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

Environmental Enteric Dysfunction, Aflatoxin Exposure, and Poor Growth Outcomes in Uganda

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DISCLOSURES

- I have no actual or potential conflict of interest in relation to this presentation

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PROBLEM

- Undernutrition underlies 3.1 million child deaths annually, or 45% of all childhood mortality.

- Stunting, or a length- or height-for-age Z-score (LAZ or HAZ) < -2 relative to the World Health Organization (WHO) growth standard median, affects ~151 million (22%) children < 5.
  - Increased morbidity and mortality from infections
  - Diminished cognitive function
  - Fewer years and poorer performance in school
  - Reduced economic productivity
  - Increased risk of chronic disease later in life
  - Increases risk of babies born LBW

Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries

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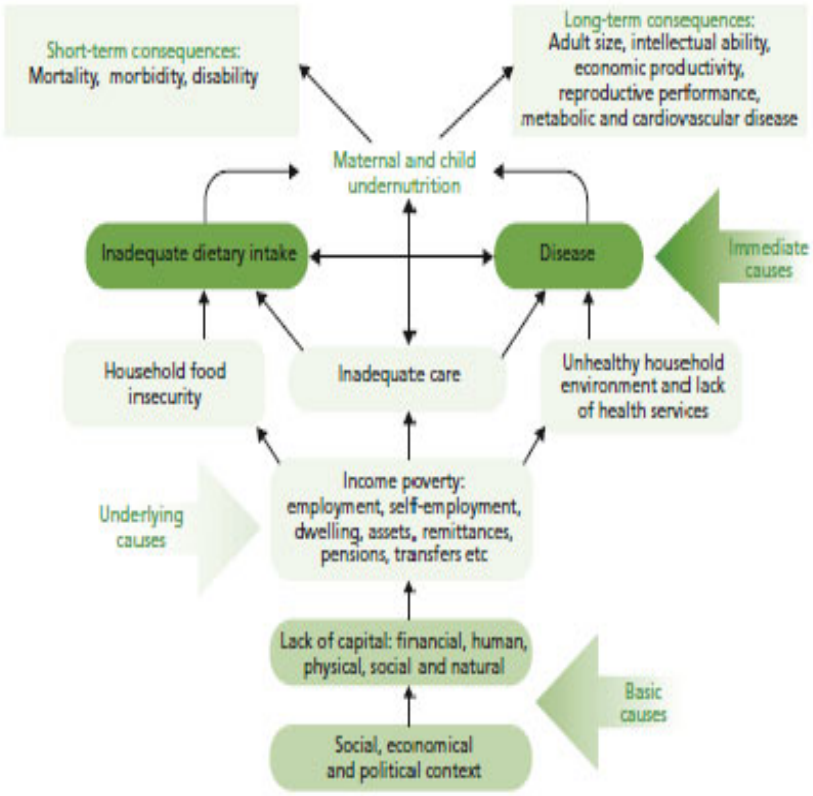
KNOWLEDGE GAP

We know that adequate nutrition alone is not enough:

- 10 best nutrition specific interventions implemented with 90% coverage in the highest burden countries would reduce global stunting by 20% (Lancet 2013)

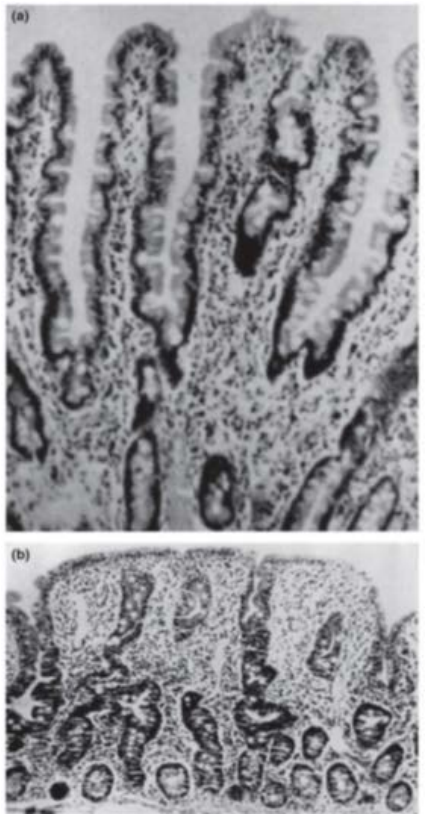
And diarrheal disease fails to explain much of the gap:

- WASH interventions implemented at 99% coverage would reduce diarrhea incidence by 30%, which would reduce the prevalence of stunting by only 2.4% (Lancet 2008)



ENVIRONMENTAL ENTERIC DYSFUNCTION

- A healthy small intestine serves many functions in the body, including aiding in the digestion and absorption of food and in immune response.
- EED is a subclinical, inflammatory disorder of the small intestine characterized by altered gut morphology, reduced absorptive capacity, and impaired barrier function.
- It is postulated that EED develops throughout infancy as the result of chronic exposure to enteropathogens due to living in poor water, sanitation, and hygiene (WASH) conditions.



AFLATOXINS

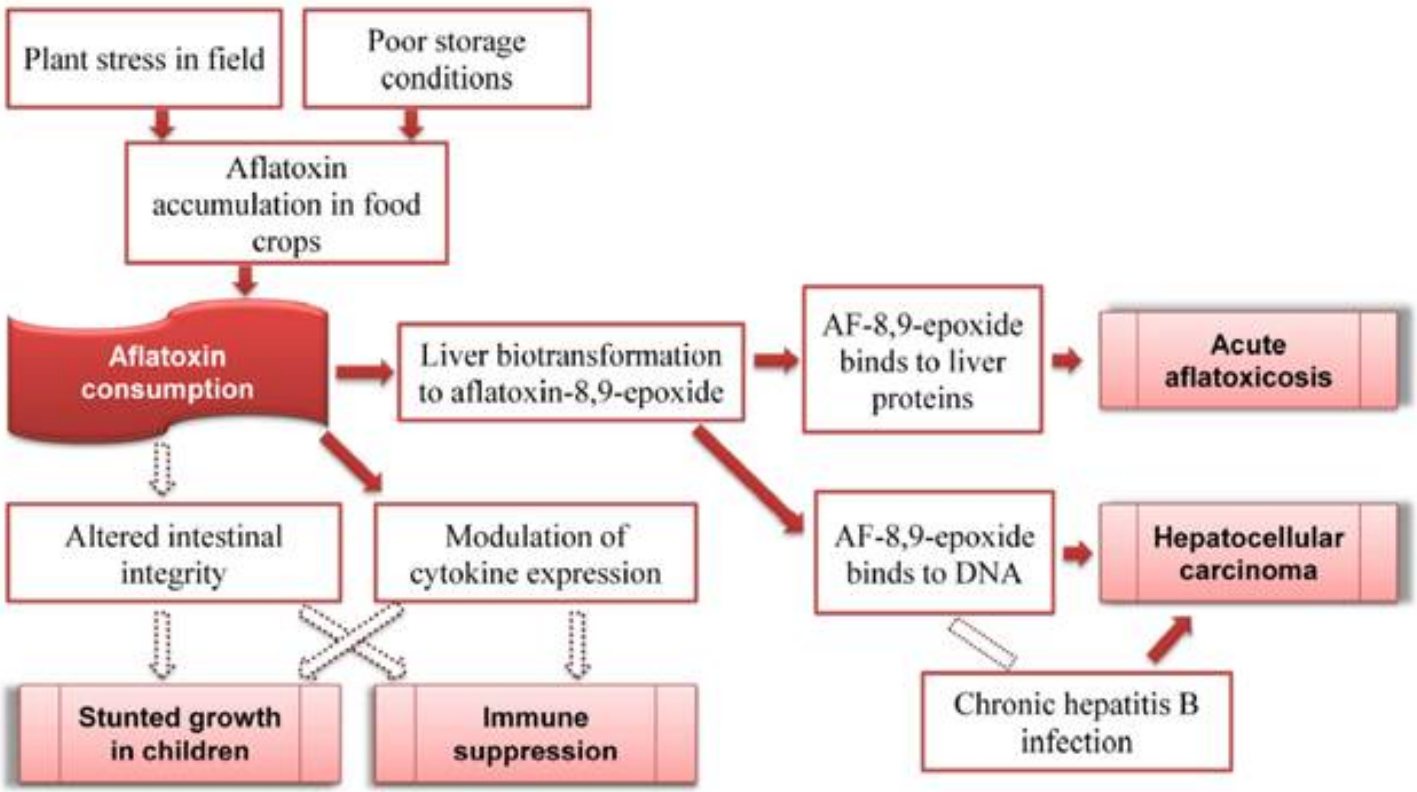
- Aflatoxins are naturally-occurring, toxic secondary metabolites of *Aspergillus* molds, particularly *A. flavus* and *A. parasiticus*.
  - Aflatoxin B_1 (AFB_1) is the most common and toxic of the varieties.

- Widespread in the food supply, particularly in LMICs due to poor harvest and storage practices
  - Ex. corn, cassava, wheat, rice, tree nuts, peanuts, chilies, and spices
  - ~ 4.5 billion people chronically exposed

- They have been linked to a number of carcinogenic, teratogenic, and immunotoxic health effects, especially liver cancer.

- They can cross the placental barrier, and both in utero and infant exposure have been linked to poor growth and development.

AFLATOXINS



From: Ogodo AC, Ugbogu OC. Public health significance of aflatoxin in food industry—A review. European Journal of Clinical and Biomedical Sciences. 2016;2(5):51-8.

STUDY OBJECTIVE

To examine the association between EED biomarkers (L:M ratios and anti-flagellin/anti-LPS Igs) and aflatoxin biomarkers (AFB1-Lys) in pregnant women aged 18-45 years and subsequent adverse birth outcomes (shorter gestational age, lower birth weight and length, and smaller head circumference) in Mukono District, Uganda

STUDY SETTING

METHODOLOGY

- Prospective cohort study (n=258) conducted between February and November 2017
- Pregnant women were recruited at their first prenatal visit to Mukono Health Center IV (about 16 weeks gestation)
- Associations were assessed with STATA 15 software using (multivariate) linear regression models

Inclusion criteria	Exclusion criteria
Between 18 and 45 years old	Severely malnourished (BMI < 16.0 kg/m2)
Residing within 10 km. of Mukono Town	Severely anemic (Hb < 7 g/dl)
Carrying a singleton pregnancy	HIV-positive
	Planning to move from Mukono District

METHODOLOGY: 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)

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

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BIRTH CHARACTERISTICS

TABLE 2
Birth outcome characteristics for 220 newborn infants in Mukono, Uganda [1]

Birth characteristic	Mean ± SD or *n* (%)
Female	115 (52.3)
Gestational age, wk	39.7 ± 2.1
Preterm, <37 wk	15 (6.8)
Birth weight, kg	3.3 ± 0.5
Birth length, cm	48.1 ± 3.2
Head circumference, cm	35.2 ± 1.5
LBW, <2500 g	8 (3.6)
SGA, <10th percentile	24 (11.3)
Weight-for-length *z* score	0.47 ± 1.54
Weight-for-age *z* score	−0.10 ± 1.01
Length-for-age *z* score	−0.44 ± 1.07
Wasted, <−2 SD	13 (6.5)
Stunted, <−2 SD	15 (7.2)

1LBW, low birth weight; SGA, small for gestational age.

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)	0.02 (−0.24, 0.29)	0.04 (−0.21, 0.30)	0.01 (−0.22, 0.24)	0.03 (−0.11, 0.16)	0.01 (−0.11, 0.13)
	$P = 0.761$	$P = 0.858$	$P = 0.746$	$P = 0.901$	$P = 0.712$	$P = 0.842$
%LE	0.02 (−0.25, 0.29)	0.006 (−0.27, 0.28)	−0.03 (−0.29, 0.24)	−0.03 (−0.27, 0.20)	−0.008 (−0.15, 0.13)	−0.009 (−0.13, 0.11)
	$P = 0.897$	$P = 0.968$	$P = 0.850$	$P = 0.776$	$P = 0.915$	$P = 0.881$
Anti-flagellin IgA	−0.26 (−0.96, 0.44)	−0.37 (−1.10, 0.36)	0.11 (−0.57, 0.79)	−0.15 (−0.79, 0.49)	0.05 (−0.31, 0.41)	−0.11 (−0.44, 0.23)
	$P = 0.463$	$P = 0.322$	$P = 0.743$	$P = 0.643$	$P = 0.785$	$P = 0.533$
Anti-LPS IgA	−0.24 (−1.06, 0.58)	−0.25 (−1.10, 0.60)	−0.36 (−1.15, 0.43)	−0.48 (−1.22, 0.25)	−0.21 (−0.63, 0.21)	−0.28 (−0.67, 0.10)
	$P = 0.566$	$P = 0.564$	$P = 0.372$	$P = 0.193$	$P = 0.323$	$P = 0.152$
Anti-flagellin IgG	−0.79 (−1.66, 0.08)	−0.89 (−1.77, −0.01)	−0.68 (−1.52, 0.16)	−0.80 (−1.55, −0.05)	−0.38 (−0.83, 0.06)	−0.44 (−0.83, −0.05)
	$P = 0.075$	$P = 0.047$*	$P = 0.110$	$P = 0.036$*	$P = 0.089$	$P = 0.029$*
Anti-LPS IgG	−0.98 (−1.82, −0.15)	−1.01 (−1.87, −0.17)	−0.50 (−1.32, 0.32)	−0.79 (−1.54, −0.04)	−0.29 (−0.72, 0.15)	−0.40 (−0.79, −0.01)
	$P = 0.021$*	$P = 0.019$*	$P = 0.234$	$P = 0.039$*	$P = 0.197$	$P = 0.043$*

[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.

In adjusted linear regression models, higher ln 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

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ORIGINAL ARTICLE

WILEY | Maternal & Child Nutrition

Maternal aflatoxin exposure during pregnancy and adverse birth outcomes in Uganda

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TABLE 2 Association between maternal aflatoxin exposure during pregnancy (ln AFB-Lys levels) and birth characteristics for 220 mother-infant pairs in Mukono district, Uganda, using unadjusted and adjusted linear regression models[a]

	Unadjusted model	Adjusted model[a]
Weight, kg	−0.07 (−0.14, −0.002) p = 0.045	−0.07 (−0.13, −0.003) p = 0.040
Length, cm	−0.09 (−0.41, 0.24) p = 0.598	−0.10 (−0.42, 0.22) p = 0.532
Weight-for-age z-score	−0.16 (−0.32, −0.006) p = 0.041	−0.16 (−0.30, −0.01) p = 0.037
Weight-for-length z-score	−0.15 (−0.40, 0.10) p = 0.238	−0.15 (−0.40, 0.11) p = 0.267
Length-for-age z-score	−0.06 (−0.23, 0.11) p = 0.444	−0.07 (−0.24, 0.10) p = 0.406
Head circumference, cm	−0.24 (−0.48, −0.005) p = 0.045	−0.26 (−0.49, −0.02) p = 0.035
Head circumference-for-age z-score	−0.22 (−0.42, −0.02) p = 0.030	−0.23 (−0.43, −0.03) p = 0.023
Gestational age at birth, weeks	−0.11 (−0.44, 0.22) p = 0.526	−0.07 (−0.41, 0.26) p = 0.663

Cells present β coefficient, 95% confidence interval, and p-value.

[a]Adjusted linear regression model controls for maternal age, weight, pulse pressure, and years of education in all models. Infant gestational age at birth was controlled for in all models except for when an outcome variable.

In adjusted linear regression models, higher ln maternal AFB-Lys levels were associated with lower weight, lower WAZ, smaller head circumference, and lower HCZ in infants at birth

DISCUSSION

- Biomarkers of both maternal EED and aflatoxin exposure during pregnancy were associated with negative birth outcomes.

- AFB-Lys levels were detected in all 247 samples, indicating widespread dietary aflatoxin exposure in the study population.

- No significant associations were observed between EED and aflatoxin biomarkers

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QUESTIONS

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