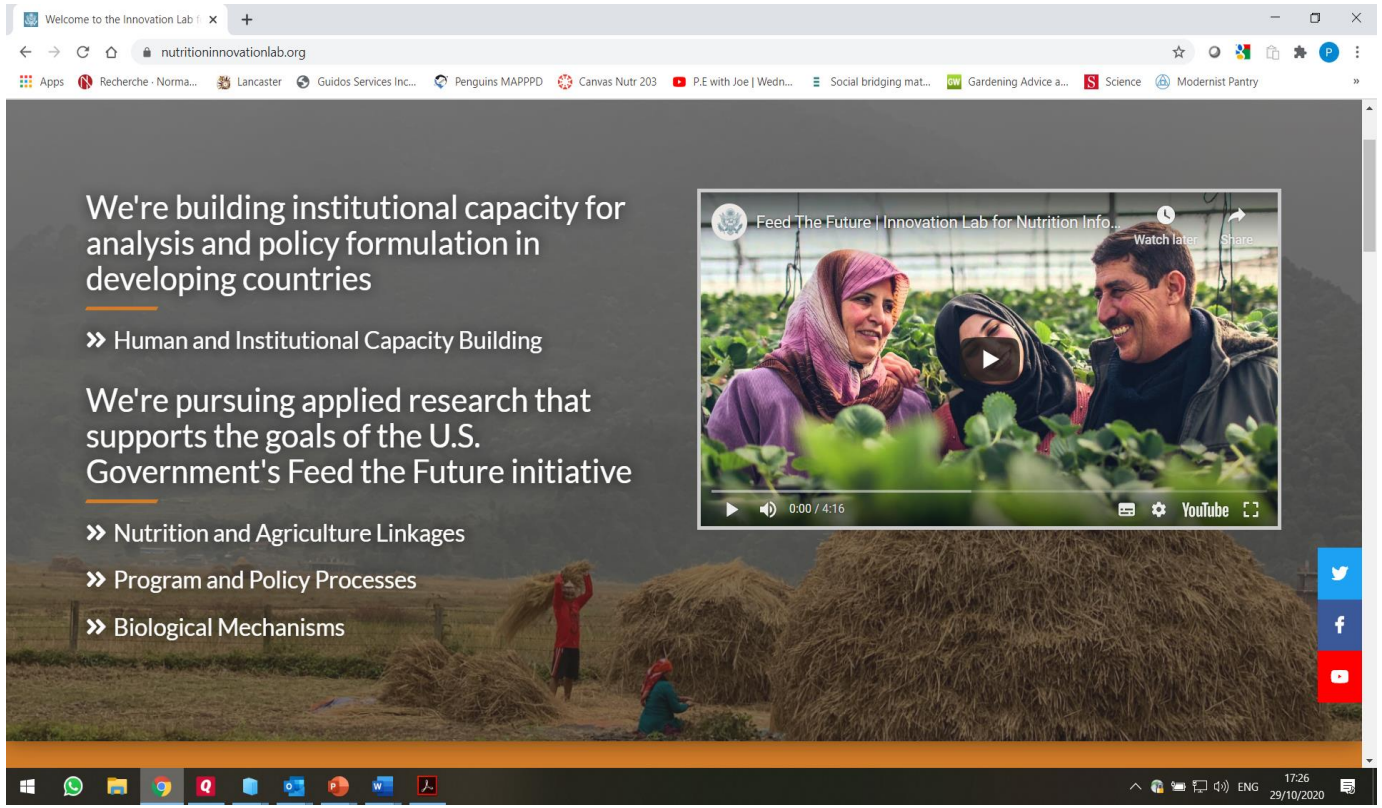

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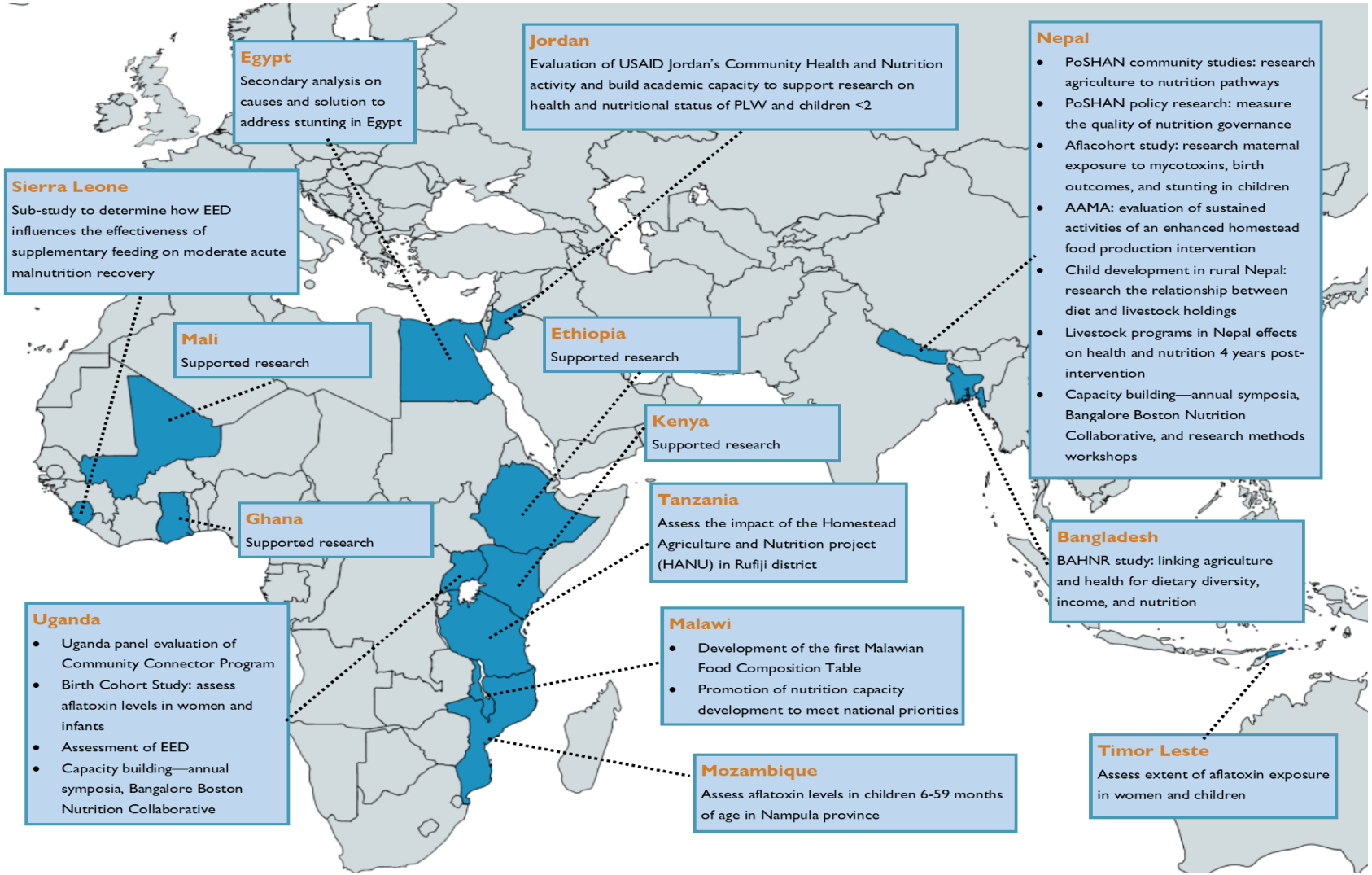

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Mycotoxins, Environmental Enteric Dysfunction, and Inflammation:
Implications for Research and Programming on Child Growth and Nutrition

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Mycotoxins, Environmental Enteric Dysfunction, and Inflammation:

Implications for Research and Programming on Child Growth and Nutrition

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DISCLOSURES

- I have no disclosures in relation to this presentation.

Maternal and Child Undernutrition 3

What works? Interventions for maternal and child undernutrition and survival

*Zulfiqar A Bhutta, Tahmeed Ahmed, Robert E Black, Simon Cousens, Kathryn Dewey, Elsa Giugliani, Batool A Haider, Betty Kirkwood, Saul S Morris, H P S Sachdev, Meera Shekar, for the Maternal and Child Undernutrition Study Group**

The Lancet 2008;371:417-440.

Sufficient evidence for implementation in all 36 countries	Evidence for implementation in specific, situational contexts
Maternal and birth outcomes	
Iron folate supplementation	Maternal supplements of balanced energy and protein
Maternal supplements of multiple micronutrients	Maternal iodine supplements
Maternal iodine through iodisation of salt	Maternal deworming in pregnancy
Maternal calcium supplementation	Intermittent preventive treatment for malaria
Interventions to reduce tobacco consumption or indoor air pollution	Insecticide-treated bednets
Newborn babies	
Promotion of breastfeeding (individual and group counselling)	Neonatal vitamin A supplementation
	Delayed cord clamping
Infants and children	
Promotion of breastfeeding (individual and group counselling)	Conditional cash transfer programmes (with nutritional education)
Behaviour change communication for improved complementary feeding*	
Zinc supplementation	Deworming
Zinc in management of diarrhoea	Iron fortification and supplementation programmes
Vitamin A fortification or supplementation	Insecticide-treated bednets
Universal salt iodisation	
Handwashing or hygiene interventions	
Treatment of severe acute malnutrition	

*Additional food supplements in food-insecure populations.

Table 1: **Interventions that affect maternal and child undernutrition**

	Proportional reduction in deaths before			Relative reduction in prevalence of stunting at			Millions (%) of DALYs averted at
	12 months	24 months	36 months	12 months	24 months	36 months	36 months
General nutrition interventions	14·8%	13·9%	13·4%	21·7%	17·8%	15·5%	33·8 (13·3%)
Micronutrient interventions	10·0%	11·3%	12·1%	10·3%	15·9%	17·4%	31·3 (12·3%)
Disease control interventions	3·0%	2·7%	2·6%	3·7%	2·9%	2·7%	6·6 (2·6%)

Table 14: **Effect of combinations of nutrition-related interventions on mortality and stunting in 36 countries (99% coverage)**

	Proportional reduction in deaths before			Relative reduction in prevalence of stunting at			Millions (%) of DALYs averted at
	12 months	24 months	36 months	12 months	24 months	36 months	36 months
99% coverage with all interventions	24·0%	24·4%	24·7%	33·1%	35·8%	35·5%	63·4 (25·1%)
90% coverage with all interventions	22·0%	22·2%	22·4%	31·1%	32·4%	32·1%	57·5 (22·7%)
70% coverage with all interventions	17·3%	17·3%	17·3%	22·7%	24·1%	23·6%	44·3 (17·5%)

Table 15: **Effect of all nutrition-related interventions on mortality and stunting in 36 countries, by coverage level**

Am. J. Trop. Med. Hyg., 89(4), 2013, pp. 709–716
doi:10.4269/ajtmh.12-0568
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Formative Research on Hygiene Behaviors and Geophagy among Infants and Young Children and Implications of Exposure to Fecal Bacteria

Francis M. Ngure,* Jean H. Humphrey, Mduduzi N. N. Mbuya, Florence Majo, Kuda Mutasa, Margaret Govha, Exevia Mazarura, Bernard Chasekwa, Andrew J. Prendergast, Valerie Curtis, Kathyrn J. Boor, and Rebecca J. Stoltzfus

Division of Nutritional Sciences, Cornell University, Ithaca, New York; Department of International Health, Johns Hopkins Bloomberg School of Public Health, Johns, Baltimore, Maryland; Zvitambo Project, Harare, Zimbabwe; Centre for Pediatrics, Queen Mary University of London, London, United Kingdom; The Hygiene Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom

TABLE 5

Infant feces (diaper wash waste water) disposal, Shurugwi District, Midlands Province, Zimbabwe

Method of disposal	Age group, years				
Fecal disposal	< 3	3–6	6–12	12–18	Total no. (%)
Garbage/pit	1	4	4	3	12 (48)
Tossed in yard	0	1	3	1	5 (20)
Latrine	1	1	0	2*	4 (16)
Buried in garden	0	0	0	2	2 (8)
Not seen	1	1	0	0	2 (8)
Total, no. (%)	3 (12)	7 (28)	7 (28)	8 (32)	25 (100)

*The two feces disposed in the latrine for 12–18-month-old children were by the same caregiver.

TABLE 7

Overall mean and number of samples (%) in each category of *Escherichia coli* counts, Shurugwi District, Midlands Province, Zimbabwe

Vector	No. samples	*E. coli* positive, no. (%)		*E. coli*	No. samples under each category of counts (%)			
		Samples positive	Households positive	Mean (95% CI)*	< 100	100–10,000	10,000–1,000,000	> 1,000,000
Food (porridge)	15	0 (0)	0 (0)	0 (0–0)	0 (0)	0 (0.0)	0 (0)	0 (0)
Water	43	14 (33)	12 (55)	2 (1–3)	13 (30)	1 (2)	0 (0)	0 (0)
Breast	36	0 (0)	0 (0)	0 (0–0)	0 (0)	0 (0.0)	0 (0)	0 (0)
Hand swabs								
Index child's left fingers	37	4 (11)	3 (14)	1 (0–2)	4 (11)	0 (0.0)	0 (0)	0 (0)
Index child's right fingers	37	2 (5)	2 (9)	1 (0–2)	1 (3)	1 (3)	0 (0)	0 (0)
Siblings dominant hand	20	1 (5)	1 (5)	1 (0–2)	1 (5)	0 (0)	0 (0)	0 (0)
Caregiver's dominant hand	43	13 (30)	11 (50)	4 (2–8)	9 (21)	3 (7)	1 (2)	0 (0)
Environmental samples								
Index child's cup and spoon	40	7 (18)	5 (23)	2 (1–4)	4 (10)	3 (8)	0 (0)	0 (0)
Kitchen floor	42	25 (60)	18 (82)	42 (14–130)	6 (14)	14 (33)	5 (12)	0 (0)
Soil								
Field soil	22	1 (5)	1 (5)	1 (0–2)	1 (5)	0 (0)	0 (0)	0 (0)
Trodden path to pit	43	17 (40)	14 (64)	5 (3–8)	12 (28)	5 (12)	0 (0)	0 (0)
Kitchen door step	43	24 (56)	16 (73)	17 (7–43)	9 (21)	15 (34)	0 (0)	0 (0)
Laundry area	43	30 (70)	18 (82)	69 (22–212)	10 (23)	16 (37)	4 (9)	0 (0)
Chicken feces	42	22 (100)	22 (100)	10.3 (4.7–22.67) m	0 (0)	1 (2)	7 (17)	34 (81)

*CI = confidence interval. Mean counts are geometric means (95% CI) colony-forming units (CFU)/gram for food, soil, and chicken feces, CFU/mL for water, and CFU/swab for breast, hand swabs, and environmental samples. No. households = 22. m = million.

In addition to testing fingers, food, and drinking water of infants, three infants actively ingested 11.3 ± 9.2 (mean ± SD) handfuls of soil and two ingested chicken feces 2 ± 1.4 times in 6 hours… A one-year-old infant ingesting 1 gram of chicken feces in a day would consume 4,700,000–23,000,000 E. coli.

ENVIRONMENTAL ENTERIC DYSFUNCTION (EED)

- EED is a subclinical condition of the small intestine characterized by:
  - Villous atrophy;
  - Crypt hyperplasia;
  - Increased intestinal permeability;
  - Inflammatory cell infiltrate;
  - Malabsorption.
- Exact cause is unknown, but EED likely results from chronic fecal-oral exposure to enteropathogens that commonly occurs in poor sanitary conditions.

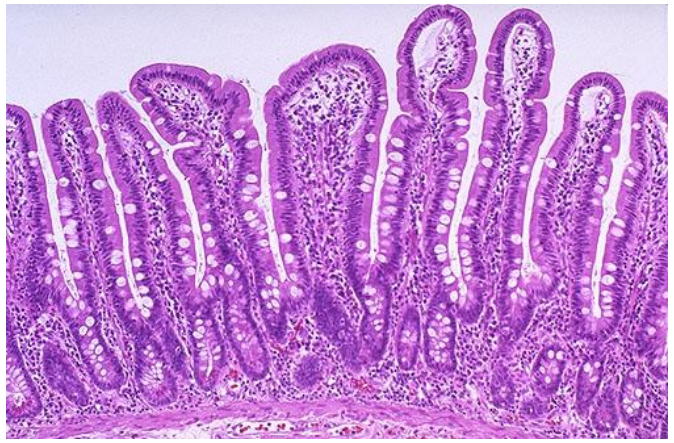

Figure A. Villi of small intestine – normal histology

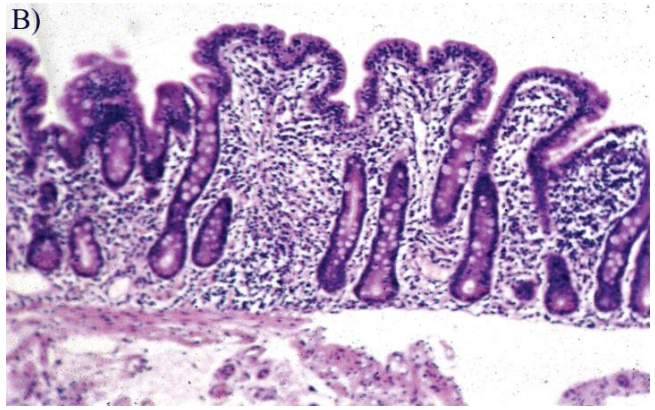

Figure B. Villi of small intestine – enteric dysfunction

Korpe and Petri. Trends Mol Med, 2012; 18(6):328-36.
Figure A: pathologyoutlines.com; Figure B: nature.com/ajg/journal/v100/n1

Environmental Enteric Dysfunction: Pathogenesis, Diagnosis, and Clinical Consequences

Table 1. Biomarkers to Assess Environmental Enteric Dysfunction

Category	Biomarkers
1. Intestinal absorption and mucosal permeability	D-xylose, mannitol, or rhamnose absorption; lactulose paracellular uptake; α1-anti-trypsin leakage into gut lumen
2. Enterocyte mass and function	Plasma citrulline and/or conversion of alanyl-glutamine to citrulline, lactose tolerance test (as a marker of brush border damage)
3. Inflammation	Plasma cytokines, stool calprotectin, myeloperoxidase, or lactoferrin
4. Microbial translocation and immune activation	Stool neopterin, plasma LPS core antibody and/or LPS binding protein, circulating soluble CD14

Abbreviation: LPS, lipopolysaccharide.

Keusch et al. CID 2014: 59 (Suppl 4) S207

TABLE 2. Biomarker summary statistics and correlations in 18-month-old environmental enteric dysfunction study participants

Biomarker	n	GM (95% CI)	Elevated, n (%)*	Pearson correlation coefficients†												
				L:M	MPO	AAT	NEO	GLP-2	Endo IgG	Endo IgM	Endo IgA	Total IgG	Total IgM	Total IgA	CRP	AGP
L:M	446	0.06 (0.05, 0.06)	174 (39.0)	1.00												
MPO, ng/mL	498	4460.3 (4145.0, 4799.5)	420 (84.3)	0.15	1.00											
AAT, μg/mL	501	326.9 (303.1, 352.5)	278 (55.5)	0.15	0.33	1.00										
NEO, nmol/L	502	767.4 (716.5, 821.8)	502 (100)	0.11	0.01	−0.12	1.00									
GLP-2, ng/mL	490	3.0 (2.9, 3.1)		0.03	−0.05	−0.12	0.02	1.00								
Endo IgG, MU/mL	501	45.4 (41.7, 49.4)		−0.05	−0.06	−0.04	0.08	−0.05	1.00							
Endo IgM, MU/mL	505	72.6 (69.6, 75.8)		−0.10	−0.03	−0.06	−0.00	−0.04	0.13	1.00						
Endo IgA, MU/mL	463	9.7 (8.8, 10.8)		0.00	−0.02	0.00	−0.01	0.08	0.19	0.18	1.00					
Total IgG, g/L	502	16.6 (15.9, 17.4)		−0.03	−0.01	−0.01	0.01	0.15	−0.01	0.04	0.14	1.00				
Total IgM, g/L	503	1.0 (1.0, 1.1)		−0.08	0.03	−0.05	−0.00	−0.07	0.07	0.49	0.15	0.13	1.00			
Total IgA, g/L	503	0.7 (0.7, 0.8)		0.10	−0.03	−0.06	0.08	0.03	0.01	0.02	0.25	0.10	0.39	1.00		
CRP, mg/L	505	1.20 (1.03, 1.38)	103 (20.4)	0.12	0.18	0.12	0.06	−0.08	0.02	−0.11	−0.05	0.03	0.09	0.11	1.00	
AGP, mg/dL	505	104.8 (101.9, 107.7)	281 (55.6)	0.09	0.13	0.07	0.11	0.02	0.01	−0.10	0.04	0.08	0.15	0.25	0.55	1.00

AAT = α-1 antitrypsin; AGP = α-1 acid glycoprotein; CI = confidence interval; CRP = C-reactive protein; Endo, endotoxin core antibody; GLP-2 = glucagon-like peptide-2; GM = geometric mean; IgA = immunoglobulin A, IgG = immunoglobulin G; IgM = immunoglobulin M; L:M = lactulose:mannitol ratio; MPO = myeloperoxidase; NEO = neopterin.

*Cutoffs for elevated biomarker values: L:M >0.07 (7); MPO >2000 ng/mL (13,30); AAT >270 μg/mL (13,30); NEO >70 nmol/L (13); CRP >5 mg/L (31); AGP >100 mg/dL (31).

†Cell values are Pearson correlation coefficients between log-transformed biomarkers with outliers removed. Correlations of absolute value ≥ 0.121 are significant at the $P \leq 0.01$ level; correlations of absolute value $0.097 < r \leq 0.116$ are significant at the $P \leq 0.05$ level; correlations of absolute value $0.086 \leq r \leq 0.077$ are significant at the $P \leq 0.1$ level.

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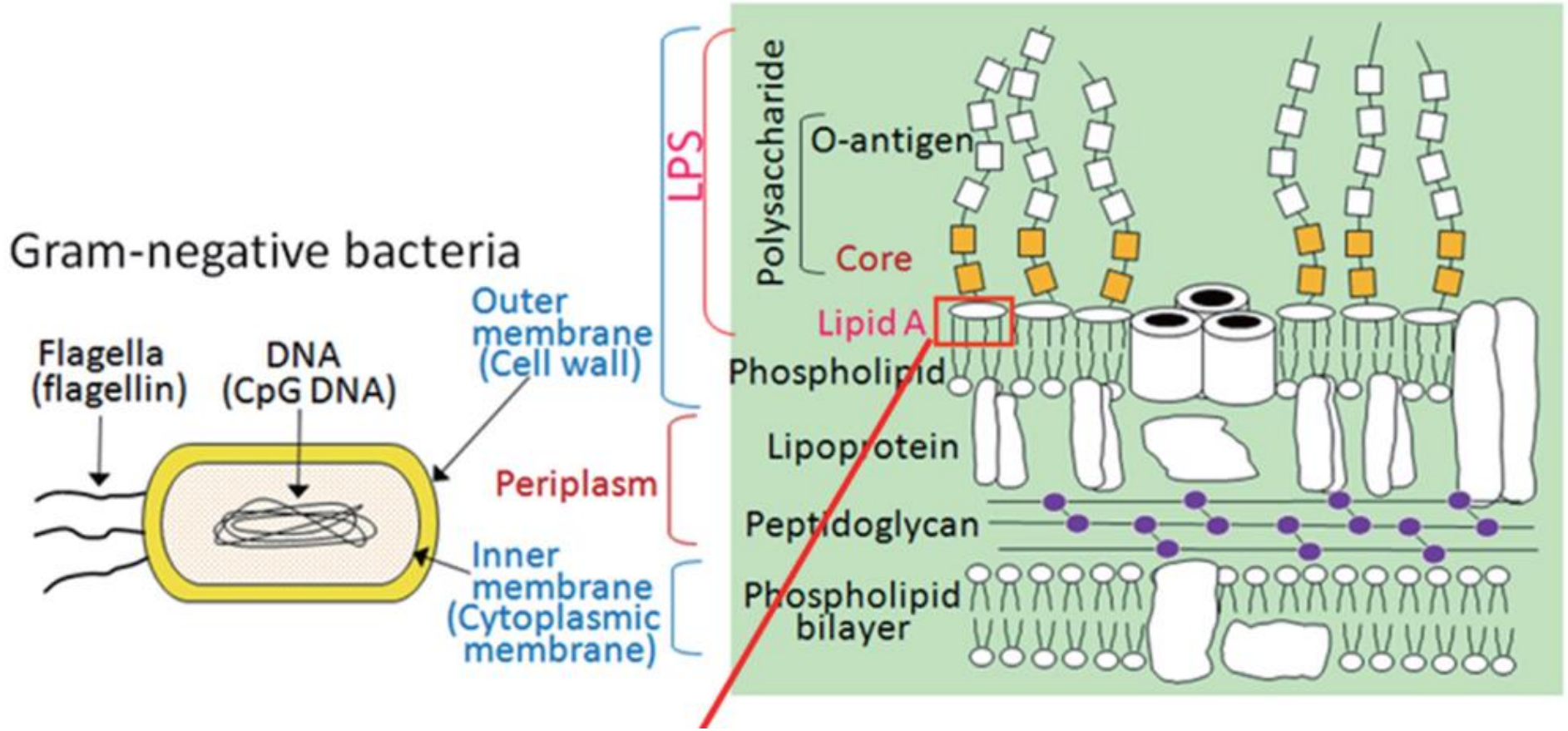

Front. Immunol., 24 May 2013 | https://doi.org/10.3389/fimmu.2013.00109

Elevations in serum anti-flagellin and anti-LPS Igs are related to growth faltering in young Tanzanian children[1,2]

*Christine M McDonald,[3] Karim P Manji,[4] Kerri Gosselin,[3] Hao Tran,[6] Enju Liu,[7] Rodrick Kisenge,[4] Said Aboud,[5] Wafaie W Fawzi,[7–9] Andrew T Gewirtz,[6] and Christopher P Duggan[3,7,9]**

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Am J Clin Nutr 2016;103:1548–54

TABLE 2
Anti-flagellin and anti-LPS Ig concentrations at 6 wk of age as predictors of subsequent stunting, wasting, and underweight[1]

	Stunting				Underweight				Ev
	Events/infants, *n*	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Events/infants, *n*	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	
Anti-flagellin IgA quartile[2]			0.93		0.75			0.03		0.007	
1 (0.00–0.14)	40/147	1.00		1.00		19/141	1.00		1.00		
2 (0.15–0.22)	40/147	0.91 (0.59, 1.42)		0.99 (0.62, 1.57)		25/147	1.29 (0.71, 2.35)		1.39 (0.75, 2.58)		
3 (0.23–0.37)	39/147	0.86 (0.55, 1.34)		0.97 (0.61, 1.54)		33/146	1.78 (1.01, 3.13)		2.22 (1.24, 3.99)		
4 (0.38–2.01)	43/147	1.04 (0.67, 1.60)		1.09 (0.69, 1.71)		30/139	1.78 (1.00, 3.17)		2.02 (1.11, 3.67)		
Anti-LPS IgA quartile			0.24		0.45			0.01		0.02	
1 (0.00–0.16)	38/146	1.00		1.00		20/142	1.00		1.00		
2 (0.17–0.30)	36/148	0.88 (0.56, 1.39)		0.91 (0.57, 1.45)		25/146	1.17 (0.64, 2.11)		1.16 (0.63, 2.15)		
3 (0.31–0.53)	39/147	1.04 (0.66, 1.62)		0.97 (0.62, 1.54)		28/144	1.48 (0.84, 2.63)		1.57 (0.87, 2.85)		
4 (0.54–2.82)	49/147	1.24 (0.81, 1.89)		1.16 (0.75, 1.79)		34/141	1.92 (1.10, 3.34)		1.84 (1.03, 3.27)		
Anti-flagellin IgG quartile			0.44		0.08			0.007		0.009	
1 (0.00–0.30)	32/146	1.00		1.00		16/142	1.00		1.00		
2 (0.31–0.42)	48/148	1.65 (1.05, 2.58)		1.54 (0.97, 1.45)		28/146	1.85 (1.00, 3.43)		1.11 (0.58, 2.13)		
3 (0.43–0.61)	42/147	1.41 (0.89, 2.23)		1.72 (1.07, 2.77)		32/145	2.10 (1.15, 3.84)		1.98 (1.06, 3.70)		
4 (0.62–2.56)	40/147	1.30 (0.82, 2.07)		1.52 (0.94, 2.45)		31/140	2.31 (1.26, 4.24)		1.94 (1.04, 3.62)		
Anti-LPS IgG quartile			0.63		0.50			0.03		0.01	
1 (0.00–0.42)	38/147	1.00		1.00		18/142	1.00		1.00		
2 (0.43–0.64)	48/147	1.28 (0.84, 1.96)		1.19 (0.77, 1.85)		32/146	1.93 (1.07, 3.48)		1.66 (0.90, 3.04)		
3 (0.65–0.99)	39/148	1.02 (0.65, 1.59)		1.15 (0.73, 1.83)		23/144	1.41 (0.75, 2.64)		1.59 (0.83, 3.03)		
4 (1.00–3.03)	37/146	0.97 (0.63, 1.52)		1.20 (0.75, 1.92)		34/141	2.25 (1.26, 4.03)		2.31 (1.25, 4.27)		

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

Jacqueline M Lauer,[1,2] Shibani Ghosh,[2,3] Lynne M Ausman,[2,3] Patrick Webb,[2,3] Bernard Bashaasha,[4] Edgar Agaba,[2] Florence M Turyashemererwa,[5] Hao Q Tran,[6] Andrew T Gewirtz,[6] Juergen Erhardt,[7] and Christopher P Duggan[1,2,8]

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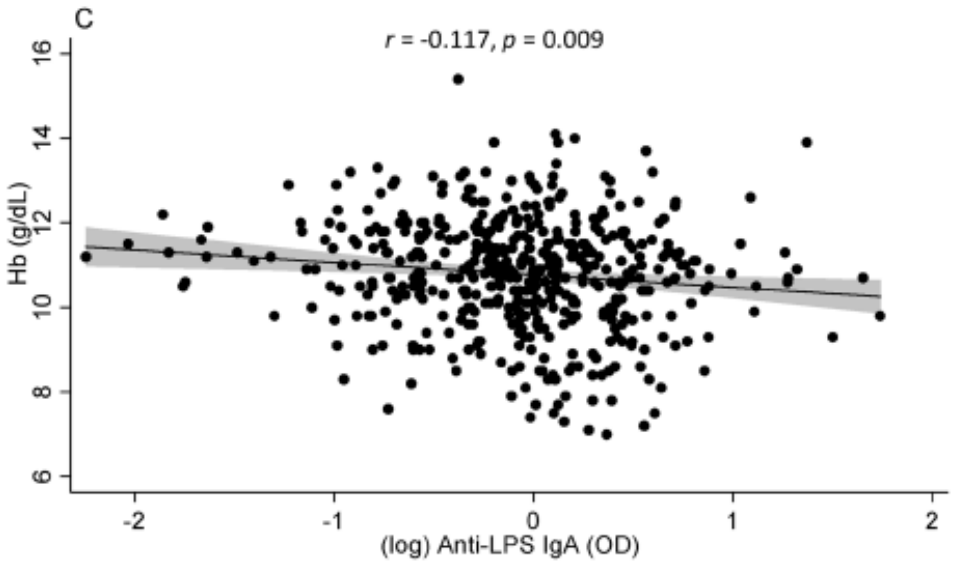

Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda

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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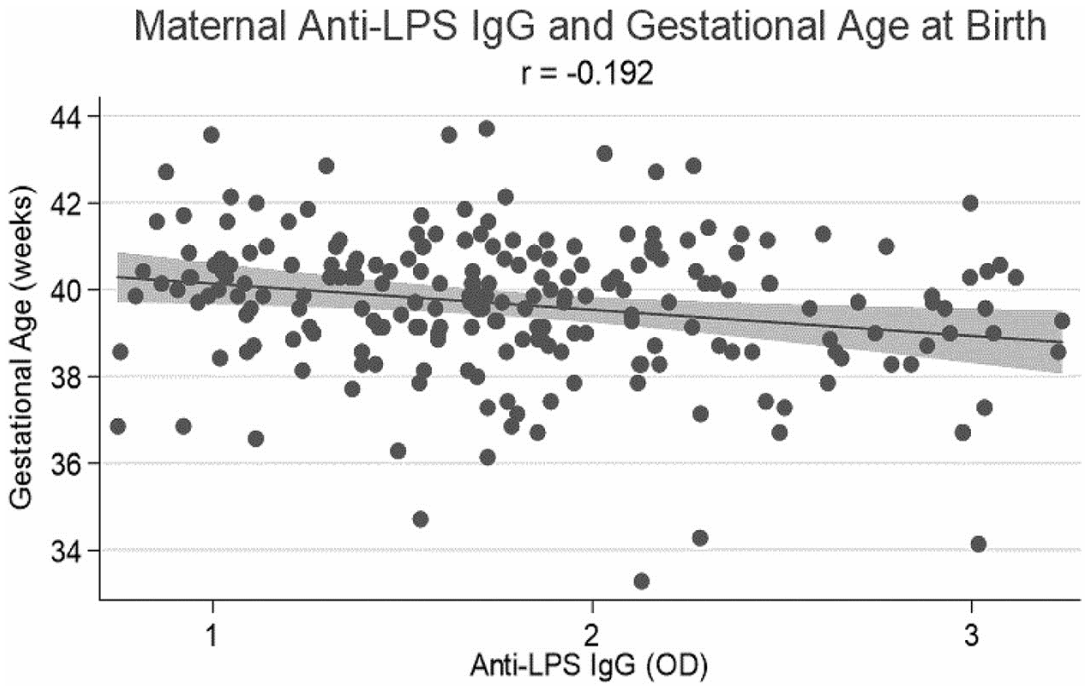

Higher concentrations of anti-flagellin IgG and anti-LPS IgG were **significantly associated with shorter length of infant gestational age at birth, lower length at birth, and lower LAZ at birth**

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.

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.

- 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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The U.S. Government's Global Hunger & Food Security Initiative

Mycotoxins, the Microbiome and Environmental Enteric Dysfunction

Shibani Ghosh, PhD
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Tufts UNIVERSITY | GERALD J. AND DOROTHY R. Friedman School of Nutrition Science and Policy

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The stunting syndrome in developing countries

Andrew J. Prendergast[1,2,3], Jean H. Humphrey[2,3]

[1]Centre for Paediatrics, Blizard Institute, Queen Mary University of London, UK. [2]Zvitambo Institute for Maternal

Risk factors
Aflatoxin exposure
Other mycotoxin exposure
EED
Inflammation

Birth outcomes
Low birth weight
Small for Gestational Age
Low weight for age/weight for height (WAZ, WLZ)
Head circumference for Age
Short for GA (LAZ), stunted at birth

Risk factors
Aflatoxin exposure
Other mycotoxin exposure
EED, inflammation and the microbiome

Outcomes
Attained length/LAZ, WAZ and WLZ at 2 or 5 years
Risk of being stunted, underweight, wasted at 2 or 5 years
Recovery from Moderate Acute Malnutrition

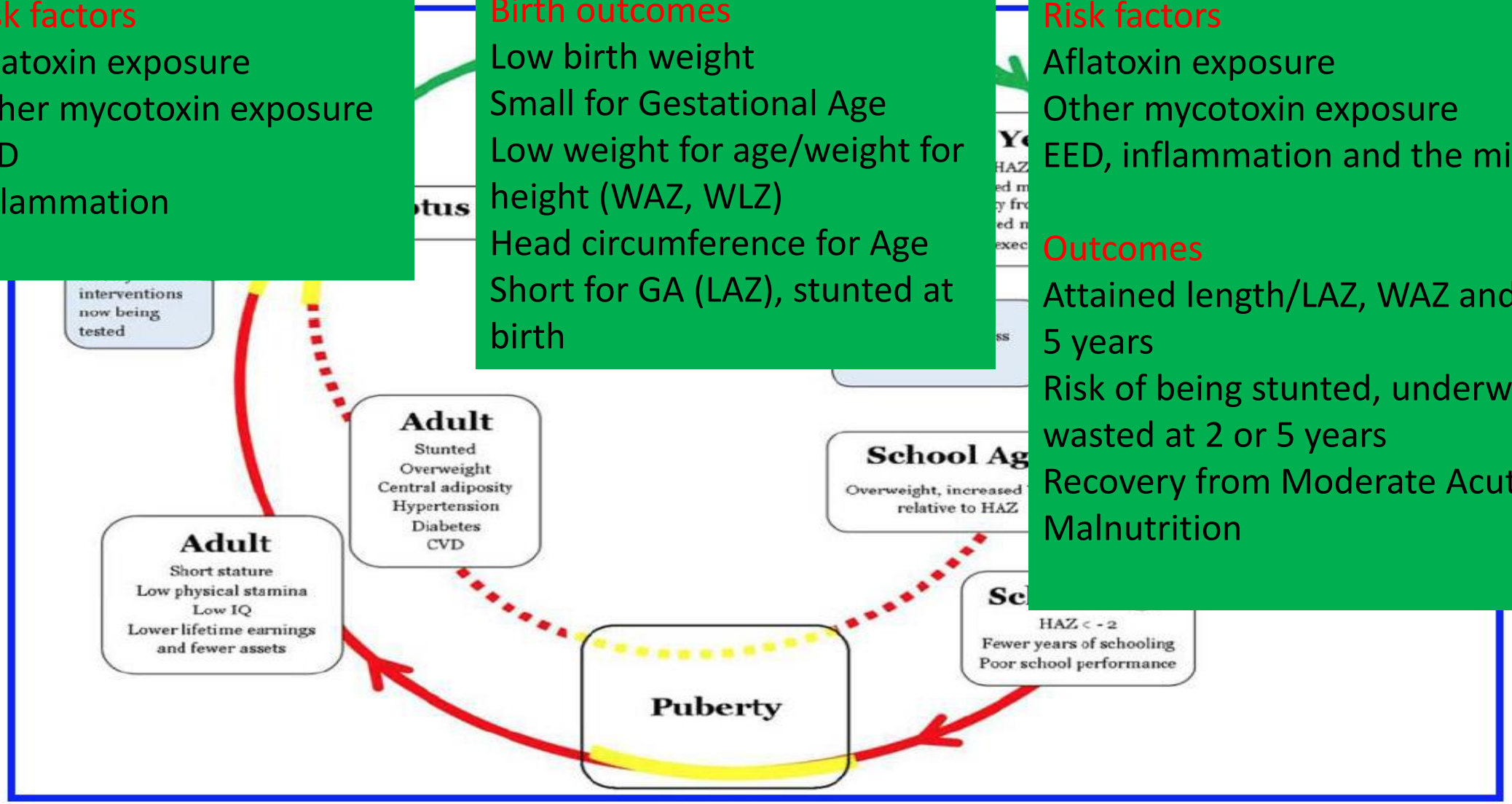


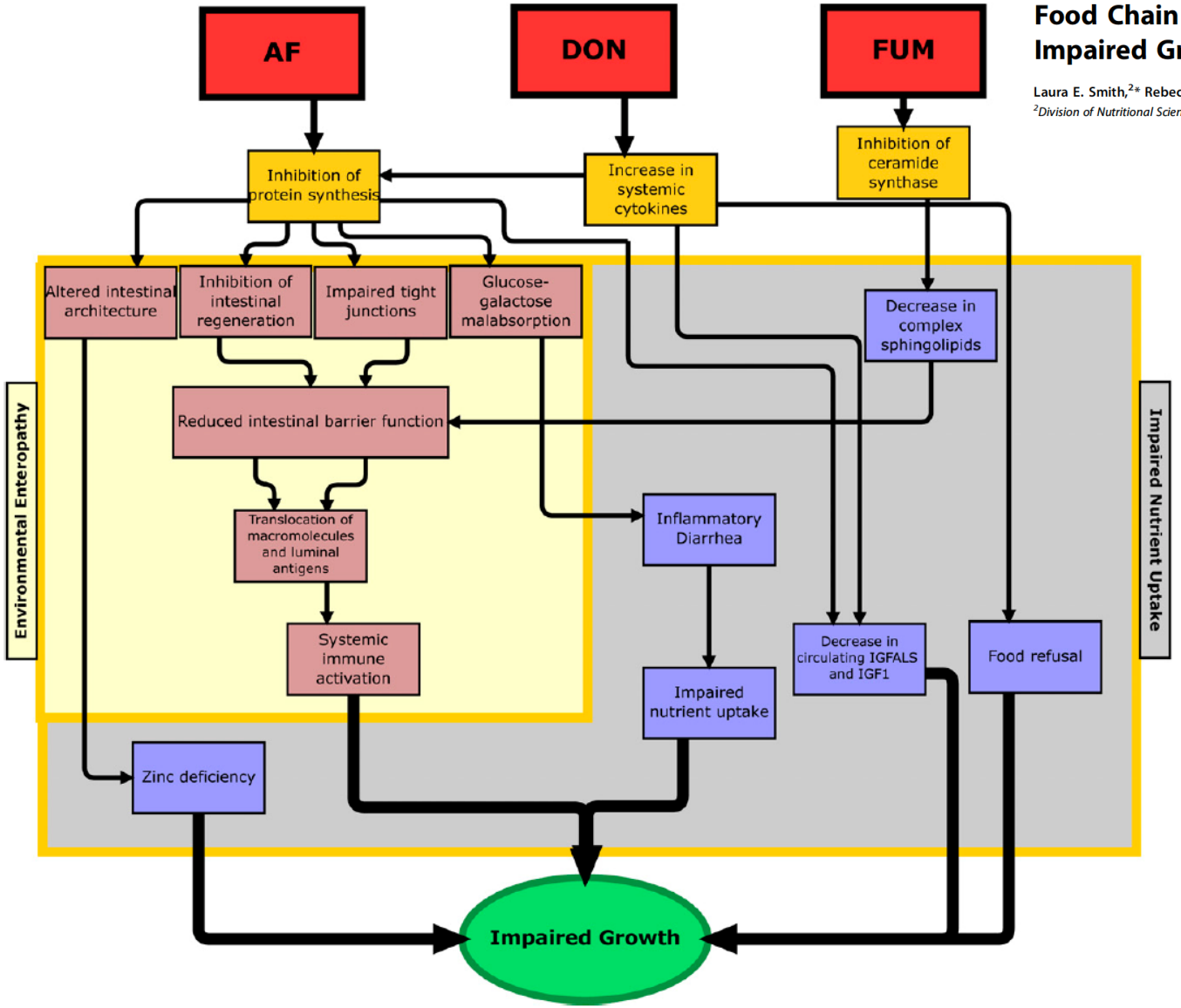
Figure 1 The stunting syndrome. The green pathway denotes the period between conception and 2 years (‘*the first 1000 days*’)

NUTRITION INNOVATION LAB STUDIES

- Timor Leste (n=513): Cross sectional national survey conducted as part of the Timor Leste Food and Nutrition Survey of 2013, children < 59 months of age
- Mozambique (n=894): Cross sectional survey representative of 10 districts of Nampula province, Mozambique, children 6 months to 59 months of age
- Uganda:
  - Mukono Cohort (Longitudinal birth cohort following up pregnant women through birth in Mukono district) (n= 254)
  - Gulu Cohort (Longitudinal birth cohort called PreNaps that followed pregnant women through early infancy in Gulu district (n=403)
  - Uganda Birth cohort (longitudinal birth cohort following pregnant women through 12 months infant age in 8 districts in rural Uganda (n=5000 mother-infant dyads)
- Nepal (n=1675) : Aflacohort Study- a longitudinal birth cohort that followed 1675 mother-infant dyads from pregnancy through 26 months of age
- Sierra Leone (n= 520) : USAID Food Aid Quality Review Four Foods MAM treatment study, Pujehun district of Sierra Leone, children under 59 months of age, diagnosed with moderate acute malnutrition

WHAT CAN WE SAY ABOUT THE INTERACTIONS OF MYCOTOXINS, EED AND MICROBIOME?

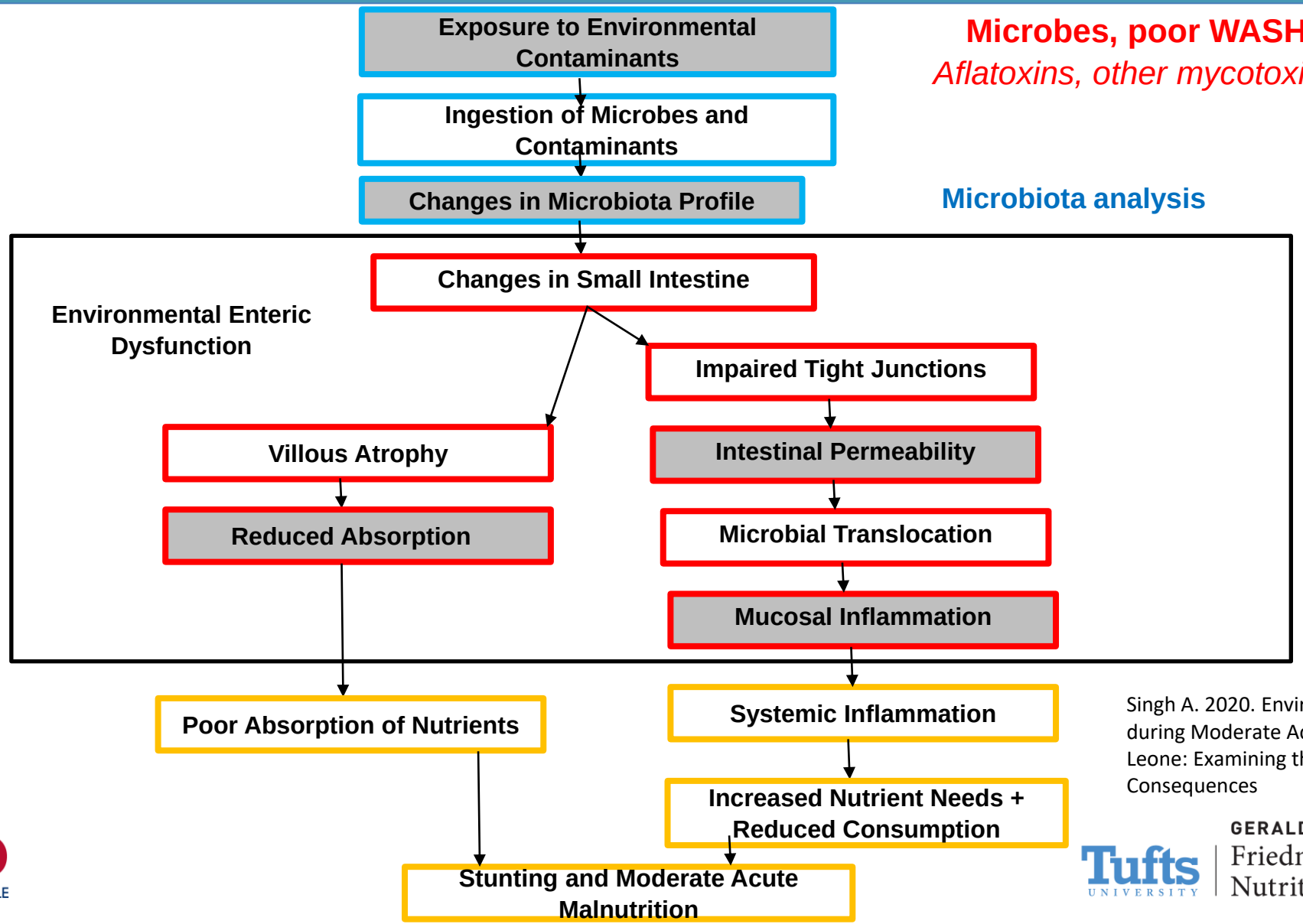
EXAMPLES: AFLACOHORT NEPAL AND FOUR FOODS STUDY, SIERRA LEONE



Food Chain Mycotoxin Exposure, Gut Health, and Impaired Growth: A Conceptual Framework[1]

Laura E. Smith,[2]* Rebecca J. Stoltzfus,[2] and Andrew Prendergast[3]
[2]Division of Nutritional Sciences, Cornell University, Ithaca, NY; Queen Mary University of London, UK; and [3]Zvitambo Project, Harare, Zimbabwe

Adv. Nutr. 3: 526–531, 2012; doi:10.3945/an.112.002188.



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.

Singh A. 2020. Environmental Enteric Dysfunction during Moderate Acute Malnutrition in Sierra Leone: Examining the Burden, Causes and Consequences

MYCOTOXIN EXPOSURE AT 18-22 MONTHS OF AGE: AFLACOHORT NEPAL

	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 AND MYCOTOXINS: AFLACOHORT NEPAL

	Aflatoxin B1	Ochratoxin A	Fumonisin B1	DON	L:M ratio	% LE	% ME
Aflatoxin B1	1.0000						
Ochratoxin A	**0.2575***	1.0000					
Fumonisin B1	0.0001	-0.0727	1.0000				
Deoxynivalenol	-0.0456	-0.0298	**0.3401***	1.0000			
L:M ratio	**0.0779***	**0.1208***	0.0423	**0.1019***	1.0000		
%LE	0.0137	0.0658	-0.0158	-0.0369	**0.4944***	1.0000	
%ME	-0.0518	-0.0321	-0.0540	**-0.1280***	**-0.3252***	**0.6611***	1.0000
LMER	**0.0779***	**0.1208***	0.0423	**0.1019***	**1.0000***	**0.4944***	**-0.3252***

L:M, lactulose:mannitol ratio; LE= Lactulose excreted, ME= Mannitol excreted
[1] Excludes children with <10 mL of urine

INDIVIDUAL MYCOTOXINS AND L:M RATIO AT 18-22 MONTHS AND ANTHROPOMETRY AT 24-26 MONTHS

	Dependent	Stunting, OR (95%CI)	Underweight, OR (95%CI)	Low head circumference, OR (95%CI)
Model 1	Aflatoxin B1, pg/mg albumin	1.28 (1.08, 1.52) **	1.18 (1.00, 1.38)**	1.12 (0.94, 1.32)
	L:M ratio	1.19 (0.92, 1.54)	1.01 (0.77, 1.32)	1.05 (0.79, 1.42)
Model 2	Ochratoxin A, ng/mL	1.05 (0.86, 1.29)	0.92(0.72, 1.19)	0.92(0.62, 1.36)
	L:M ratio	1.19 (0.92, 1.54)	1.02 (0.78, 1.34)	1.06 (0.77, 1.45)
Model 3	Fumonisin B1, pg/mg creatinine	1.06(0.94, 1.18)	1.08(0.99, 1.17)	0.93(0.80, 1.07)
	L:M ratio	1.23 (0.96, 1.59)	1.03 (0.79, 1.33)	1.07 (0.84, 1.38)
Model 4	Deoxynivalenol, ng/mg creatinine	1.05(0.86, 1.28)	0.99(0.84, 1.16)	1.03(0.86, 1.23)
	L:M ratio	1.15 (0.85, 1.58)	0.97 (0.73, 1.29)	1.02 (0.79, 1.34)

Cells present individual models and ORs, 95% confidence interval, and p-value.

Logistic regression models with L:M ratio plus length/weight at birth (or 3 months for head circumference), child's minimum dietary diversity (yes/no) and mother's schooling included as covariates; Due to their skewed distribution, outcomes were natural log (ln) transformed prior to all analyses.

* p<0.05, **p<0.01, ***p<0.001

MULTIPLE MYCOTOXINS AND LM RATIO

Dependent	Stunting, %	Underweight, %	Low head circumference, %
	Model 1	Model 2	Model 3
Aflatoxin B1, pg/mg albumin	**1.26****	**1.22****	1.13
	(1.09, 1.46)	**(1.07, 1.41)**	(1.93, 1.39)
Ochratoxin A, ng/mL	0.96	0.86	0.83
	(0.73, 1.25)	(0.60, 1.24)	(0.51, 1.36)
Fumonisin B1, pg/mg creatinine	1.03	1.06	0.9
	(0.93, 1.14)	(0.96, 1.19)	(0.78, 1.03)
Deoxynivalenol, ng/mg creatinine	1.03	0.96	1.15
	(0.84, 1.25)	(0.79, 1.16)	(0.97, 1.36)
L:M ratio	1.13	0.95	0.98
	(0.82, 1.54)	(0.71, 1.28)	(0.71, 1.36)

Cells present ORs (dichotomous outcomes), 95% confidence interval, and *p*-value.
Logistic regression models with L:M ratio plus length/weight/head circumference at birth (or 3 months for head circumference), child's minimum dietary diversity (yes/no) and mother's schooling included as covariates; Due to their skewed distribution, outcomes were natural log (ln) transformed prior to all analyses.

INDIVIDUAL MYCOTOXINS AND L:M RATIO

	Dependent	L:M ratio β (95% CI)
Model 1	Aflatoxin B1, pg/mg albumin	0.02 (-0.05, 0.09)
Model 2	Ochratoxin A, ng/mL	**0.09 * (0.01, 0.19)**
Model 3	Fumonisin B1, pg/mg creatinine	0.01 (-0.01, 0.04)
Model 4	Deoxynivalenol, ng/mg creatinine	**0.08* (0.01, 0.15)**

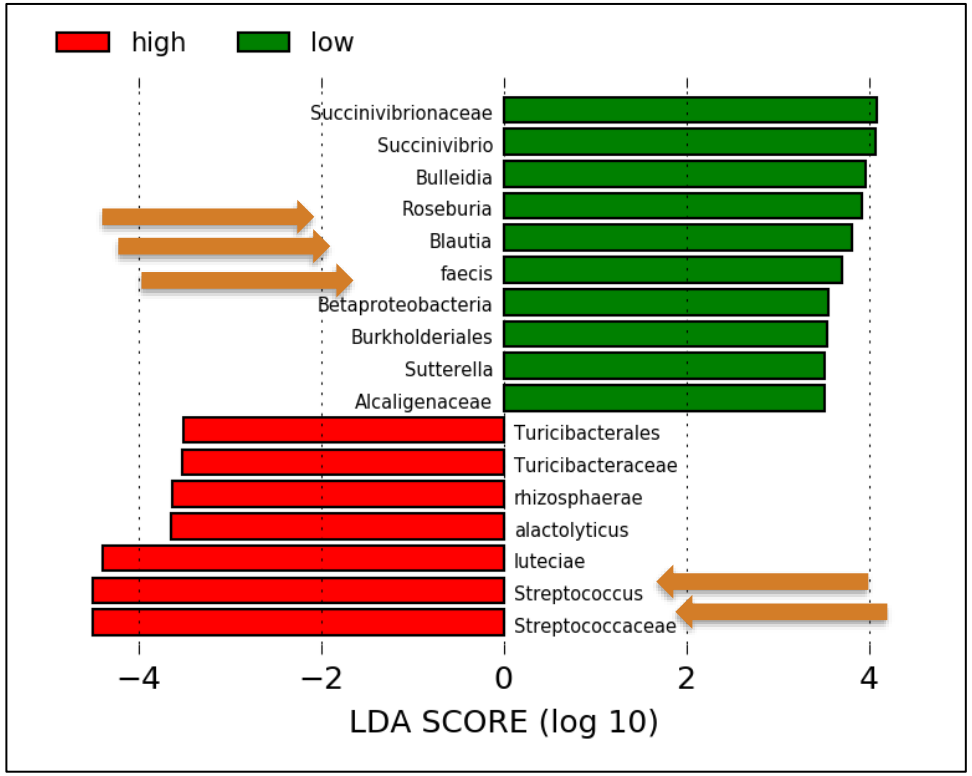
Cells present β coefficient, 95% confidence interval, and p-value.
Models adjusted for type of toilet facility, wealth of the household and mother's education. Improved toilet facilities include any non-shared toilet of the following types: flush/pour flush toilets to piped sewer systems, septic tanks, and pit latrines; ventilated improved pit (VIP) latrines; pit latrines with slabs; and composting toilets.

EED, MICROBIOME, AND MODERATE ACUTE MALNUTRITION IN SIERRA LEONE

- EED: High inflammation and permeability are negatively associated with both LAZ and WLZ in children with MAM (prior to treatment)
- Children with high intestinal permeability- lower length gain, lower weight gain
- Children with lower intestinal permeability were more likely to recover from moderate acute malnutrition (12-week treatment)

EED, MICROBIOME, AND MODERATE ACUTE MALNUTRITION IN SIERRA LEONE

- Gut microbiota of children with MAM were enriched in inflammogenic taxa
- Alterations of the gut microbiota were associated with MAM, and gut inflammation during EED



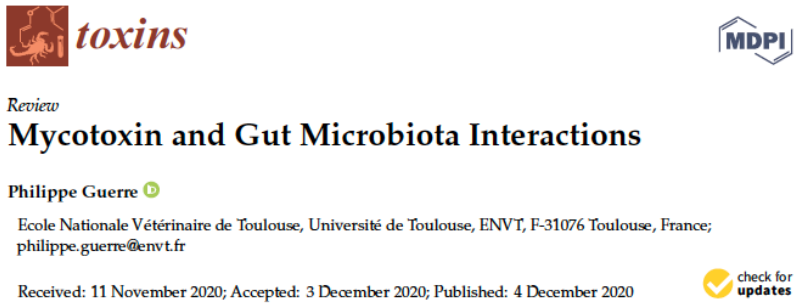
Result based on 16S rRNA V4 amplicon sequencing, followed by computational analysis in Quantitative Insights Into Microbial Ecology 2, and examination of differentially abundant taxa using Linear Discriminant Analysis Effect Size algorithm.

Singh A. 2020. Environmental Enteric Dysfunction during Moderate Acute Malnutrition in Sierra Leone: Examining the Burden, Causes and Consequences

Singh A.,* **Ghosh S.,** Ward H., Manary M., Rogers BL., and Rosenberg IH. Biomarkers of environmental enteric dysfunction differently predict recovery and growth among children with moderate acute malnutrition in Sierra Leone. American Journal of Clinical Nutrition. **March 2021** https://doi.org/10.1093/ajcn/nqaa434

MYCOTOXINS AND MICROBIOTA INTERACTIONS

- Probiotics are known to bio-transform mycotoxins to less toxic metabolites
- Changes in microbiota composition could be a consequence
  - antimicrobial properties of mycotoxins
  - the toxic effect on epithelial and immune cells in the gut releasing antimicrobial peptides
- Mycotoxin exposure to mycotoxins could lead to changes in the gut microbiota composition at the phylum, genus, and species level.
- Changes in the gut microbiota composition – modulate toxicity of mycotoxins and bacterial toxins



toxins
MDPI

Review

Mycotoxin and Gut Microbiota Interactions

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CONCLUSIONS

- Co-existence of multiple mycotoxins in Nepali infants with aflatoxins, DON and ochratoxin correlated with L-M ratio/EED
- The relationships of each of these risk factors with nutritional status confounded by individual interactions among mycotoxins and LM ratio
- The association between aflatoxin, stunting and underweight seems independent of the L-M ratio and remains significant after adjusting for diet, prior nutritional status and mother's education
- EED modulated recovery from MAM in Sierra Leone
- Altered/poor gut microbiota associated with MAM and with gut inflammation/EED prior to treatment
- Evidence on the bi-directional relationship of mycotoxins and the gut microbiota in animal studies warrants investigations in humans

CONCLUSIONS

- Our work highlights the importance of assessing the interactions between exposure to environmental toxins and microbes, the process of EED and the gut microbiota

- Given the complexities and co-existence issues, such research will be important in driving future policy and programming within the context of food systems, agriculture, nutrition and health

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Mycotoxins, EED and Inflammation: Implications for Programming

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RELATIVE RISK IS NOT STATIC

Prevalence and relative contribution of contributors to global burden of disease change over time:

- Rising treatment/prevention
- Reduced exposure
- Enhanced assessment

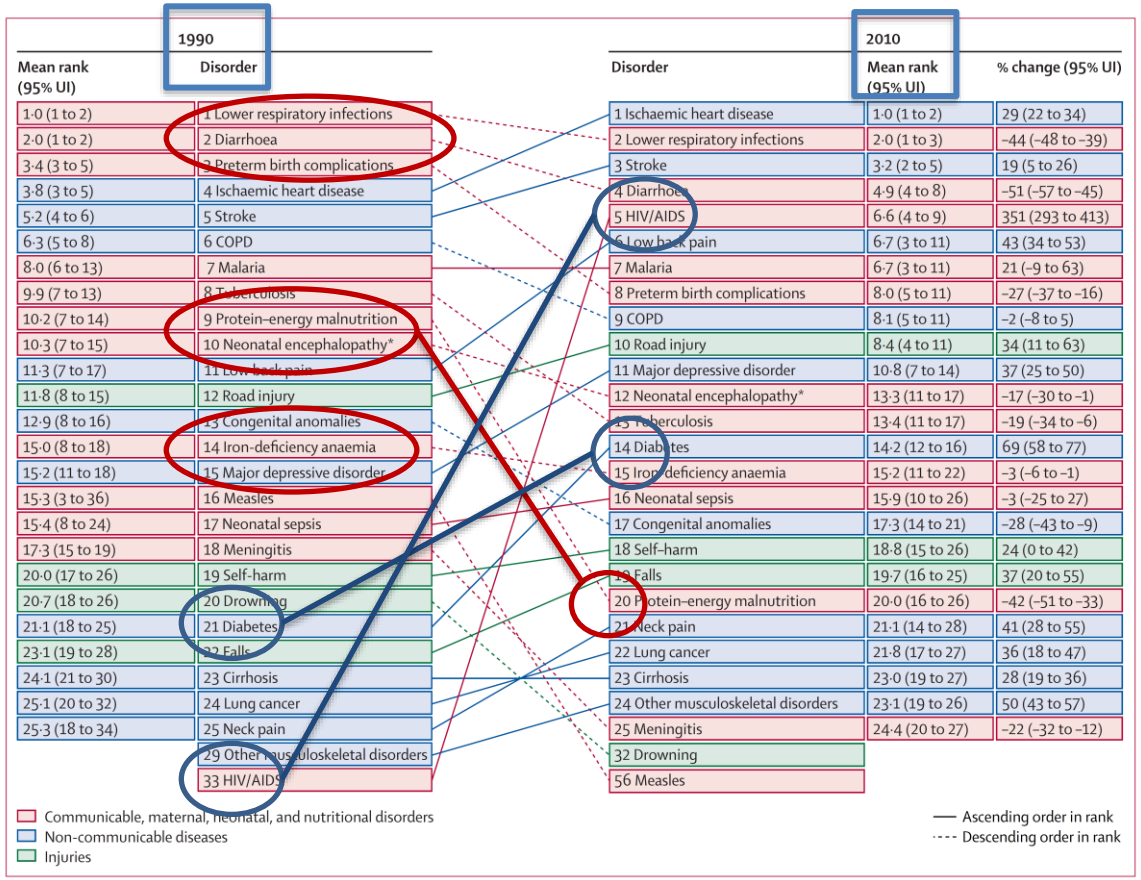
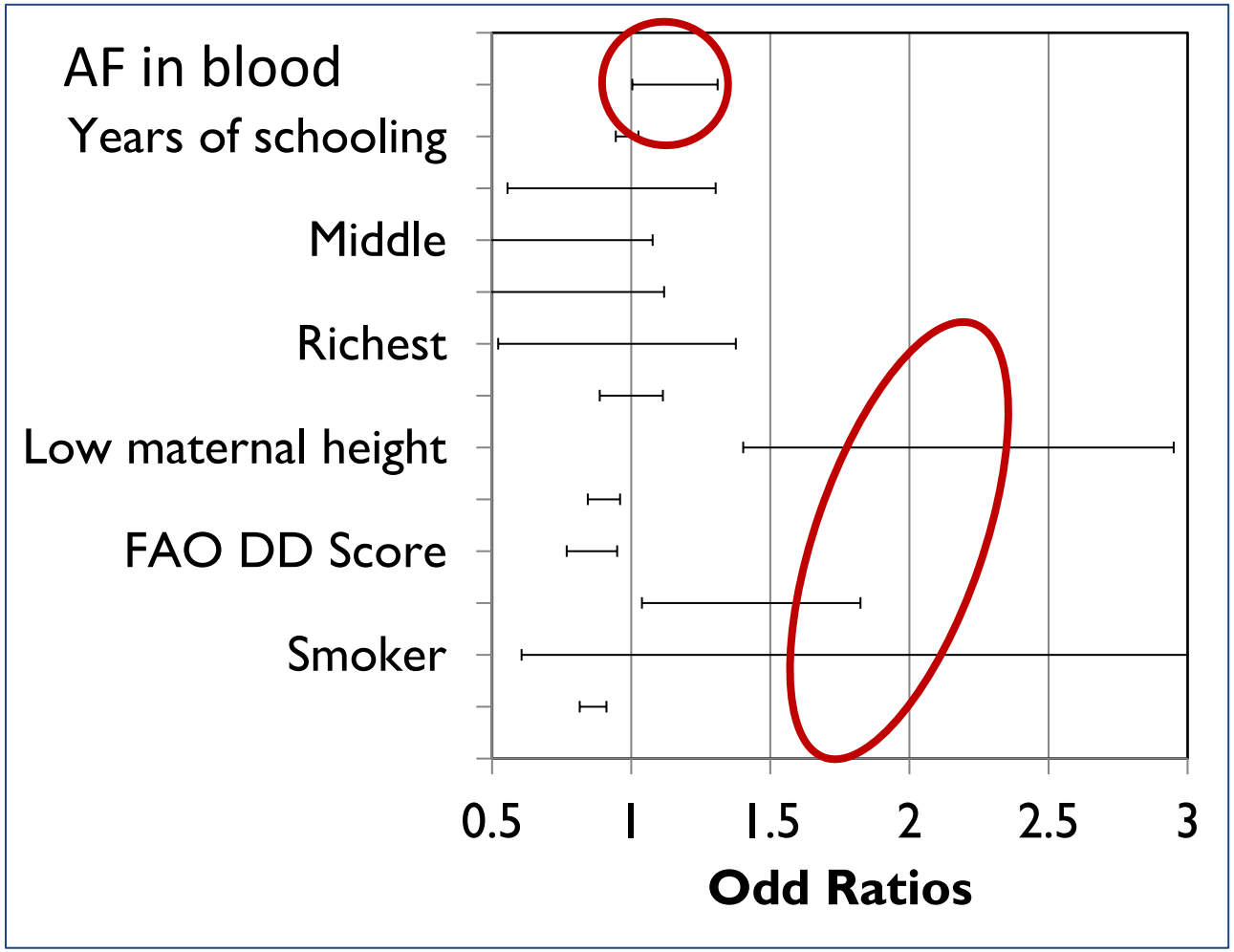


Figure 5: **Global disability-adjusted life year ranks with 95% UI for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010**

Source: Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Murray et al. Lancet 2012; 380: 2197–223*

Risk factors for Low Birth Weight in Nepal (n= 1440)



Water safety matters for health *and* nutrition

- More E. Coli linked to more *EED* in child.
- More EED in child associated with stunting and wasting.

SW **Uganda** birth cohort (n=365 children <5y)

Outcome	Unadjusted linear regression models	Adjusted linear regression models
Growth at birth		
Stunted (n = 90)	1.88 (1.23, 2.89)*	1.68 (1.22, 2.32)*
Underweight (n = 9)	0.98 (0.35, 2.76)	0.78 (0.28, 2.18)
Growth at 6 months		
Stunted (n = 86)	2.31 (1.40, 3.81)*	1.70 (1.21, 2.37)*
Underweight (n = 25)	1.70 (0.77, 3.74)	1.35 (0.61, 3.00)
Growth at 9 months		
Stunted (n = 102)	1.66 (0.94, 2.93)	1.34 (0.88, 2.02)
Underweight (n = 31)	2.36 (1.49, 3.72)*	1.81 (0.92, 3.54)
Growth at L:M test (12–16 months)		
Stunted (n = 135)	1.67 (1.10, 2.53)*	1.38 (0.88, 2.18)
Underweight (n = 34)	1.29 (0.81, 2.05)	1.10 (0.61, 1.95)

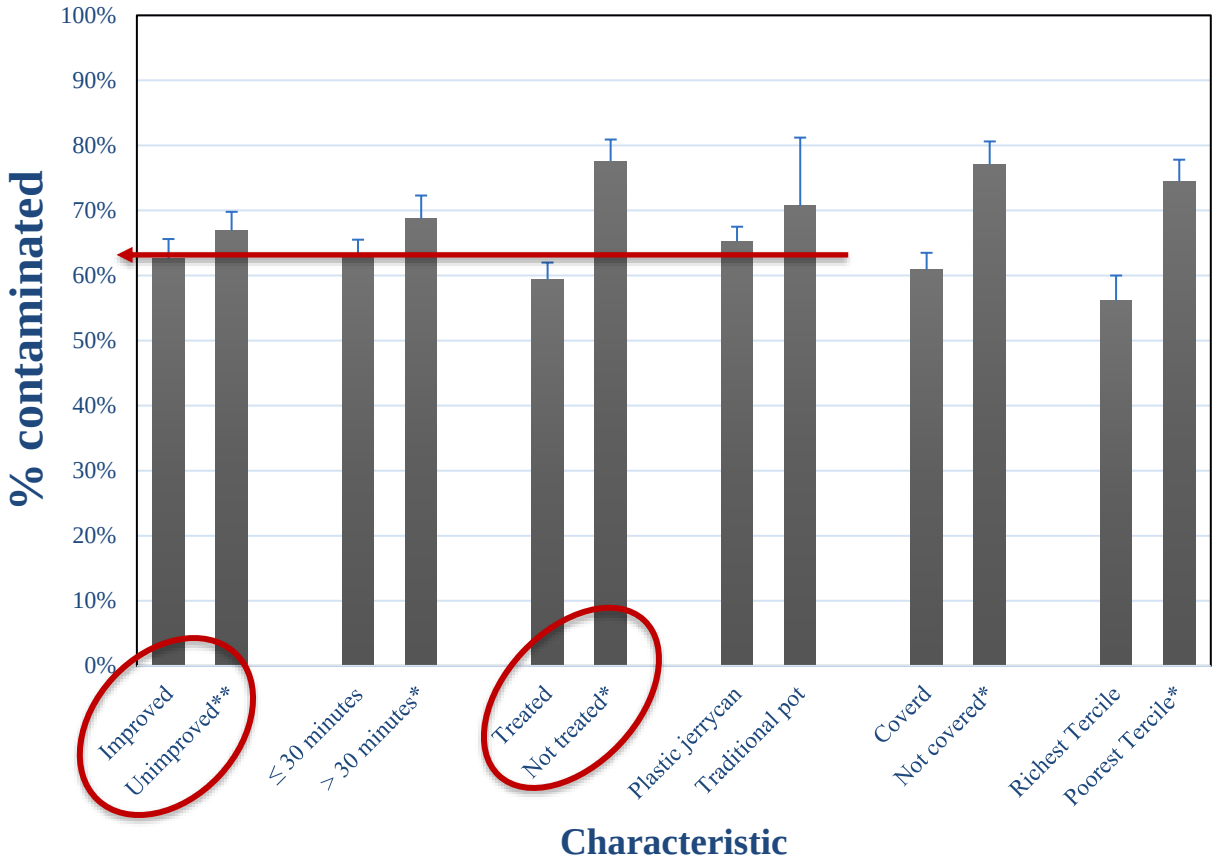
Cells present odds ratio (OR) and 95% confidence interval, * *P*-value < 0.05

Source: Lauer et al. 2018. *Am Jou Trop. Med.*

Water safety matters for health *and* nutrition

- E. Coli contamination of 'treated', 'covered' or 'improved' water sources almost as bad as unimproved.

Birth cohort in SW **Uganda** [n = 2,022 households]



Source: Lauer et al. 2018

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

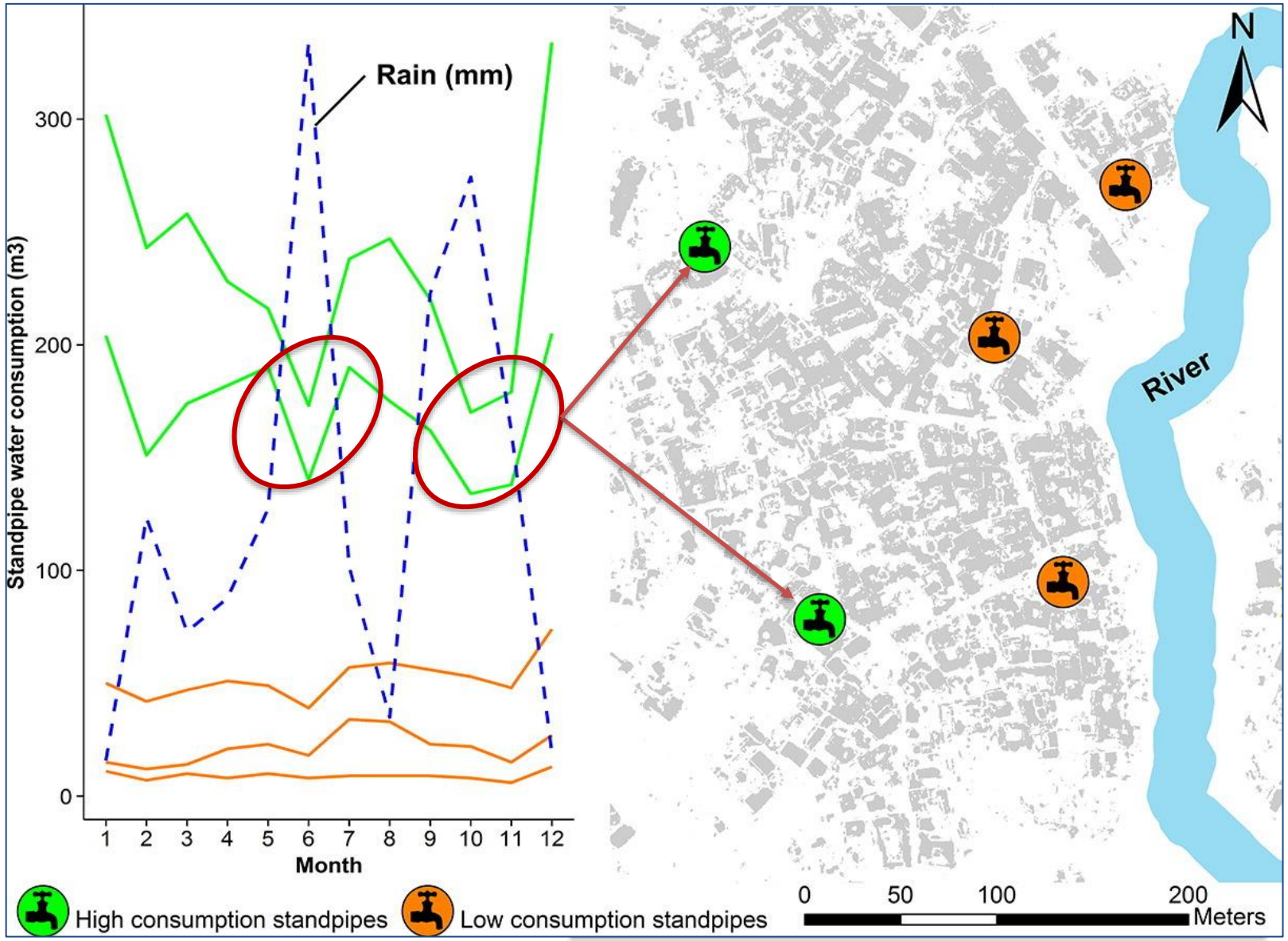
Main water source	Total	Safe, *n* (%)	Unsafe, *n* (%)
Piped	8	4 (50.0)	4 (50.0)
Public tap	45	26 (57.8)	19 (42.2)
Tube well/borehole	57	17 (29.8)	40 (70.2)
Protected well/spring	85	35 (41.2)	50 (58.8)
Unprotected well/spring	110	54 (49.1)	56 (50.9)
Rain water	15	11 (73.3)	4 (26.7)
Surface water	54	17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

Source: Lauer et al. 2018. Unsafe Drinking Water Is Associated with Environmental Enteric Dysfunction (*Am Jou Trop Med Hyg*).

Association between water quality (safe vs. unsafe)† and growth outcomes (LAZ, WAZ, and WLZ) at birth, 6 months, 9 months, and the time of the L:M test in unadjusted and adjusted linear regression models‡

Outcome	Unadjusted linear regression model	Adjusted linear regression model
Growth at birth		
LAZ	0.65 (0.06, 1.24)*	0.57 (0.10, 1.04)*
WAZ	0.18 (–0.06, 0.43)	0.15 (–0.12, 0.42)
WLZ	–0.38 (–1.04, 0.28)	–0.38 (–1.02, 0.27)
Growth at 6 months		
LAZ	0.40 (–0.27, 1.08)	0.16 (–0.24, 0.56)
WAZ	0.35 (0.18, 0.52)*	0.23 (0.06, 0.41)*
WLZ	–0.02 (–0.64, 0.60)	0.13 (–0.32, 0.58)
Growth at 9 months		
LAZ	0.25 (–0.40, 0.89)	0.10 (–0.28, 0.48)
WAZ	0.35 (0.11, 0.60)*	0.23 (–0.03, 0.49)
WLZ	0.18 (–0.33, 0.69)	0.16 (–0.31, 0.63)
Growth at L:M test (12–16 months)		
LAZ	0.39 (0.13, 0.65)*	0.29 (0.00, 0.58)*
WAZ	0.29 (0.16, 0.43)*	0.20 (0.05, 0.34)*
WLZ	0.08 (–0.24, 0.40)	0.14 (–0.17, 0.44)

L:M = lactulose:mannitol; LAZ = length-for-age *Z*-score; WAZ = weight-for-age *Z*-score; WLZ = weight-for-length *Z*-score. Cells present β coefficient and 95% confidence interval,
* *P*-value < 0.05.



Source: Kulinkina et al. 2016. Piped Water Consumption in Ghana (*Science of Total Environ.)* https://doi.org/10.1016/j.scitotenv.2016.03.148

CONCLUSIONS

- What matters as a risk factor depends on context. Know the context!
- Inflammation and stressors of all kinds (HIV, mycotoxins, e.coli) *interact* in important but not always linear ways. Behaviors matter hugely.
- Programs can't measure *everything*, but assumptions should always be tested and validated. Theories of Change should be *more rigorous and transparent* in their assumptions and expectations.
- Field-friendly metrics and measurement techniques are still limited (for assessing multiple mycotoxins in food as cooked, cleanliness of water, sanitary status of kitchens, etc.)

Q&A

THANK YOU

- To register for upcoming webinars, you can visit **NutritionInnovationLab.org** or **AdvancingNutrition.org**. More details coming soon!
- Recordings and slides for each webinar will also be posted on our websites.

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