FEED THE FUTURE INNOVATION LAB
For Collaborative Research on Nutrition

USAID FROM THE AMERICAN PEOPLE

Tufts UNIVERSITY | Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy

Obesity and Stunting in Egypt, and The Roles of Water, Sanitation, and Mycotoxins

August 4, 2015

Jeffrey K. Griffiths, MD MPH&TM
Professor of Public Health, Medicine, Nutrition, Engineering, & Veterinary Medicine
USAID Innovation Lab for Nutrition - Africa
Tufts University Boston USA

Focus of this talk

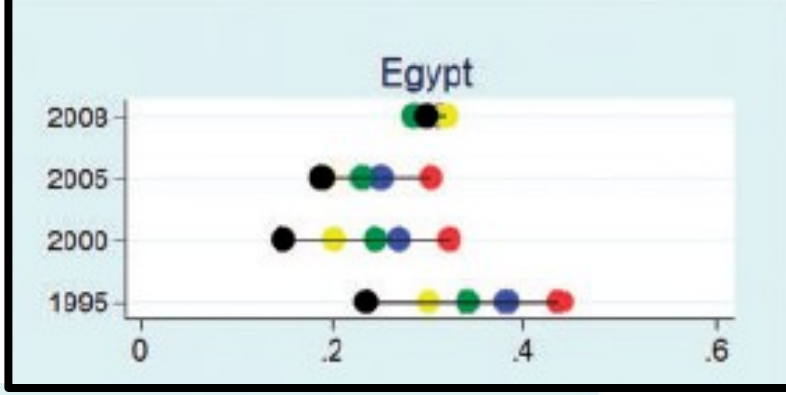
- Malnutrition and under-nutrition remain major global health issues, even as obesity and over-nutrition are on the rise.
- An operating paradigm has been that the lack of food, both calories and micronutrients is a root cause. *IT IS BUT:*
- This turns out to be too simple – new data is showing major influences of the external, and internal (microbiome), environments.

Persistent inequalities in child undernutrition: evidence from 80 countries, from 1990 to today

Caryn Bredenkamp,[1]* Leander R Buisman[2] and Ellen Van de Poel[2]

[1]World Bank, Washington, DC, USA, [2]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

International Journal of Epidemiology, 2014, 1328–1335



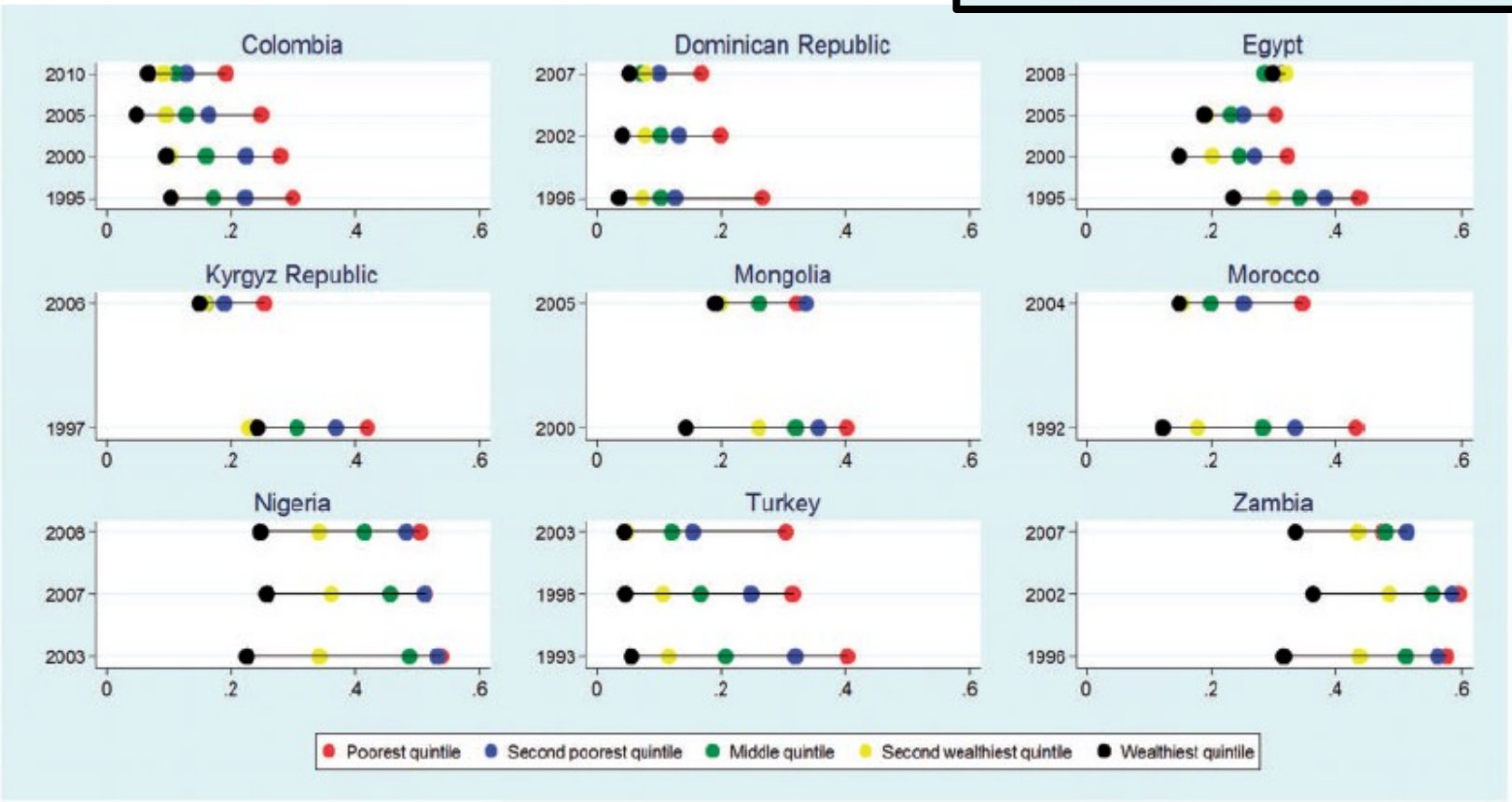
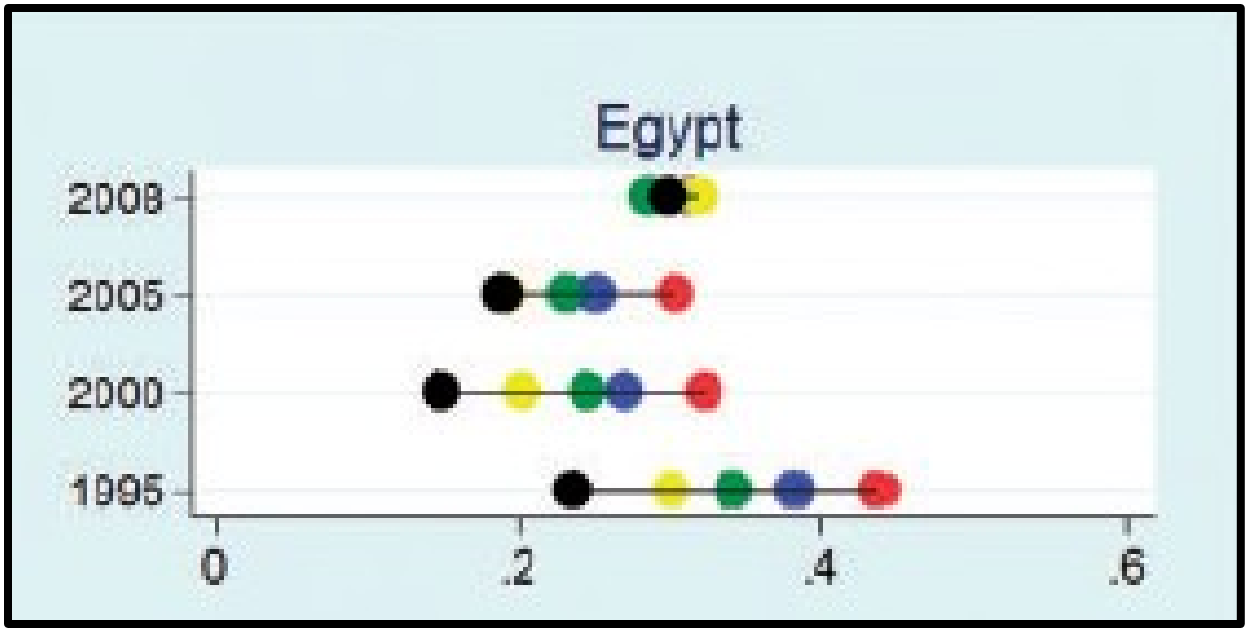


Figure 4. Changes in the distribution of the prevalence of stunting, by quintile, for selected countries with reductions in stunting prevalence and narrowing socioeconomic inequality.

Source: DHS and MICS surveys, 1990-2011.

Notes: Mean prevalence of stunting (in %) on the x-axis, survey year on the y-axis.

socioeconomic inequality has less predictive power for stunting in Egypt



and −0.4). Indeed, most Latin American countries have very high inequality. Inequality is smallest in Egypt, followed by Madagascar, Comoros, Vanuatu and Jordan, where concentration indices range between 0 and −0.05.

In Egypt…

- **The mean BMI for Egyptian women of reproductive age rose from 26.31 in 1995 to 28.52 in 2005.** Older, rural women in poor households became obese at a faster rate then younger women residing in richer, urban households. **Simultaneous stunting and obesity** is spread across all social and economic classes though the relationship is complex.
- The WFP conducted a secondary analysis of food security issues in 2011, which identified a number of information gaps around this issue. The *specific* linkages between the factors relating to stunting and the Egyptian population, are very poorly understood.
- It is suggested that key contributing factors have

Research Questions

- What is the relationship of stunting and overweight in Egyptian children across time
- What is the relationship between stunting/overweight and maternal nutritional status
- What is the relationship between child stunting/overweight and maternal diet quality
- How does stunting/overweight, diet quality and household food consumption and expenditure including consumption of high energy low nutritive value foods differ by region (as in what is the relationship of these key variables at a community/regional level)?
- What is the change over time in stunting and overweight in the Egyptian population by wealth

Methods

- Data: Egypt Demographic Health Surveys 1988, 1992-3, 1995-6, 2000, 2005, 2008 and 2014 and the Household Income, Expenditure and Consumption Survey (HIECS) data set for the years 2008 and 2012. (About 10,000 data points per survey)
- The data for each DHS year comes in multiple datasets for individuals (mothers infants, children) and household characteristics, etc. Relevant data sets that included the variables of interest were downloaded.
- Data were imported from SPSS into SAS and for each year the data for the mother were merged with the child data set using 3 key identifier followed by a merge with the household data set

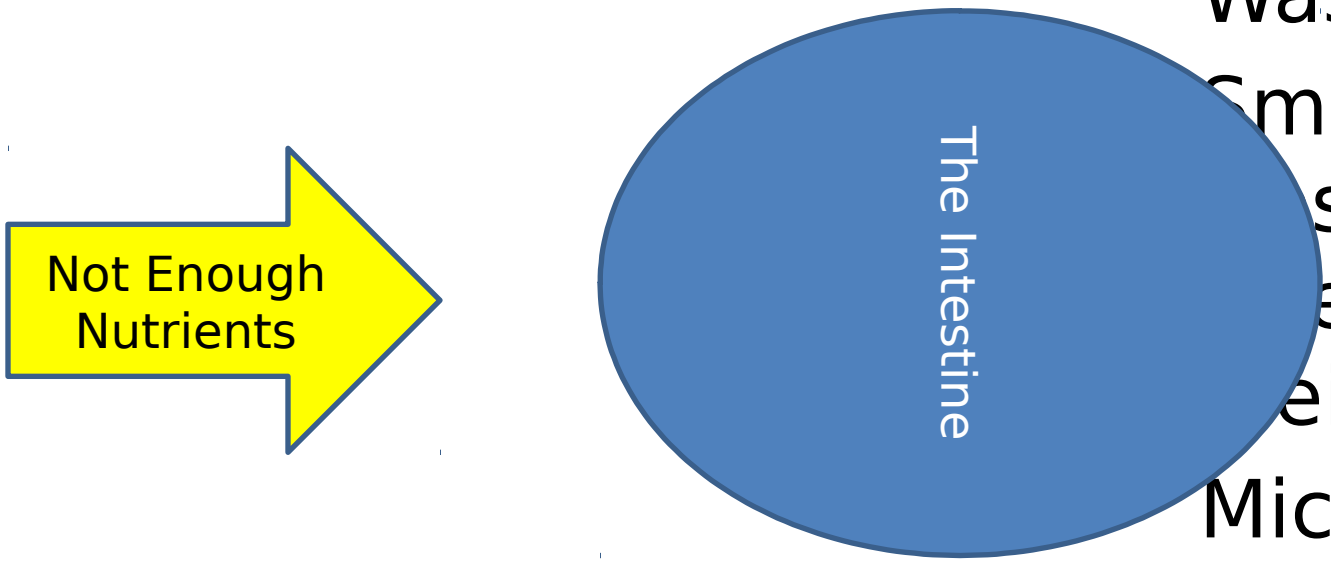
Methods

- All data on weights and heights of the children were downloaded and anthropometric indices of height for age, weight for age and weight for height were re-calculated using the WHO 2006 standards.
- To maintain consistency, the study analyst re-calculated the indices for the new survey years
- Pearson correlations coefficients will be estimated to examine associations of key variables with stunting and overweight and identify variables to be included in the step-wise regression analyses.
- Descriptive statistics including mean HAZ, mean WHZ and correlation coefficients for stunting and overweight with key variables were also estimated for different subgroups, including, sex (gender), age, urban/rural and the different regions of Egypt.
- Statistical tests to be used include log transformed linear regression analyses and/or stepwise multivariate logistic regression analysis will be conducted.

Current activities

- Per timeline submitted in the workplan
  - All data have been downloaded
  - All indices have been compared across years and re-calculated as required
  - Descriptive statistics for the different survey years are generated
  - The team is putting together the list of variables for conducting the Pearson Correlations followed by the set up of the regression models

Simple Idea – Not Enough Food = Malnutrition; Too Much = Obesity



- Stunting
- Wasting
- Small for stational e/Low Birth eight
- Micronutrient Deficiency (Fe, Zn, vitamin A)

o the fix should be – more/less food

Lancet June 2013

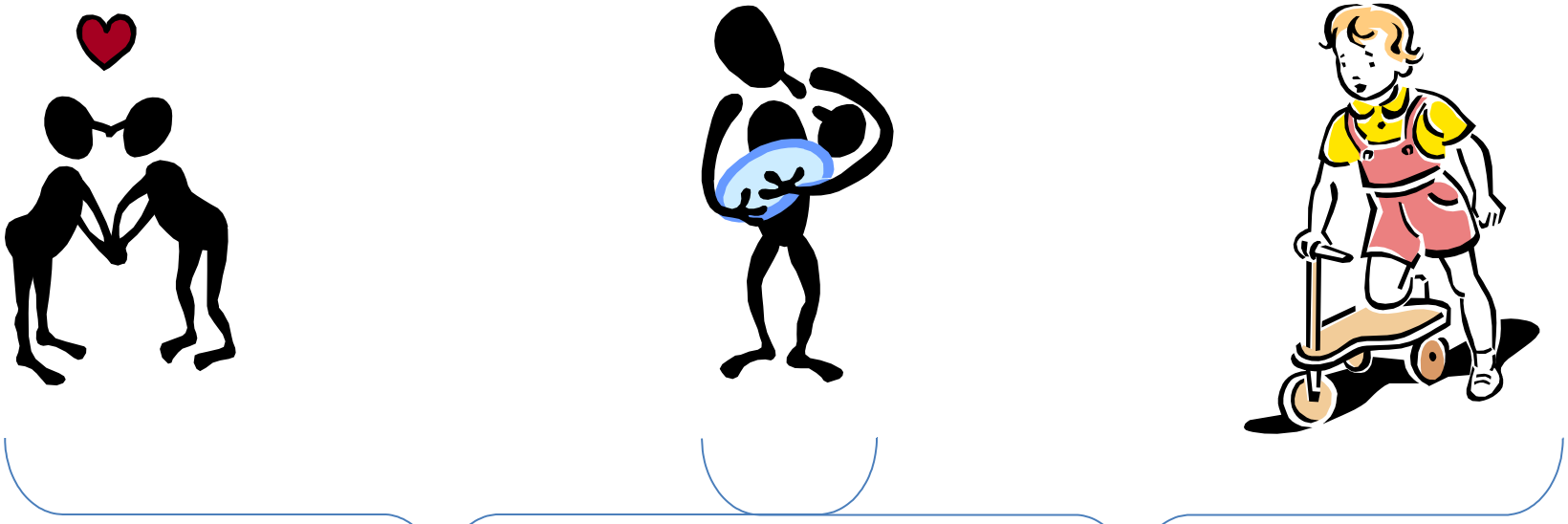
Maternal and Child Nutrition 2

Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?

Zulfiqar A Bhutta, Jai K Das, Arjumand Rizvi, Michelle F Gaffey, Neff Walker, Susan Horton, Patrick Webb, Anna Lartey, Robert E Black, The Lancet Nutrition Interventions Review Group, and the Maternal and Child Nutrition Study Group

- 800,000 neonatal / 3.1 million childhood deaths per year. 165 million stunted children.
- If top 10 <u>nutrition</u> interventions targeted to 34 countries with 90% of childhood deaths ……
- Reduce deaths by **15%**, stunting by **20%**, acute wasting by **61**%. (For < $10 billion per year).

Bad News: Lancet review (6/2013) of how much “food would fix” – not much (20%).

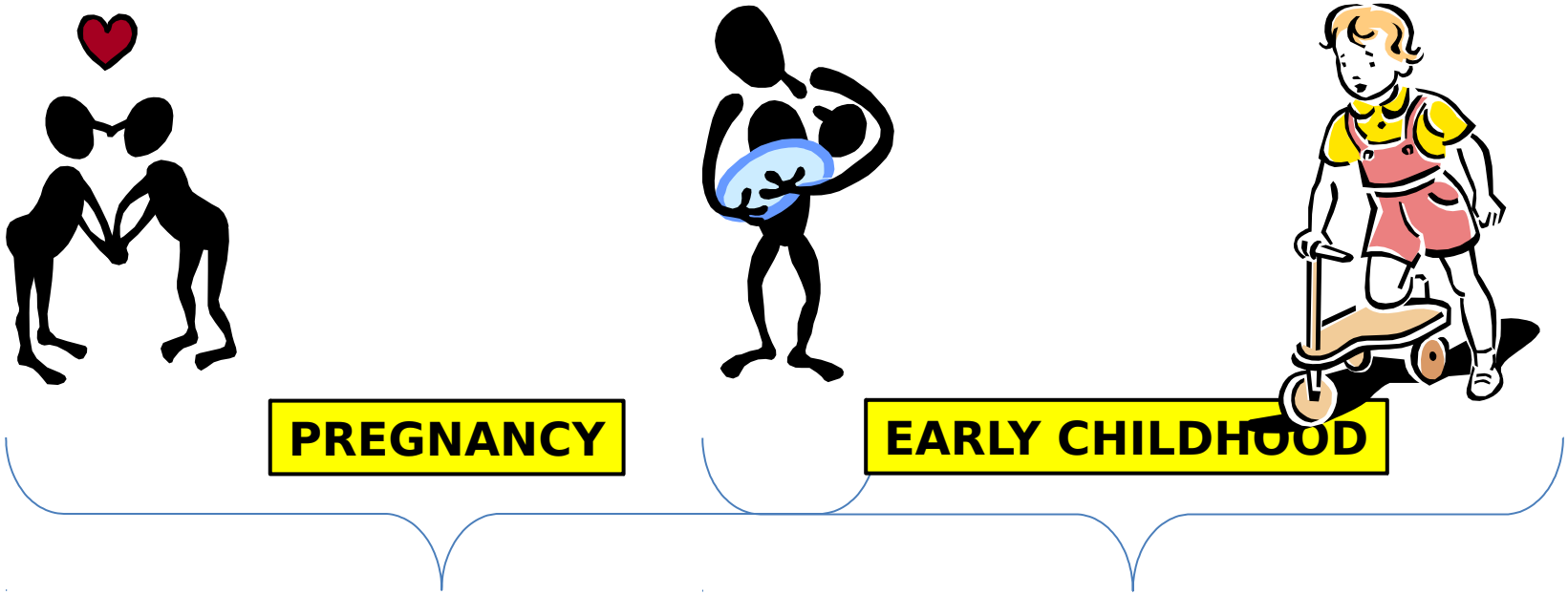


PREGNANCY **EARLY CHILDHOOD**

ADOLESCENT, PRECONCEPTION, GESTATIONAL, AND MATERNAL NUTRITION
ADEQUATE CALORIES (PROTEINS, FATS, CARBOS) IN ALL LIFE STAGES
DIVERSITY OF MICRONUTRIENTS, VITAMINS, HIGH QUALITY PROTEINS
OPTIMAL BREASTFEEDING, RESPONSIVE FEEDING PRACTICES, STIMULATION

All are *Known* Relevant Nutrition

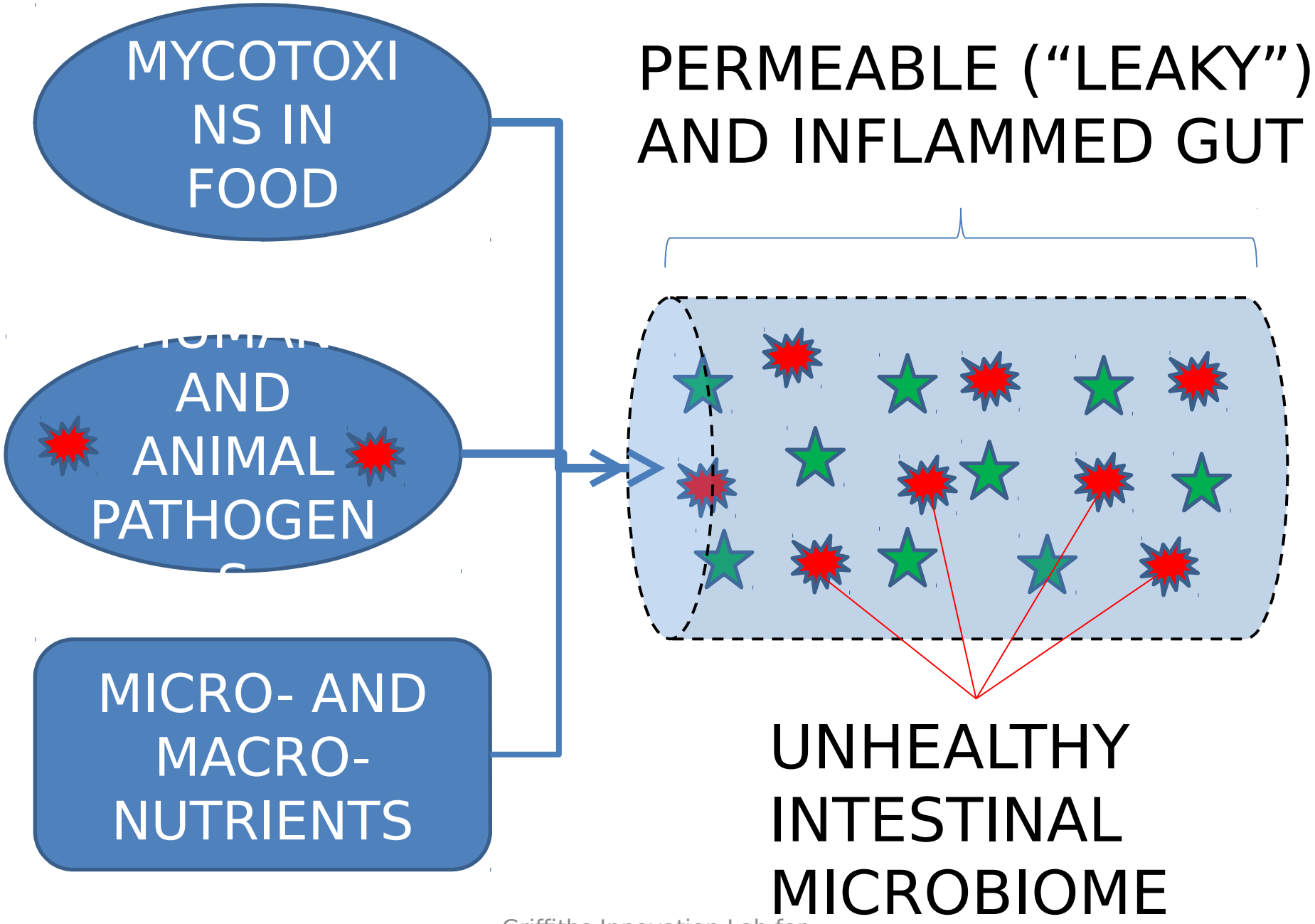
It’s not just what you eat…
It’s your external and internal environment
And how they are linked (water and sanitation)

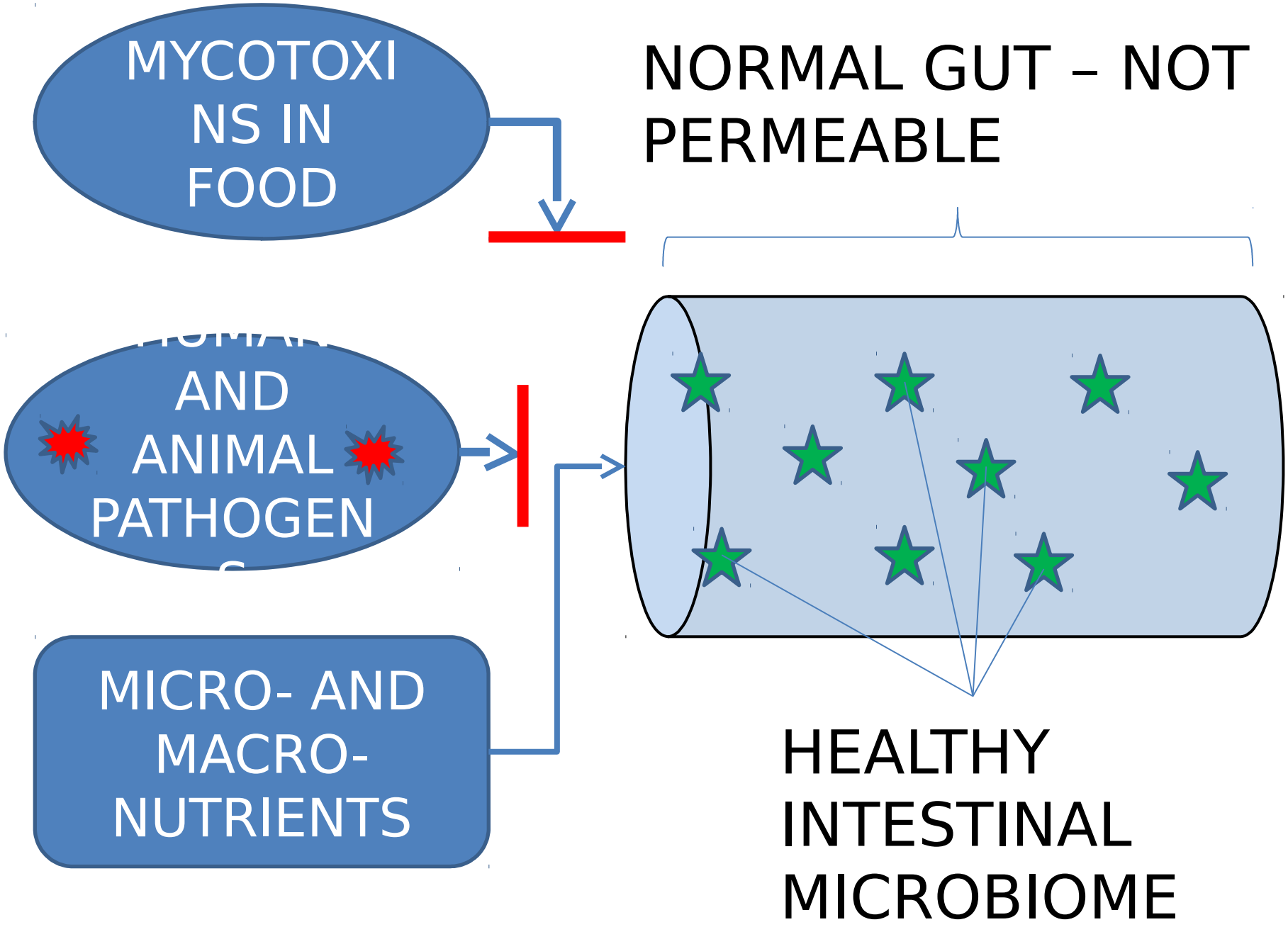


***MYCOTOXINS*:** FUNGAL FOOD TOXINS WHICH IMPAIR GROWTH AND IMMUNITY

ENVIRONMENTAL ENTEROPATHY:

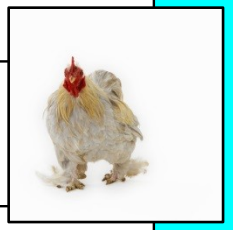
INFLAMED, LEAKY, DYSFUNCTIONAL


MYCOTOXINS IN FOOD
AND ANIMAL PATHOGEN
MICRO- AND MACRO-NUTRIENTS
PERMEABLE ("LEAKY") AND INFLAMMED GUT
UNHEALTHY INTESTINAL MICROBIOME


MYCOTOXINS IN FOOD
NORMAL GUT – NOT PERMEABLE
AND ANIMAL PATHOGEN
MICRO- AND MACRO-NUTRIENTS
HEALTHY INTESTINAL MICROBIOME

AGRICULTURAL WASTEWATER

ORGANISM	TYPICAL SOURCE
ROTAVIRUS	HUMANS; PERHAPS ANIMALS
HEPATITIS A	HUMANS
HEPATITIS E	HUMANS, **SWINE**
E. coli (bacteria)	**CATTLE,** HUMANS
Shigella species	HUMANS
Salmonella enterica (bacteria)	**CATTLE, POULTRY, SWINE, HUMANS**
Campylobacter jejuni (bacteria)	**POULTRY**
*Cryptosporidium** (protozoan)	**CATTLE,** HUMANS**, OTHER FARM ANIMALS**
*Microsporidia** (fungus)	**FARM AND DOMESTIC ANIMALS,** HUMANS
* Causes chronic diarrhea, wasting, malnutrition in people with HIV/AIDS	



Pathogens in Rural and Agricultural Water and Watersheds. USDA 2010

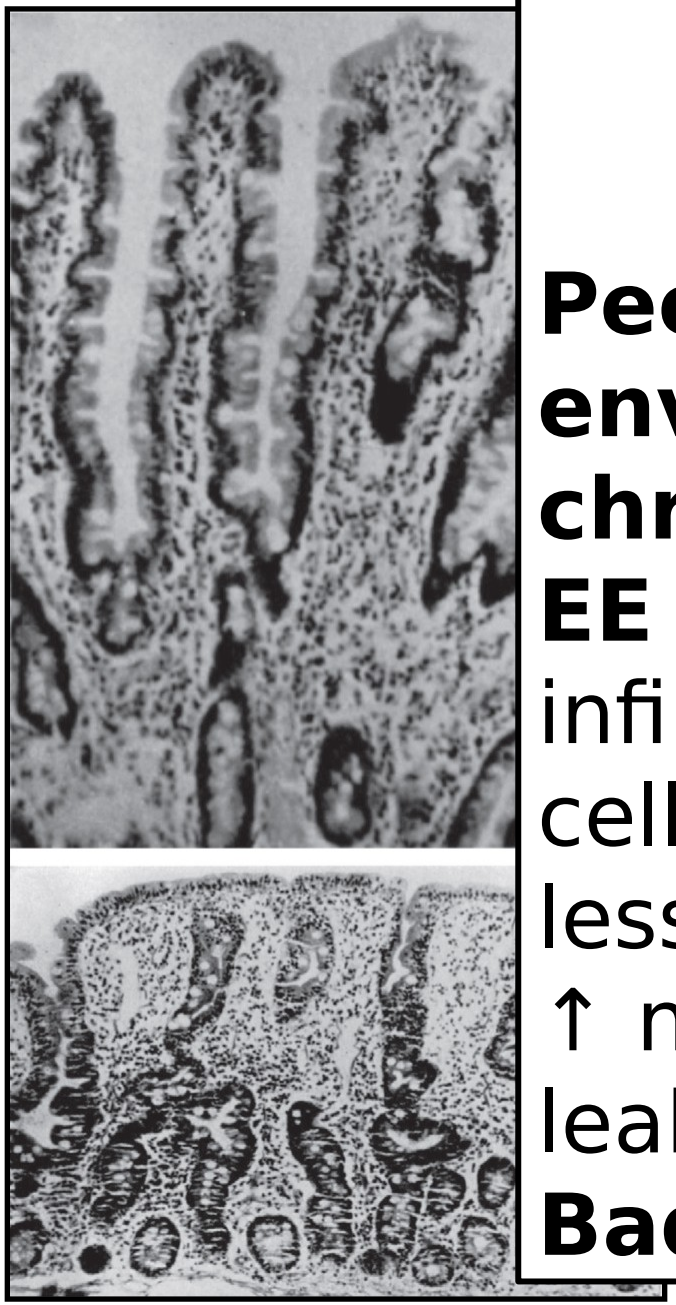
Poor Sanitation / Hygiene. Fecal Contamination of Domestic Environment

Fecal Ingestion Infants/Children and Enteric Infections

(1)Increased gut permeability (2) Bacteria (and gut contents) leak into body (3) Intestinal Inflammation

ENVIRONMENTAL ENTEROPATHY

In studies dating to 1993, 43% of stunting explained by increased gut permeability



ENVIRONMENTAL ENTEROPATHY (EE)

People living in contaminate environments have leaky, chronically inflamed intestin

EE - Short blunted villi, tissue is infiltrated with inflammatory cells. 15% less protein and 5% less carbohydrate is absorbed. ↑ nutritional needs, bacteria leak into body, leads to anemia

Bad bacteria are likely cause.

Korpe & Petri, Trends in Molecular Medicine June 2012, Vol. 18, No

Intestinal Permeability: Egypt

- Dr. Laila Hussein and colleagues (2007) at Cairo University, Giza published a study of gut permeability – the hallmark of EE – in **24 children living in El-Maragha, Sohag Governate**. Gut permeability is measured by the ability of normally excluded sugars to cross the intestine.
- Baseline mean lactulose:mannitol (expressed as a percentage of lactulose to mannitol) was **abnormally high at 4.18 % ± 0.25** (range 1.93-6.22). Only 1 of 24 children had a normal value (< 2.3%) and 8 of 24 (33%) children had permeability values in the highly abnormal range (> 5.0%).

Lunn et al Lancet 1991: **Intestinal permeability, mucosal injury, and growth faltering in Gambian infants.**

- Infants aged 2-10 months recruited into longitudinal study (n=119 ≥ 3 observations). Infants had diarrhea 7.5%, and "growth depressing permeability" 76% of the time. **43% of stunting** explained by ↑gut permeability and ↓ absorptive capacity (differential

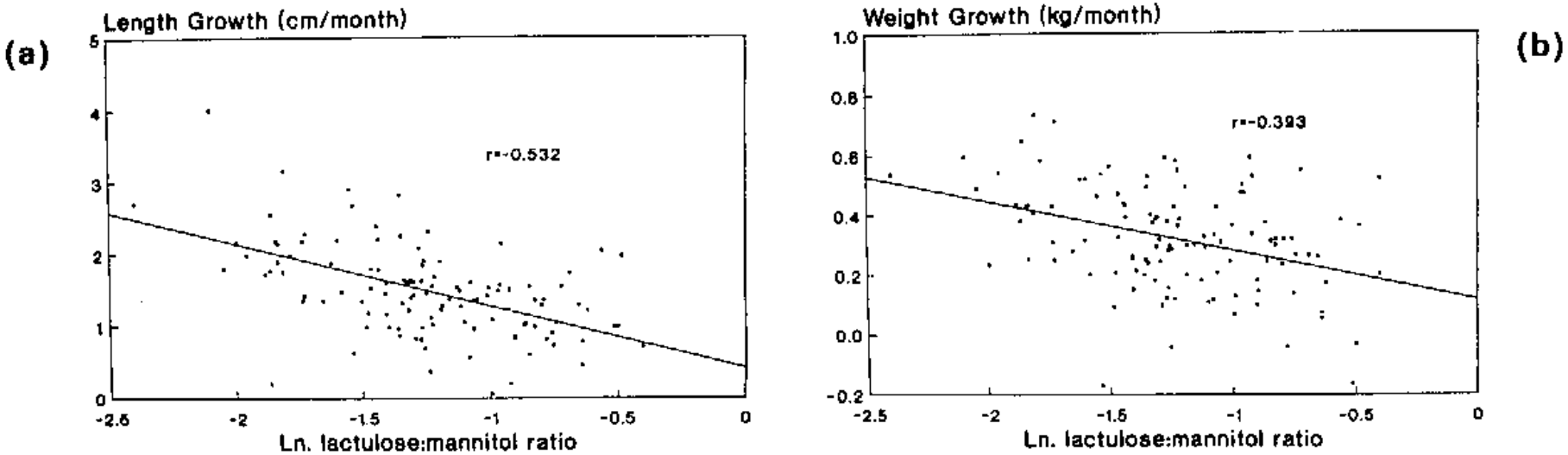
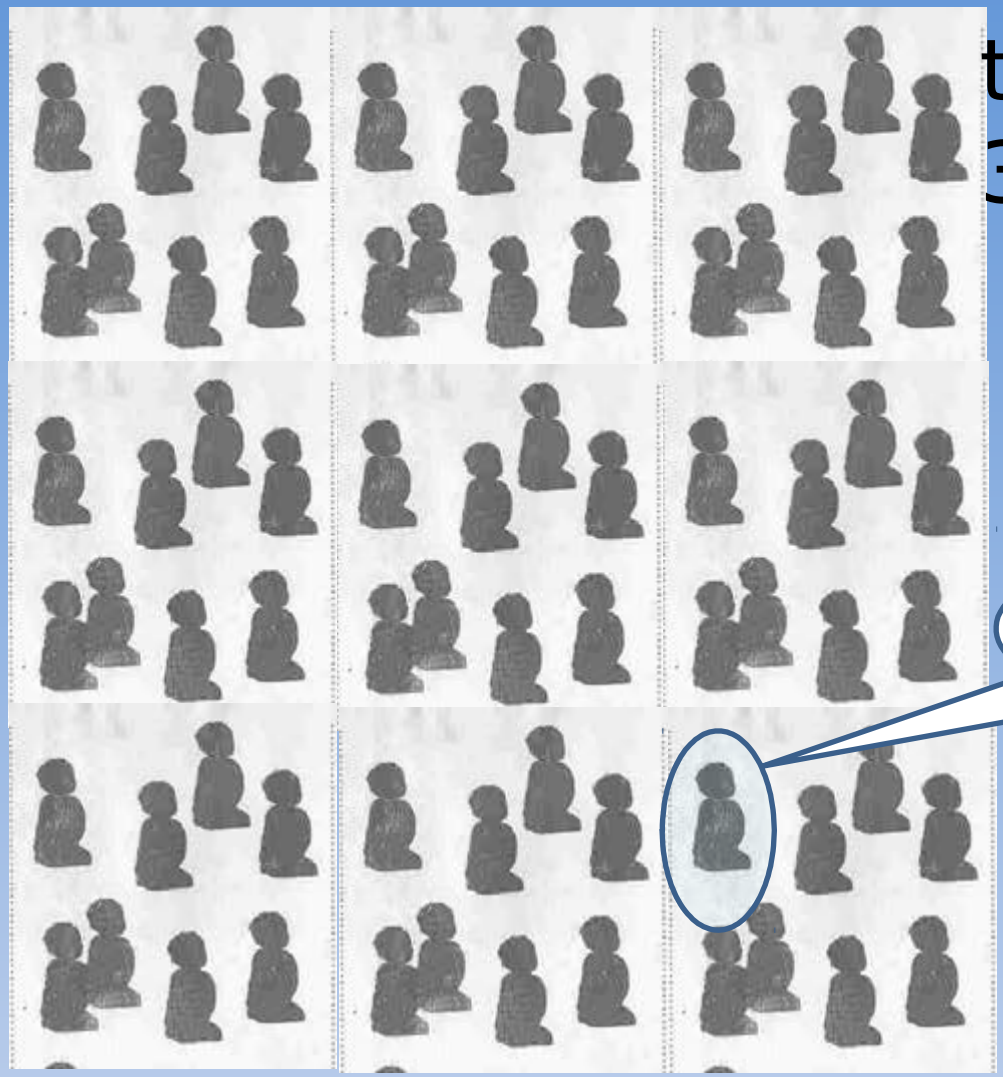


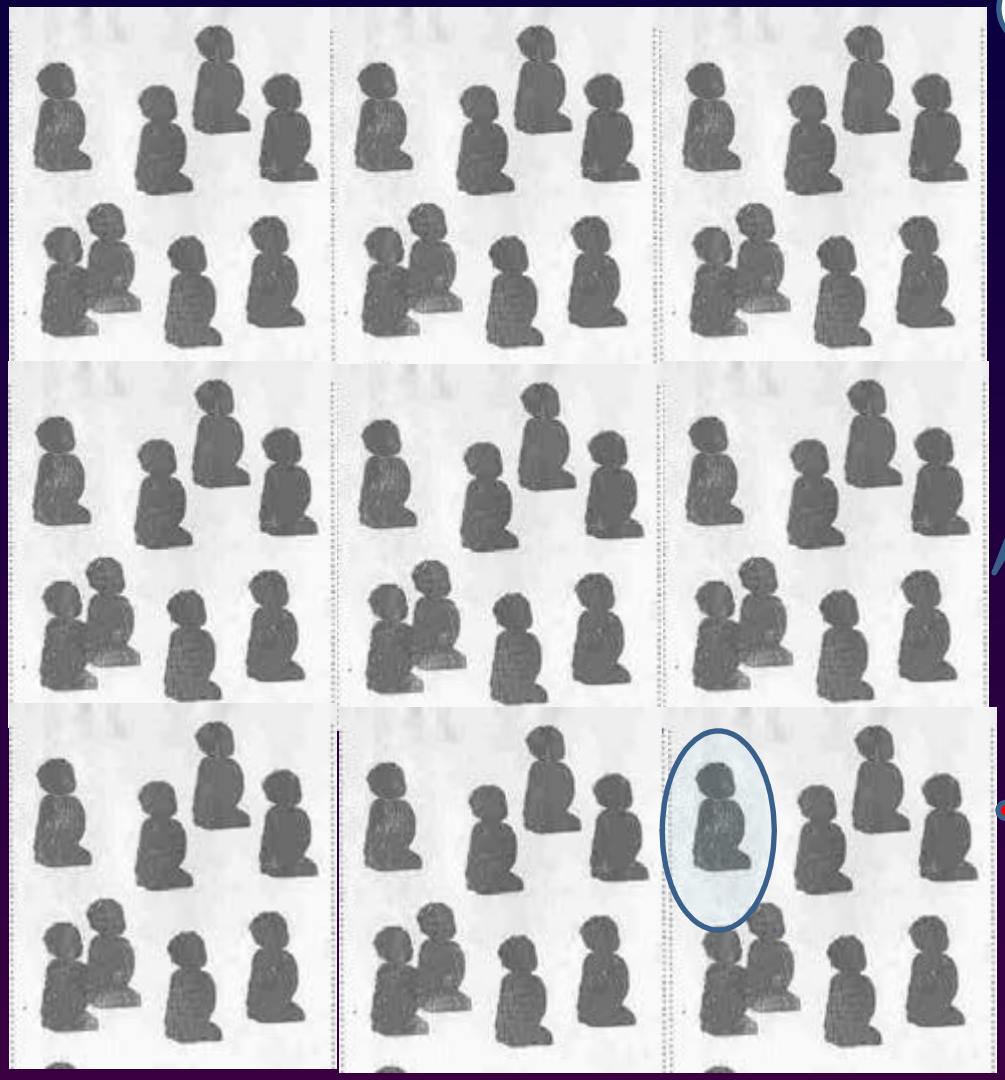
Fig 2—The relation between intestinal permeability (expressed as $\log_e$ lactulose:mannitol ratio) and mean monthly (a) length and (b) weight growth of 119 rural Gambian infants.

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

What I learned to focus on 30 years ago



Has Diarrhea
Treat To Prevent
Death,
Morbidity



ALL HAVE ENVIRONMENTAL ENTEROPATHY

Without any overt signs of ‘clinical’ illness

Handwashing is “necessary but not sufficient”

Original Research Article

Amer J Human Biol 23:621-629 (2011)

Hand-Washing, Subclinical Infections, and Growth: A Longitudinal Evaluation of an Intervention in Nepali Slums

REBECCA LANGFORD,[1*] PETER LUNN,[2] AND CATHERINE PANTER-BRICK[3]
[1]*School of Social and Community Medicine, University of Bristol, Canynge Hall, Bristol, BS8 2PS, United Kingdom*
[2]*Department of Biological Anthropology, University of Cambridge, Cambridge, CB2 3DZ, United Kingdom*
[3]*Jackson Institute for Global Affairs and Department of Anthropology, Yale University, New Haven, Connecticut*

- 1st longitudinal study to assess hand-washing and enteropathy. 45 intervention, 43 control
- ↑mucosal damage = ↓ growth ($p \leq 0.01$ HAZ, WAZ)
- **Handwashing led to 41% ↓ diarrhea morbidity**
- ***No* change in markers of mucosal damage**
- *HW alone* doesn’t address chronic subclinical infxn

Ok, so you have a leaky, inflamed gut. What lives in it?

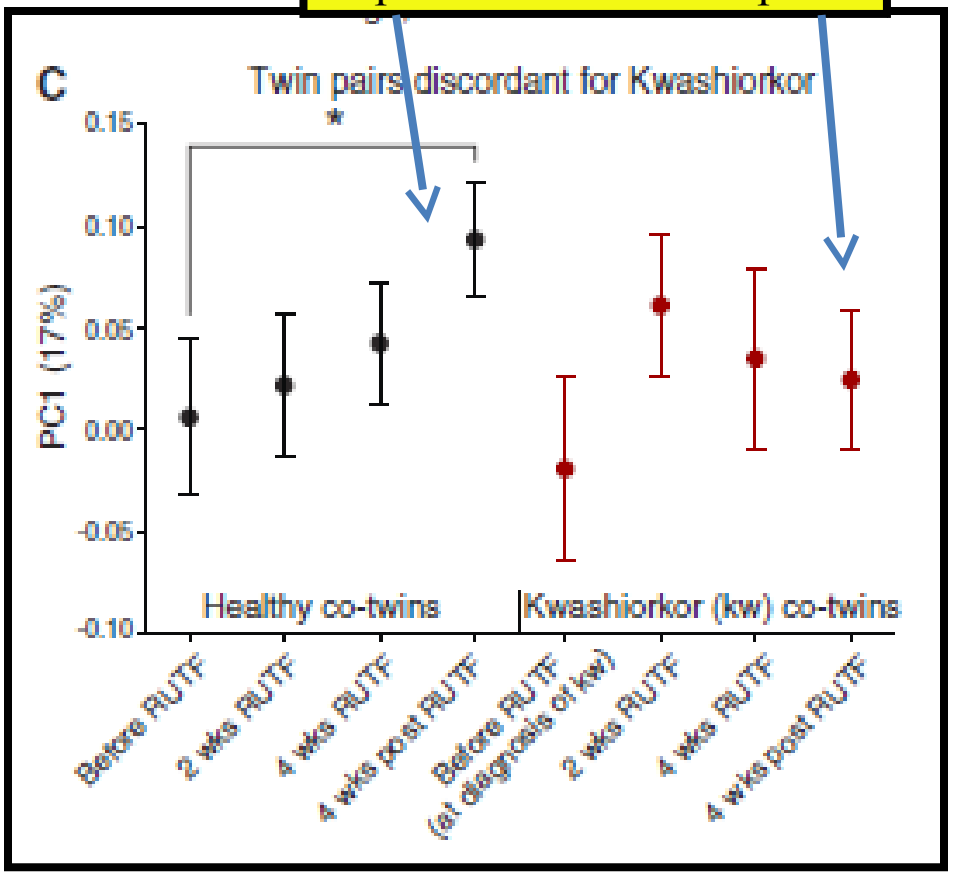
Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashiorkor

Michelle I. Smith,[1*] Tanya Yatsunenko,[1*] Mark J. Manary,[2,3,4] Indi Trehan,[2,3] Rajhab Mkakosya,[5] Jiye Cheng,[1] Andrew L. Kau,[1] Stephen S. Rich,[6] Patrick Concannon,[6] Josyf C. Mychaleckyj,[6] Jie Liu,[7] Eric Houpt,[7] Jia V. Li,[8] Elaine Holmes,[8] Jeremy Nicholson,[8] Dan Knights,[9,10]† Luke K. Ursell,[11] Rob Knight,[9,10,11,12] Jeffrey I. Gordon[1]‡

Science 339:548-554. 1 February 2013

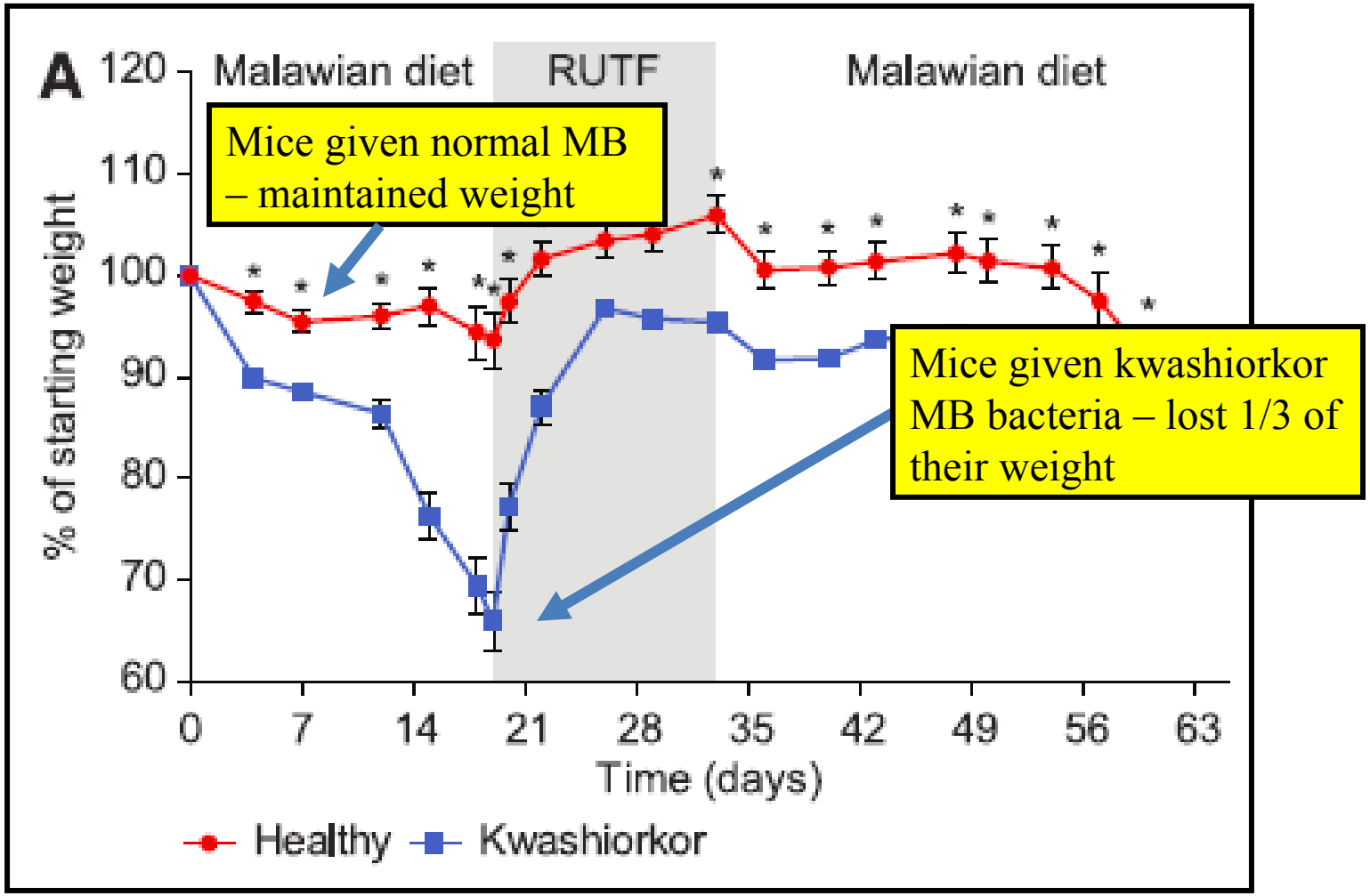
- 317 Malawian twins studied first 3 years of life
- 50% both well nourished; 43% <u>discordant</u> (one well, one malnourished); 7% both were malnourished.
- <u>Both</u> twins in discordant pairs received RUTF, a therapeutic food. Gut microbiomes (MB) studied: RUTF → transient MB improvement.

Improve Don't Improve



Then…

Gnotobiotic (sterile gut) mice – given either Normal or Kwashiorkor MB



Major adverse changes in amino acid and other gut metabolites

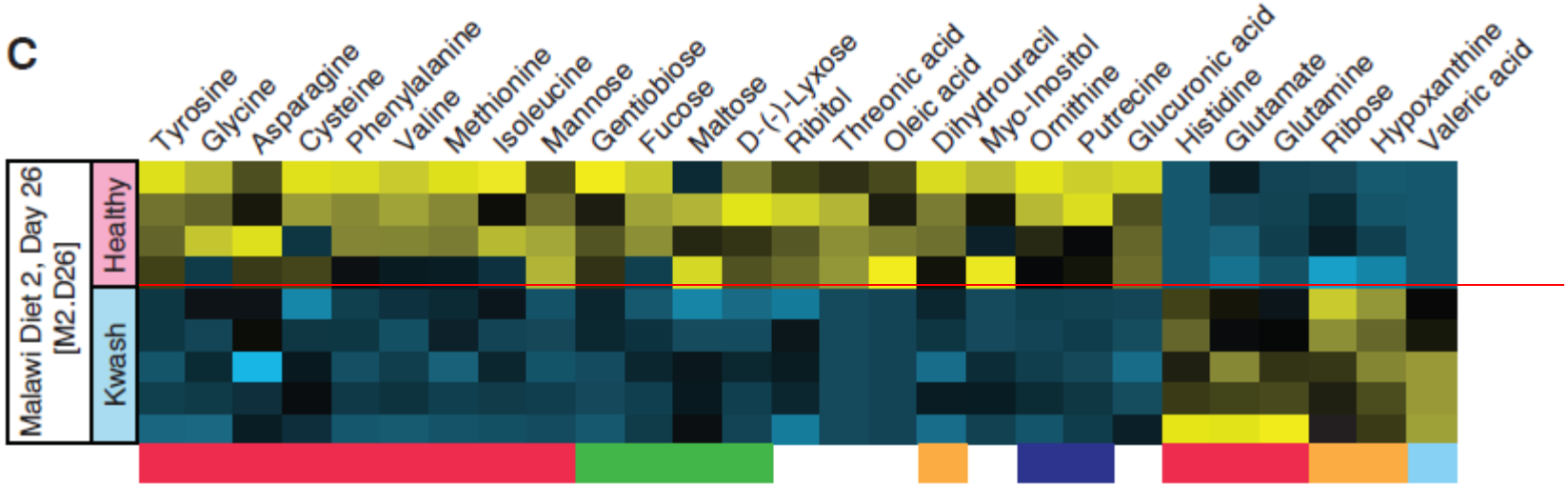
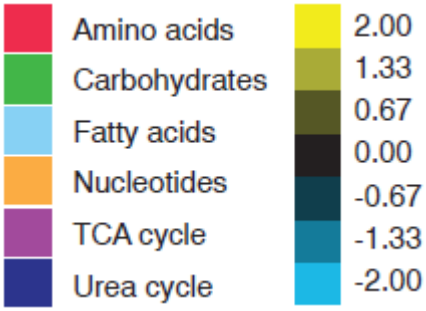


Fig. 3. Metabolites with significant differences in their fecal levels in gnotobiotic mice colonized with microbiota from discordant twin pair 196 as a function of diet. Data are from fecal samples collected 3 days before the end of (**A**) the first period of consumption of the Malawian diet (M1, day 16; abbreviated M1.D16), (**B**) RUTF treatment (RUTF.D10), and (**C**) the second period of Malawian diet consumption (M2.



Decoupled **TCA cycle** intermediates (↑ succinate) – mitochondrial metabolites – **↓energy metabolism**

Kwashiorkor microbiota + Malawi diet = **abnormal sulfur metabolism** (methionine, cysteine; protein metabolism)

INSIDE YOUR GUT

Microbiome modulates your immune system

Microbiome of 1000-1150 species produces amino acids, short-chain fatty acids, and others which feed intestinal cells and shift your metabolic stance

Diverse Microbiome

Could malnourished children benefit from being given a new microbiome?

Less Diverse Microbiome

Less Diverse Microbiome

Malnourished Child Microbiome Includes More Pathogens and Actively Promotes Weight Loss in Malnourished Children

Microbiome Actively Promotes Obesity and Insulin Resistance

Fecal Transplant: Better Insulin Sensitivity and ↑ gut butyrate

UNDER-nourished
INEFFICIENT

NORMAL BMI
[MB energy harvesting]

OVER-nourished
HYPER-EFFICIENT

INSIDE YOUR GUT

Microbiome modulates your immune system

Microbiome of 1000-1150 species produces amino acids, short-chain fatty acids, and others which feed intestinal cells and shift your metabolic stance

Diverse Microbiome

Could malnourished children benefit from being given a new microbiome?

Less Diverse Microbiome

Less Diverse Microbiome

Malnourished Child Microbiome Includes More Pathogens and Actively Promotes Weight Loss in Malnourished Children

Microbiome Actively Promotes Obesity and Insulin Resistance

Fecal Transplant: Recurrent Clostridium difficile disease

UNDER-nourished
INEFFICIENT

NORMAL BMI
[MB energy harvesting]

OVER-nourishe
HYPER-EFFICIE

Environmental Enteropathy occurs when people live in contaminated environments. It is reversible. For example, US Peace Corps volunteers develop EE when they live in rural African villages. When they return to the US, their EE goes away.

The absence of fecal material – be it human or animal – in the environment both prevents and "treats" EE.

Water/sanitation is critical to this separation.

- Dean Spears has looked at open defecation as a marker of sanitation using 140 DHS data sets from 60 countries.

How much stunting is due to poor sanitation (and possibly EE?)

How much international variation in child height can sanitation explain?

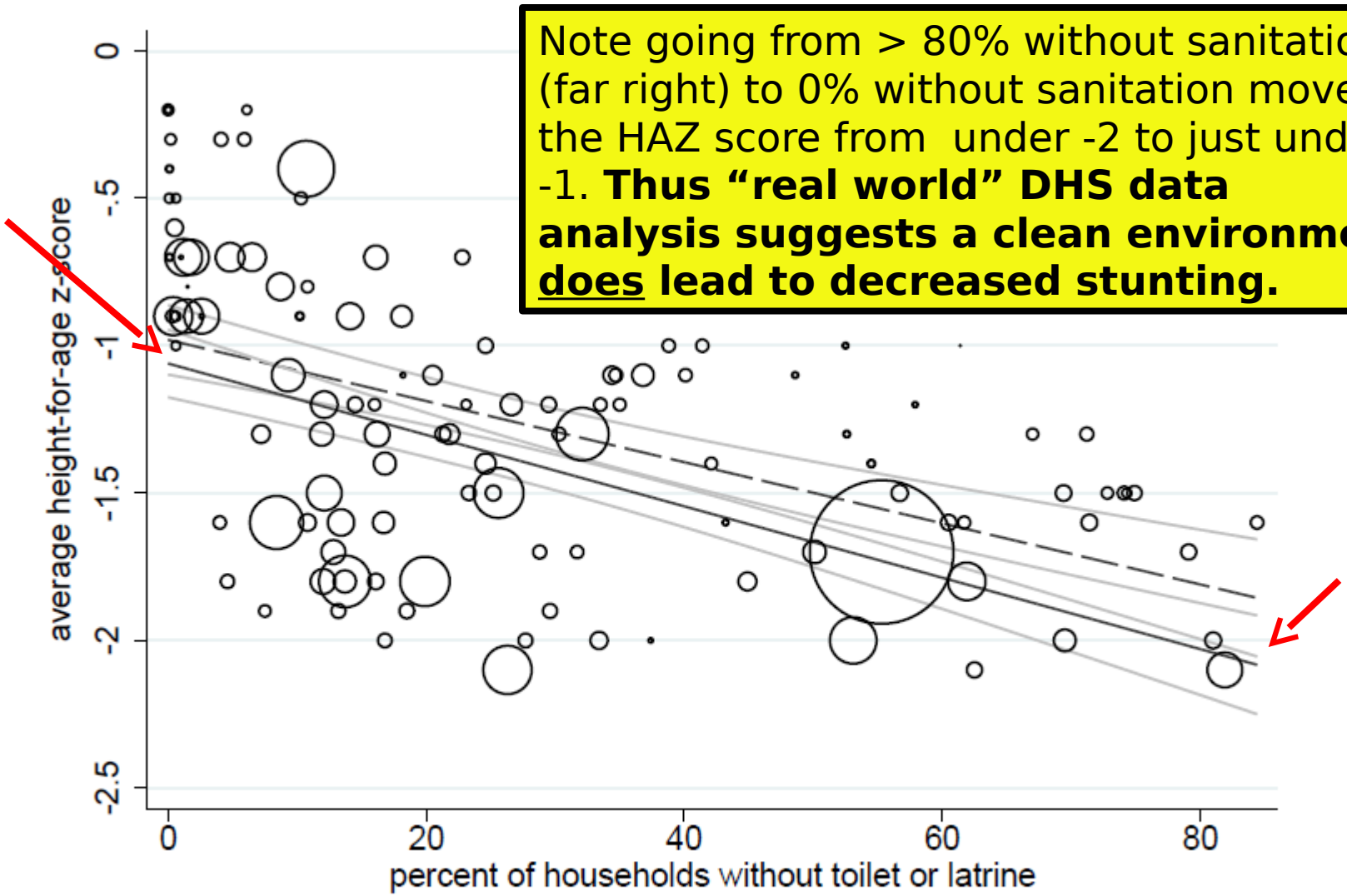
Dean Spears*

First circulated: 10 December 2012
This version: 17 January 2013

Key findings Spear's analysis of 140 DHS from 65 'developing' countries

- Open defecation (certainly a marker of a "contaminated environment") is linked to a **1.24 S.D. decrease** in the height of children.
- **Sanitation alone** accounts for **54%** of the between-country height variation (next slide).
- Open defecation and a lack of sanitation in an household, along with country GDP, predict child height *more than* mother's height or education; governance; or infrastructure.

(b) children born in the last 5 years



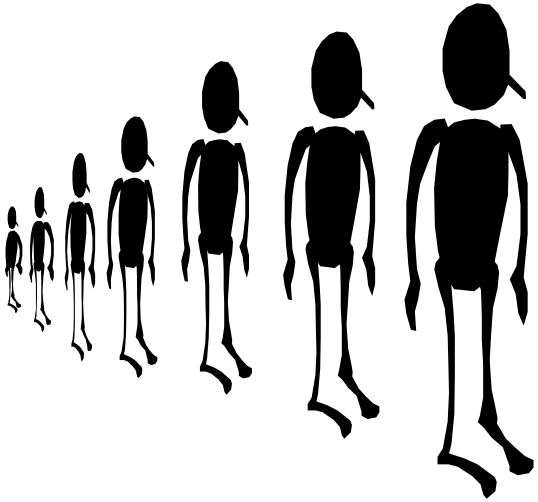
Note going from > 80% without sanitation (far right) to 0% without sanitation moves the HAZ score from under -2 to just under -1. **Thus "real world" DHS data analysis suggests a clean environment <u>does</u> lead to decreased stunting.**

Figure 1: Open defecation predicts child height, across DHS survey round country-years

Solid OLS regression lines weight by country population; dashed lines are unweighted.

Econometric analyses Spears 2013

- Sanitation predicts stunting even when income is controlled. "…The difference between Nigeria's 26% open defecation rate and India's 55% is associated with an increase in child height approximately equivalent to quadrupling GDP per capita." **Point: India would have to quadruple national income to make up for its poor sanitation as compared to Nigeria.**
- Sanitation and population density interact, open defecation harms human capital. Open defecation (no sanitation) explains **65%** of global height. <u>The policy case for sanitation as a public good is immense</u>.



Poor populations:

- > 99% will have environmental enteropathy in the absence of good water/sanitation.

- Lacking WASH and barriers to fecal contamination, they will have a different spectrum of gut bacteria (the **gut microbiome**) than people with good WASH

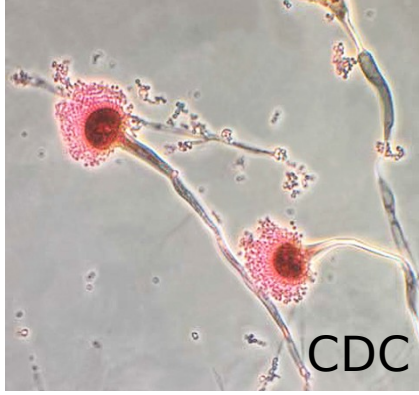
- **Next: Aflatoxins**

Aflatoxins and other mycotoxins

Drying Cassava, Kamwenge Uganda: note green/yellow fungal discoloration

oto: J K Griffiths Uganda December 2012

Aflatoxins (Aflatoxins are mycotoxins)

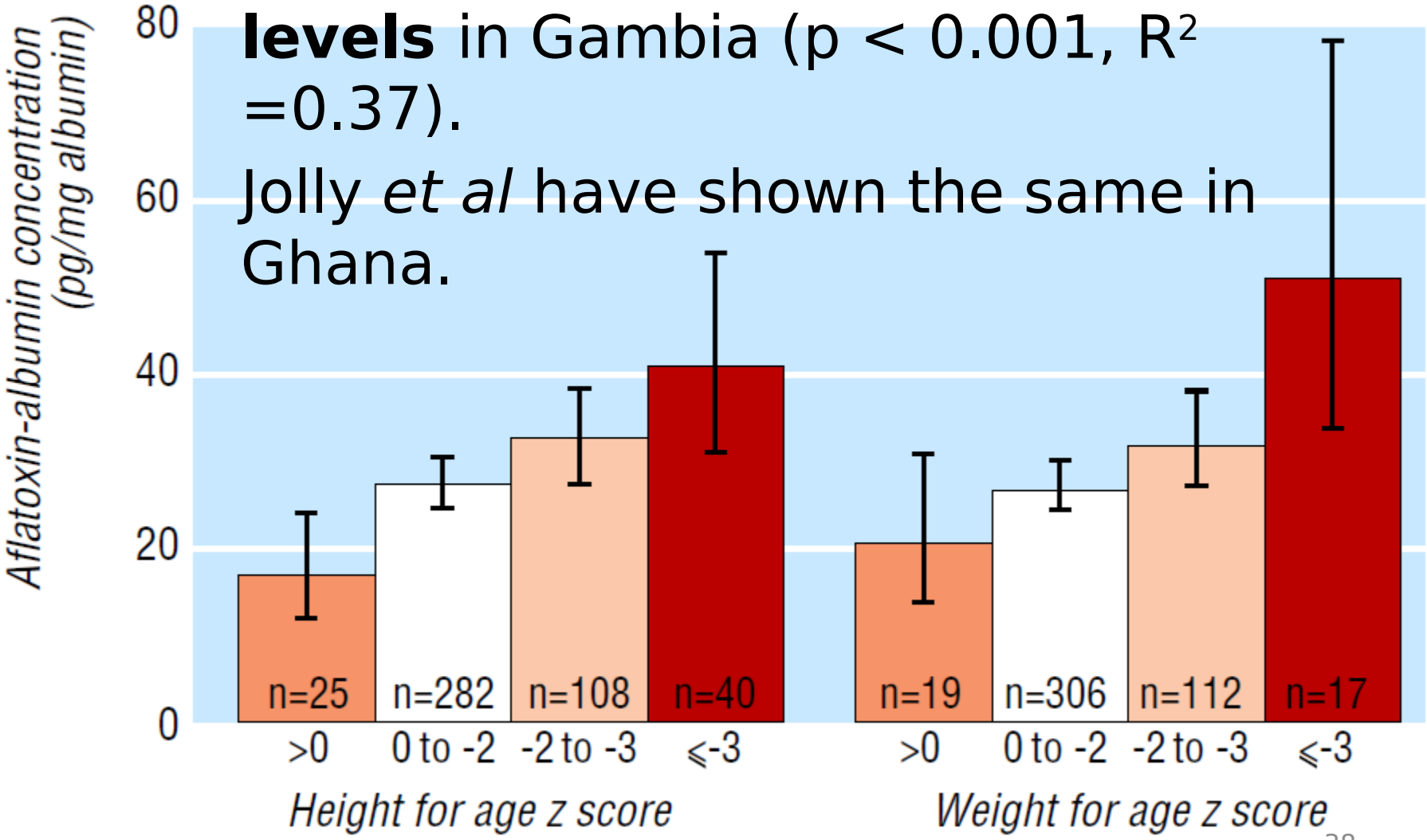


- Produced by *Aspergillus* fungus
- Known – hepatoxic & cause liver cancer in people
- Known in mammals to cause growth faltering and ↓ *in utero* growth (e.g. low birth weight)
- Associated* with lower birth weight, growth, stunting, and wasting in children
- Associated* with lower CD4 and higher viral loads (e.g. worse immunity) in people with HIV
- Widespread exposure in sub-Saharan Africa, SE Asia; maize, peanuts, many other crops.

*Some criticize these studies for only being "associative" - but it is *unethical* to give aflatoxins

Gong et al (BMJ, 2002) showed that **stunting** and **weight for age was inversely related to blood aflatoxin levels** in Gambia ($p < 0.001$, $R^2 = 0.37$).

Jolly *et al* have shown the same in Ghana.



CONTAMINATED WATER / POOR HYGIENE
(PATHOGENS, OTHER STUFF IN WATER)

ENVIRONMENTAL ENTEROPATHY & STUNTING

AFLATOXINs, DON INGESTION
(FUNGI NEED WATER/MOISTURE TO GROW)

Aflatoxins II

- Contamination occurs in the field; promoted by poor (too humid) post-harvest storage.
- Passed *in utero* and in breast milk to children
- Complementary food (e.g. porridge made from maize) is frequently contaminated – as are milk, eggs, chickens, animal meats…
- Prevention: storage without moisture/oxygen; dispersal of natural variant *Aspergillus* which lacks toxin; test and condemn crops/foods

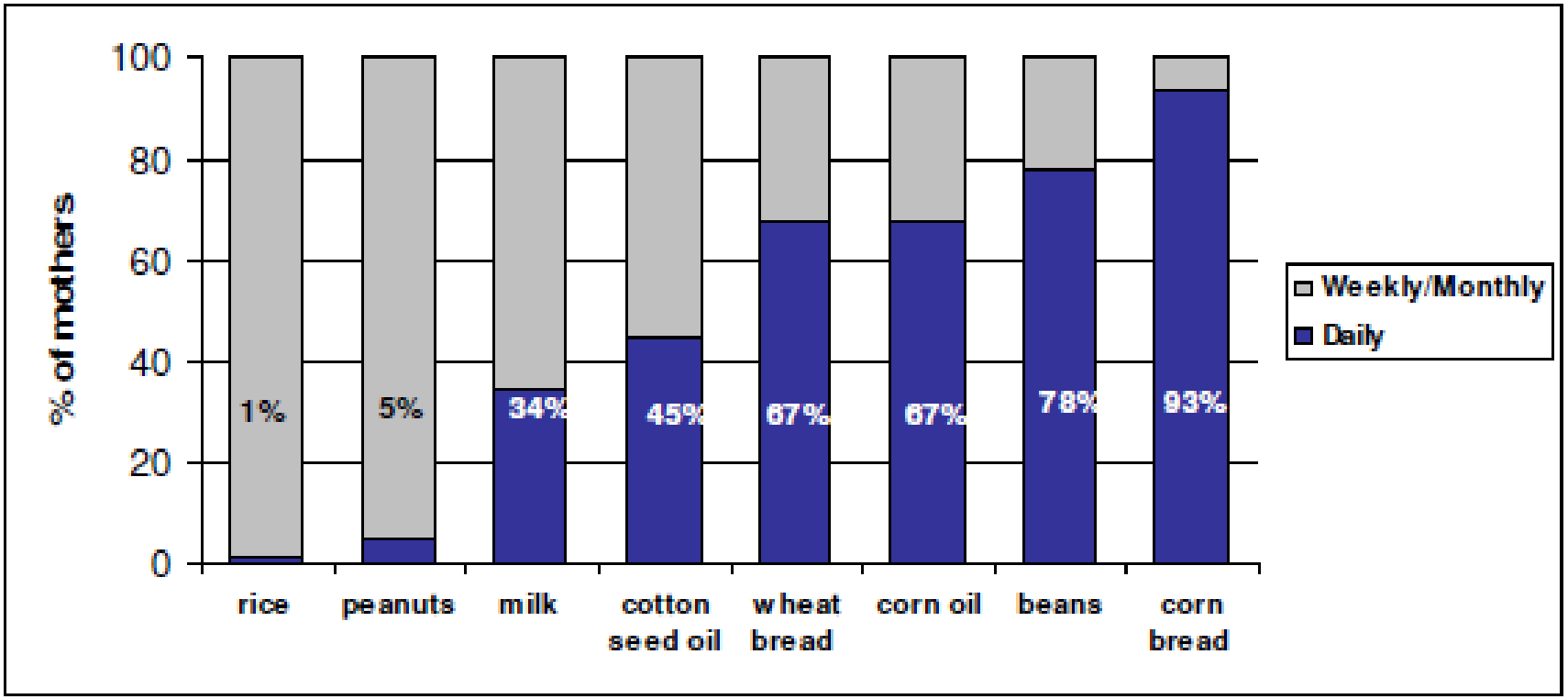
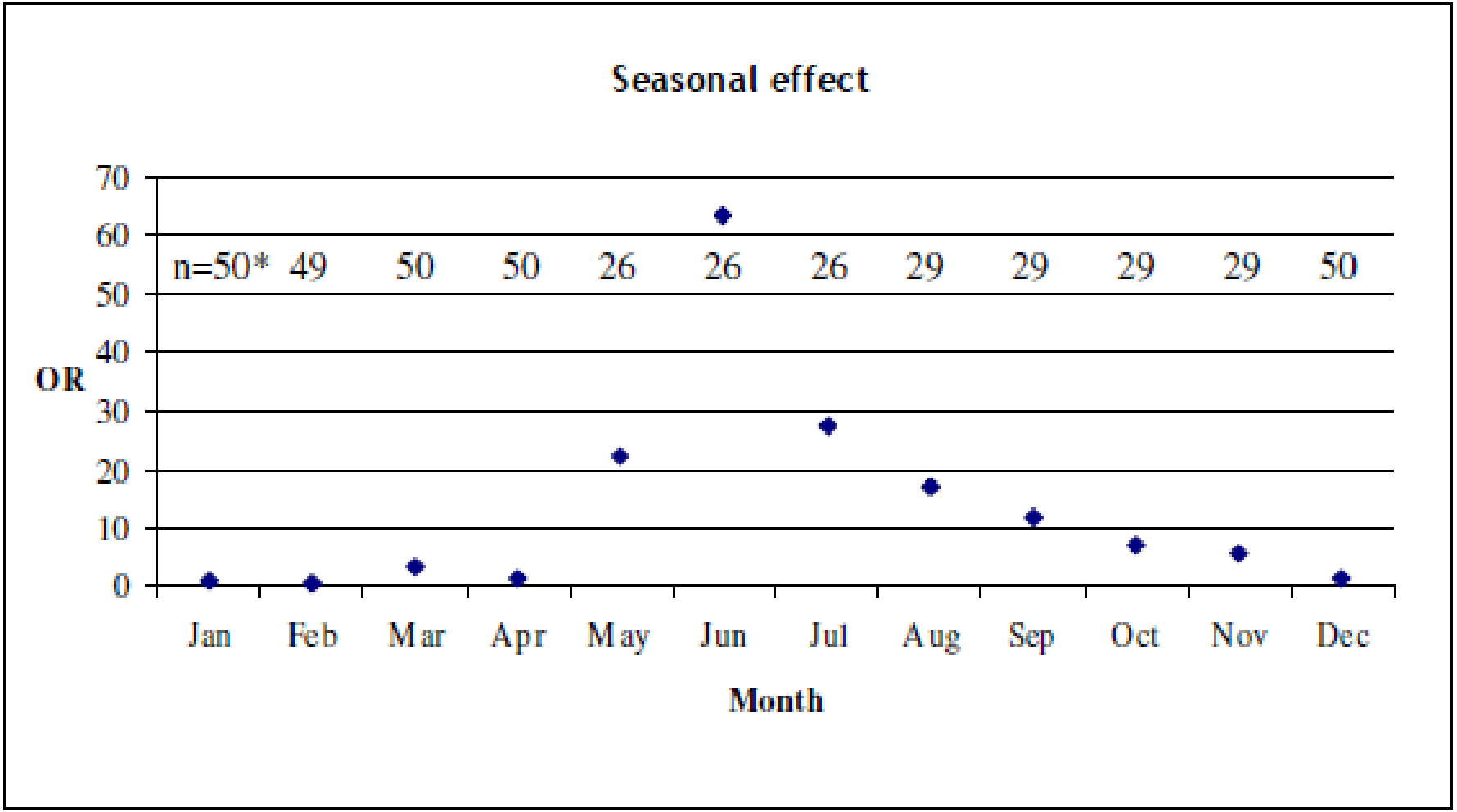


Figure 13. Food use among lactating Egyptian mothers. Frequency distributions of responses to selected foods grouped according to either daily or weekly/ monthly consumption.

Polykronaki, dissertation



*number of mothers

Figure 23. Seasonal effect on the risk of AFM_1 presence in breast milk of Egyptian mothers.

onaki screened 388 lactating women expecting 10% that ~ 10% would be breas
xin M1 positive. To her surprise 138 (36%) were aflatoxin positive.

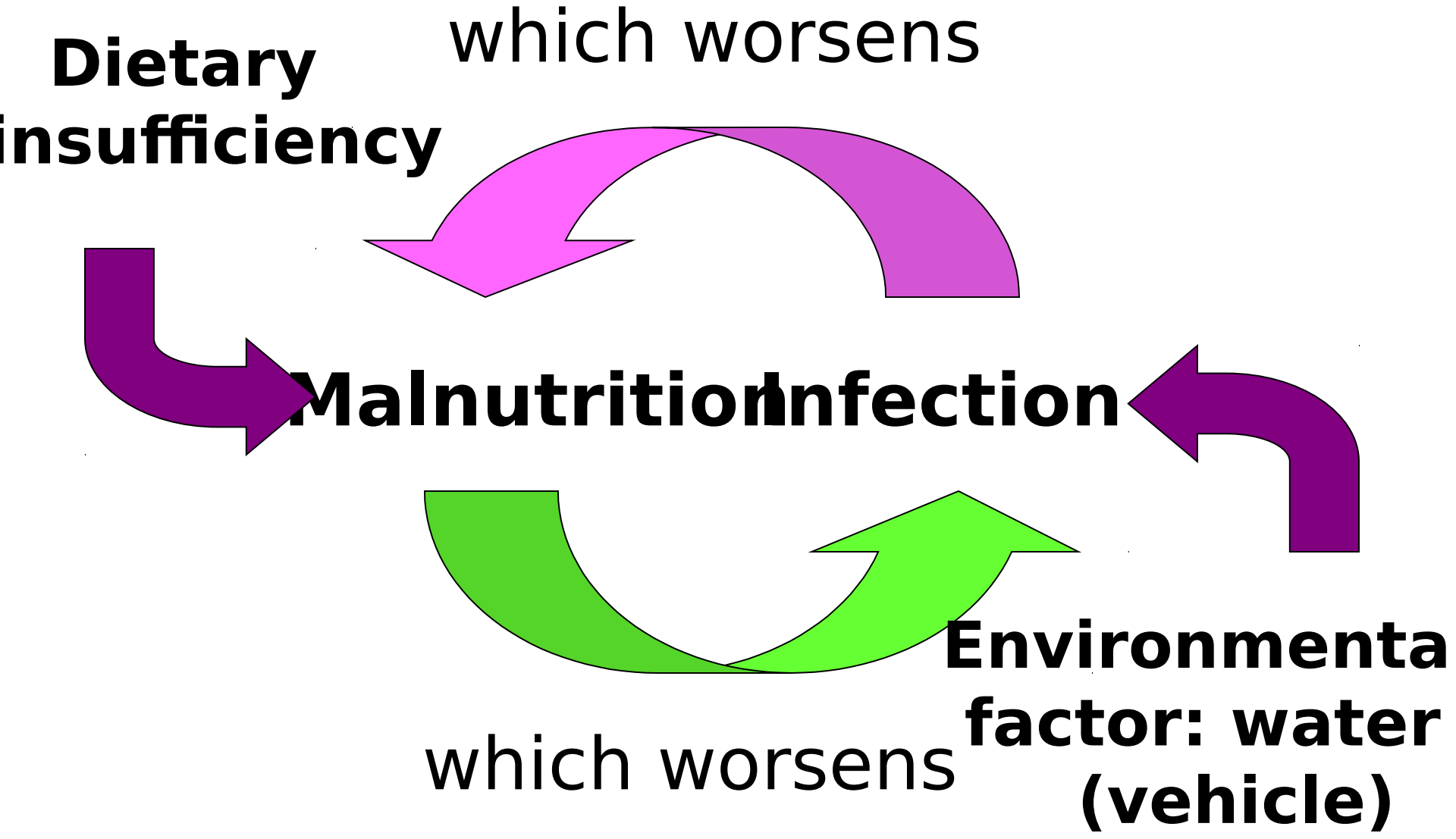
Poor populations:

-Will have monotonous, non-diverse diets lacking key nutrients

-Will likely eat aflatoxins in foods.

> 99% will have environmental enteropathy in the absence of good water/sanitation.

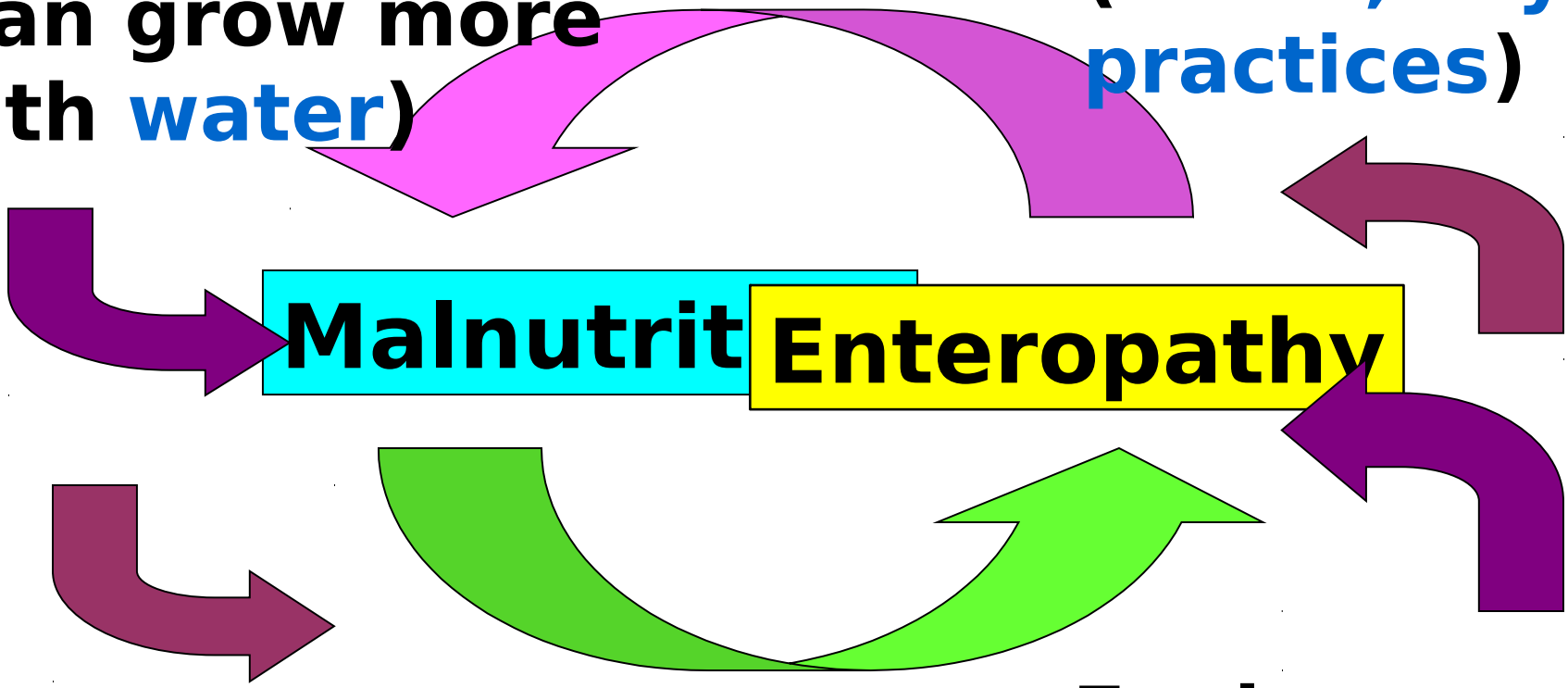
-Lacking WASH and barriers to fecal contamination, they will have a different spectrum of gut bacteria (the **gut microbiome**) than people with good WASH


which worsens
Dietary insufficiency
Malnutrition
Infection
Environmenta factor: water (vehicle)
which worsens

Dietary nsufficiency can grow more with water)

which worsens

Environmental factor: aflatoxi (water, drying practices)



ocial Practices Beliefs

which worsens

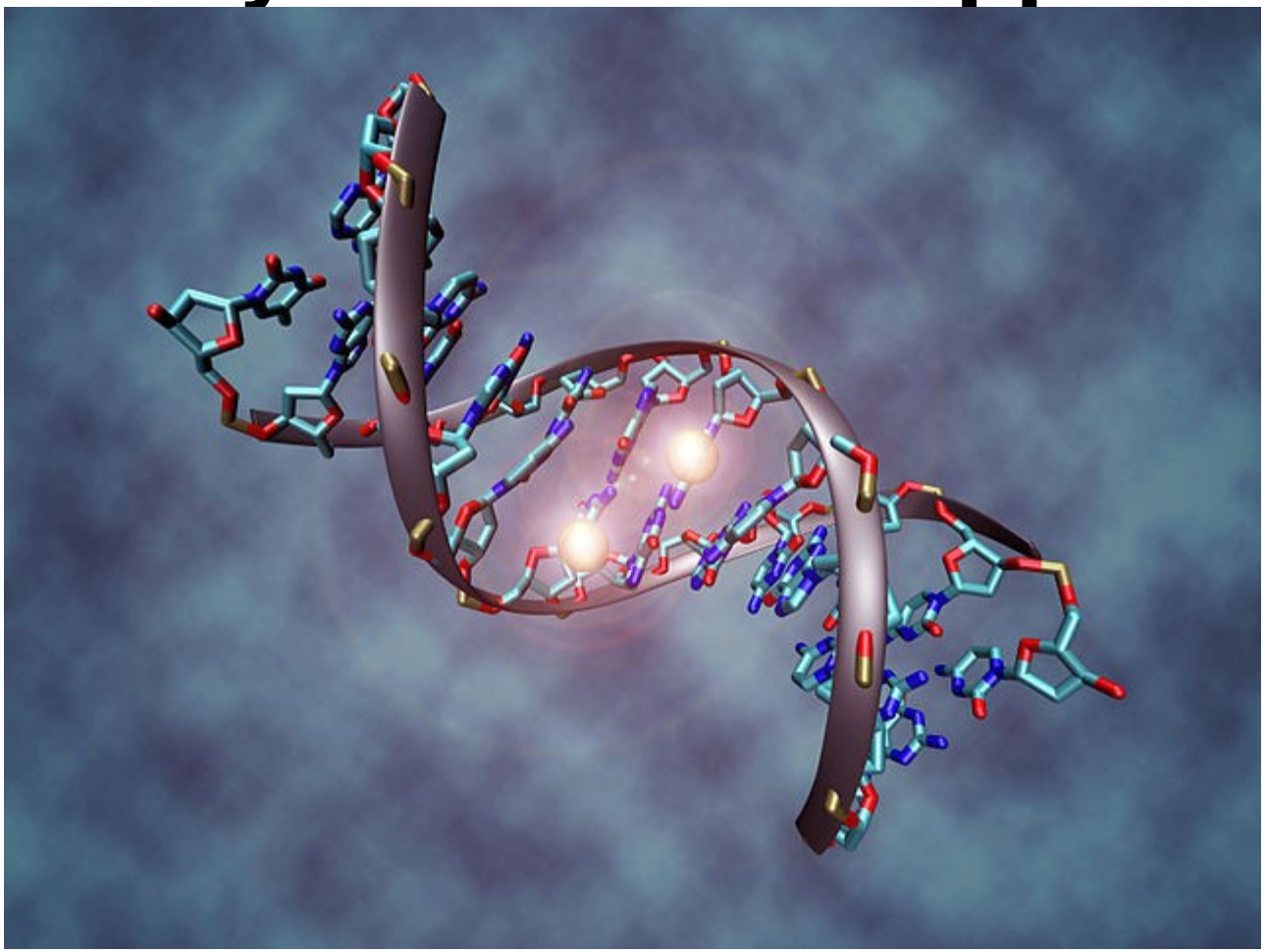
Environmenta l factor: Dirty Water

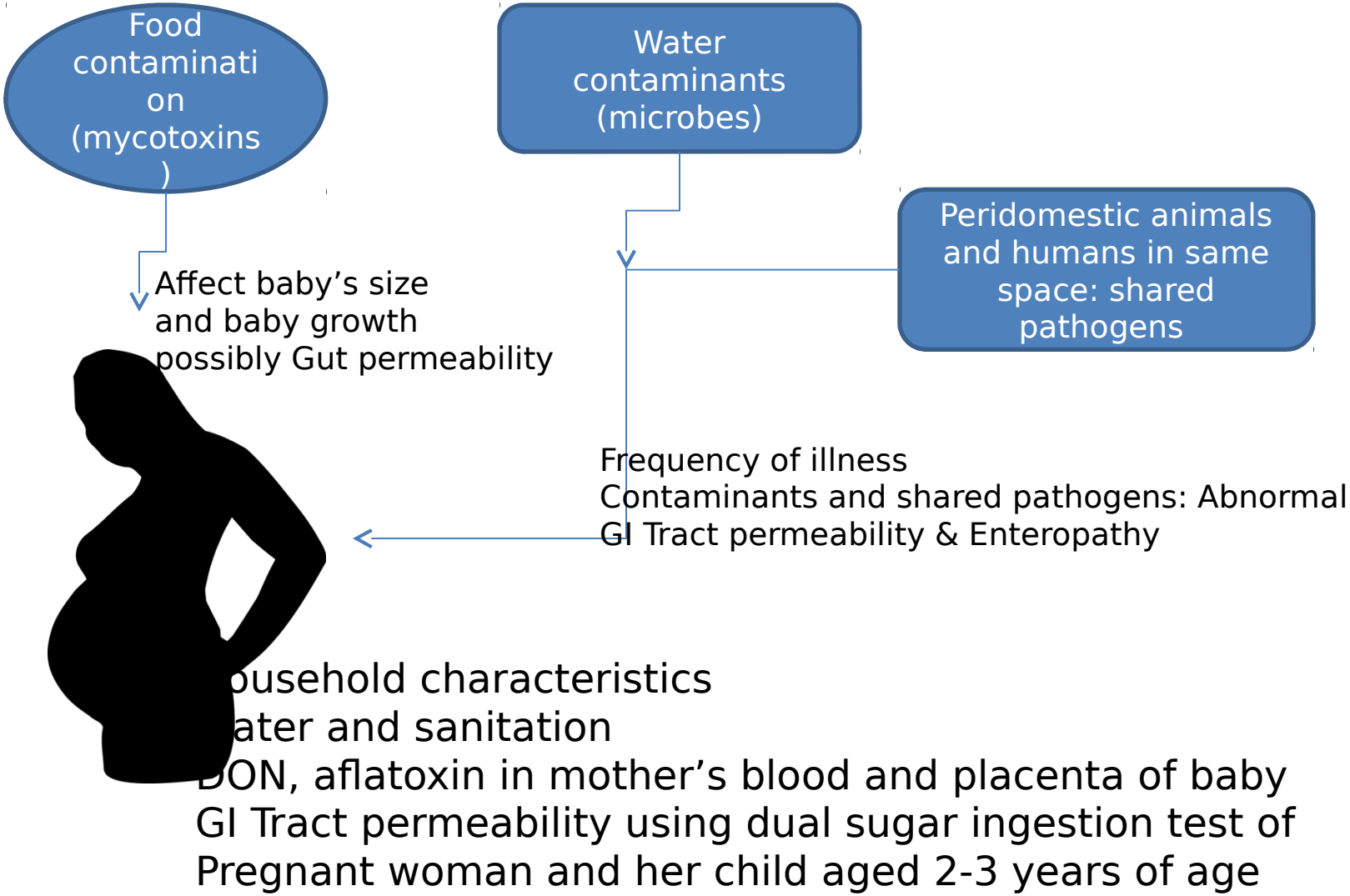
Updated

Take-Home: healthy growth requires:

- ✓ Adequate, varied nutrition with enough calories, micronutrients, and vitamins
- ✓ The absence of environmental toxins such as aflatoxin – immunosuppression, poor intra-uterine and post-natal growth, liver toxicity
- ✓ A clean environment which prevents environmental enteropathy, with its chronic inflammation and higher nutritional needs
- ✓ A normal gut microbiome which does not starve its host of nutrients and promote weight loss

- DNA methylation inactivates genes. Aflatoxins increase DNA methylation of genes relating to **growth**, **immunity** and **cancer suppression**

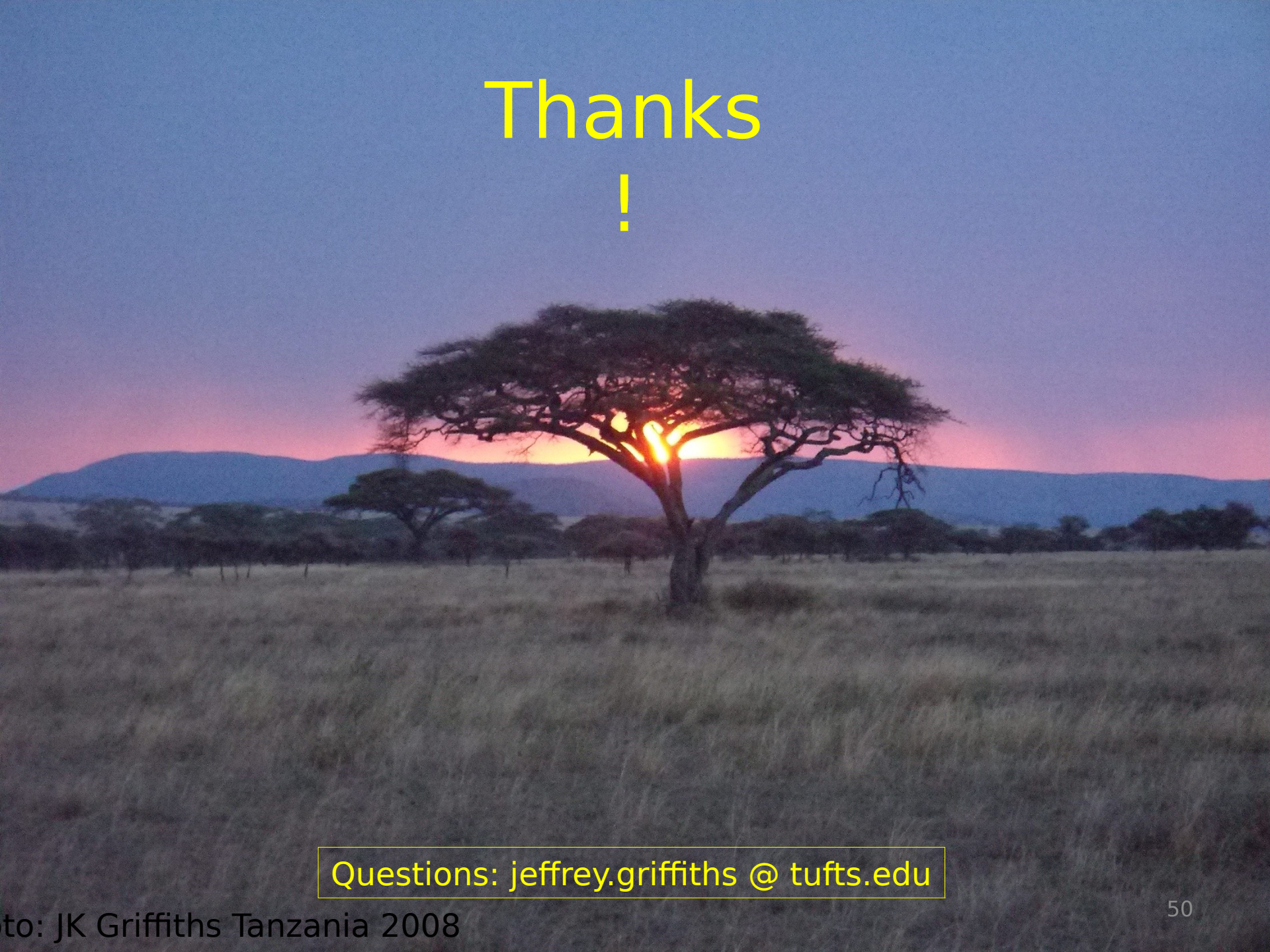




Primary data collection

Economic Costs of Stunting

- Estimates are that economies are 11% lower than potential GDP in high-stunting countries.
- Egypt GDP ~ $272 billion.
- Could be $305.6 billion without stunting.
- If could change average height for age score by 1 HAZ (2 HAZ below norm = stunting) would raise GDP by 7%.



Thanks !

Questions: jeffrey.griffiths @ tufts.edu

to: JK Griffiths Tanzania 2008