Environmental Enteric Dysfunction

Kelsey Jones MRCPCH PhD

BAPEN 2016

My work has been funded by The Wellcome Trust and The Bill & Melinda Gates Foundation

I have no conflicts of interest

Severe Acute Malnutrition

(Severe) Wasting

Mid-upper arm circumference (MUAC)
Or low weight-for-height

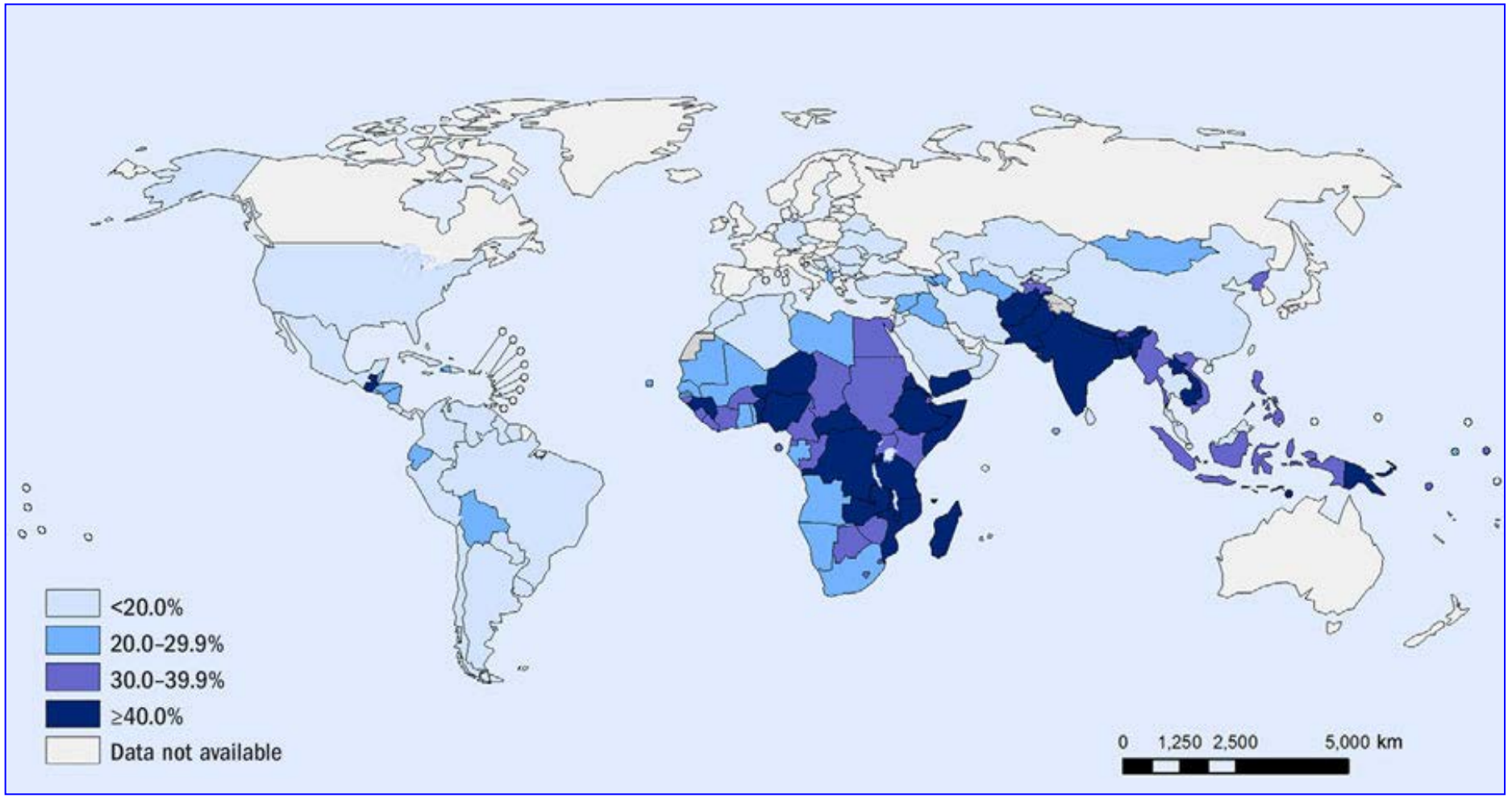
Kwashiorkor

Bilateral pedal oedema

Stunting

Low height-for-age

Global prevalence of stunting



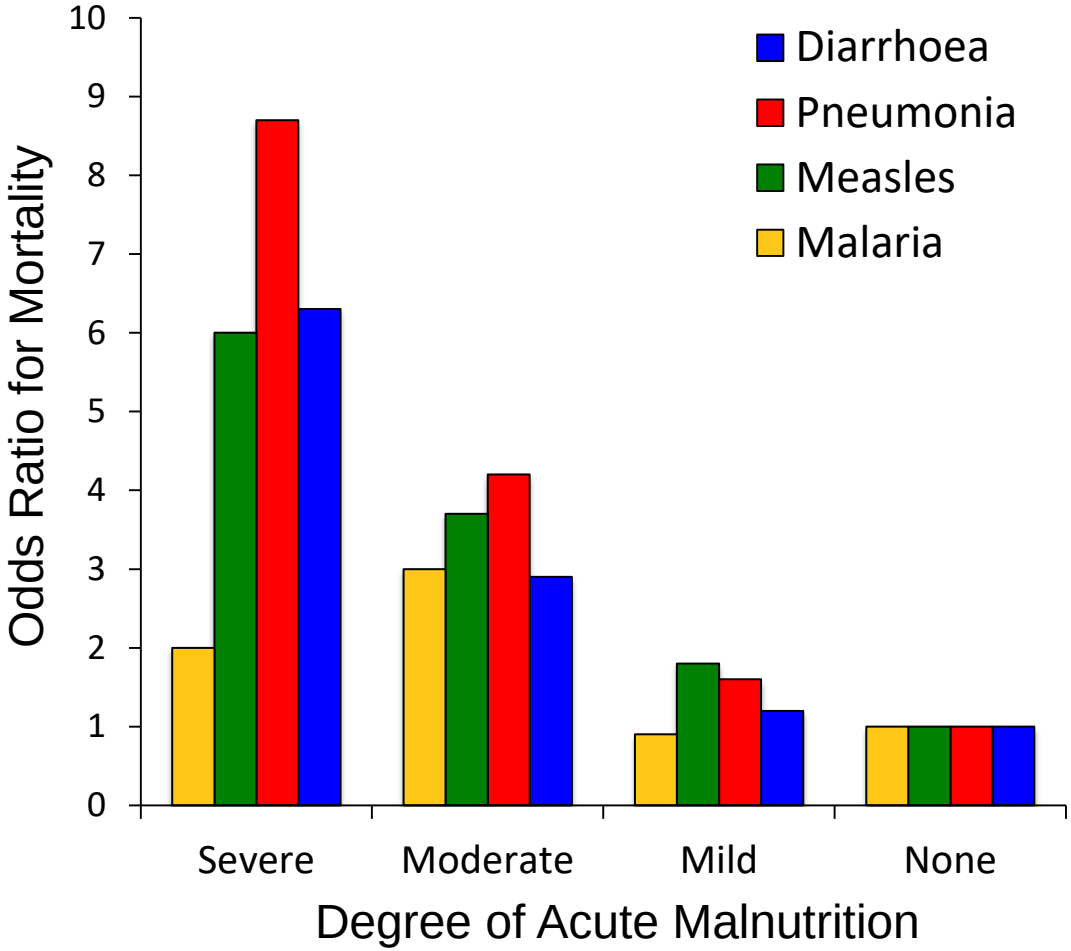
167 million children are stunted

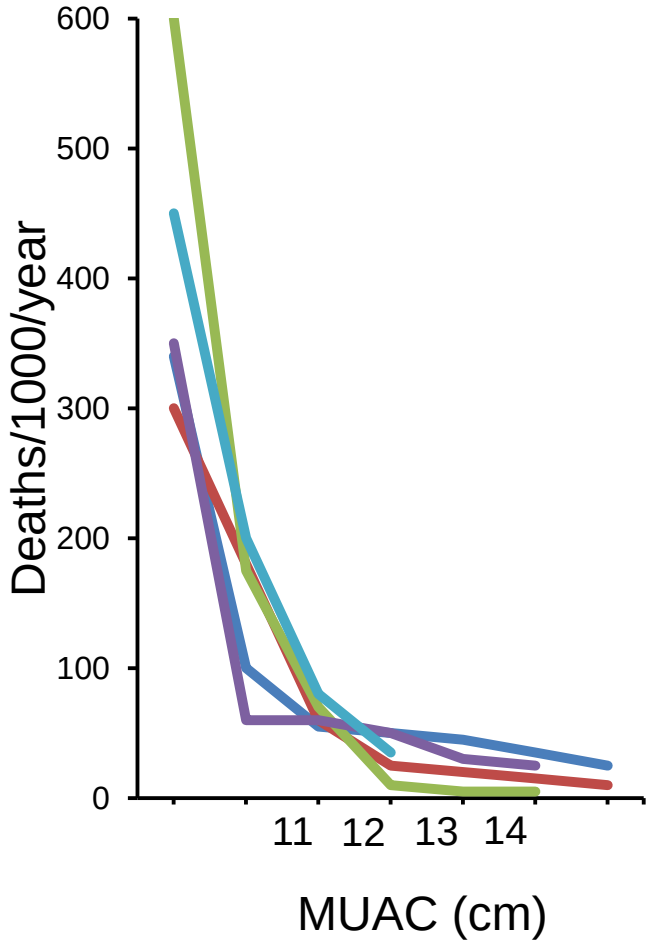
51 million children are wasted (17 million, severely)

Global burden of kwashiorkor is unknown

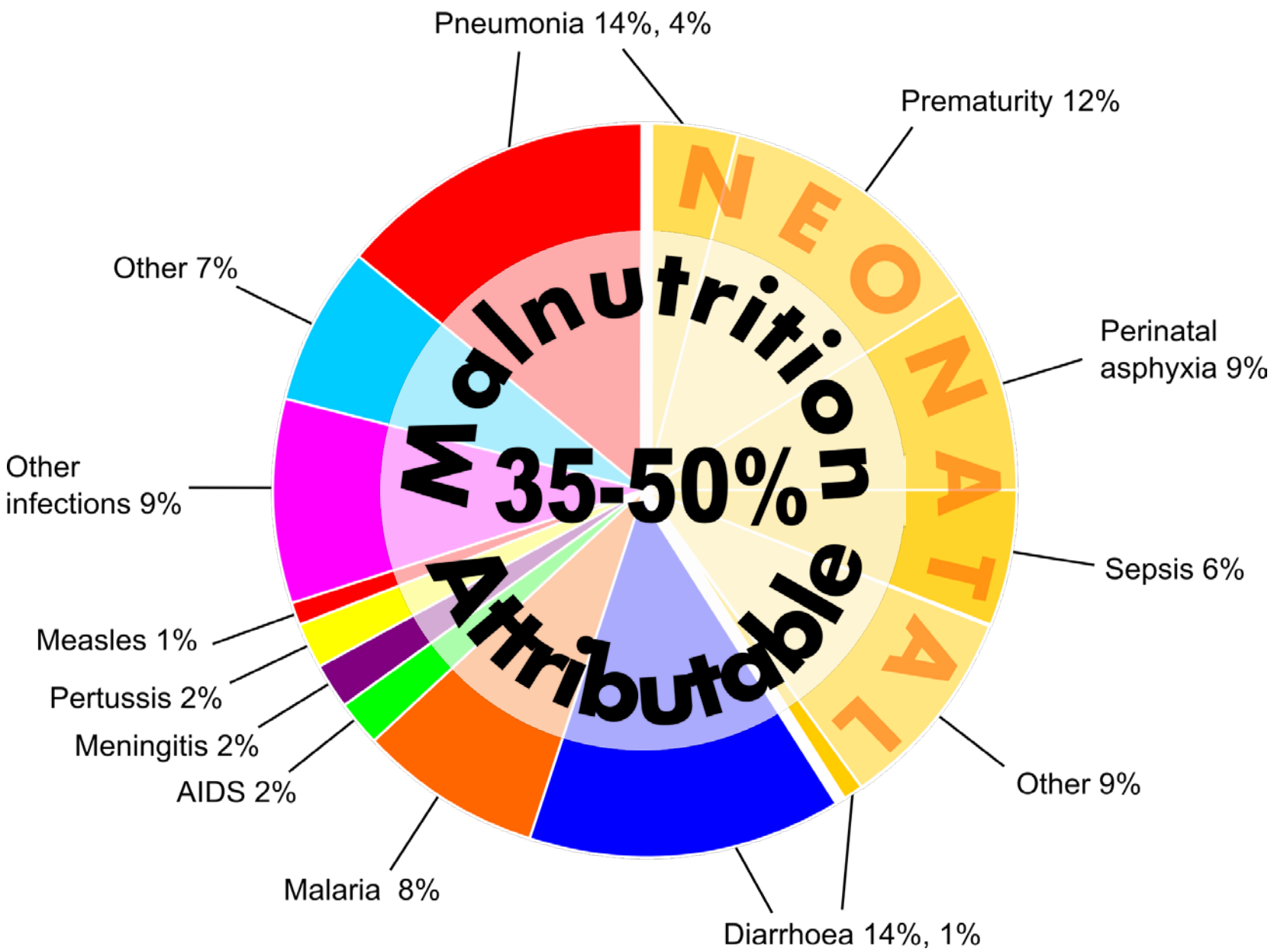
http://apps.who.int/gho/data

Acute malnutrition increases the severity of common infectious diseases and is a major driver of child death





Adapted from Black, Lancet 2012; Black, Lancet 2014



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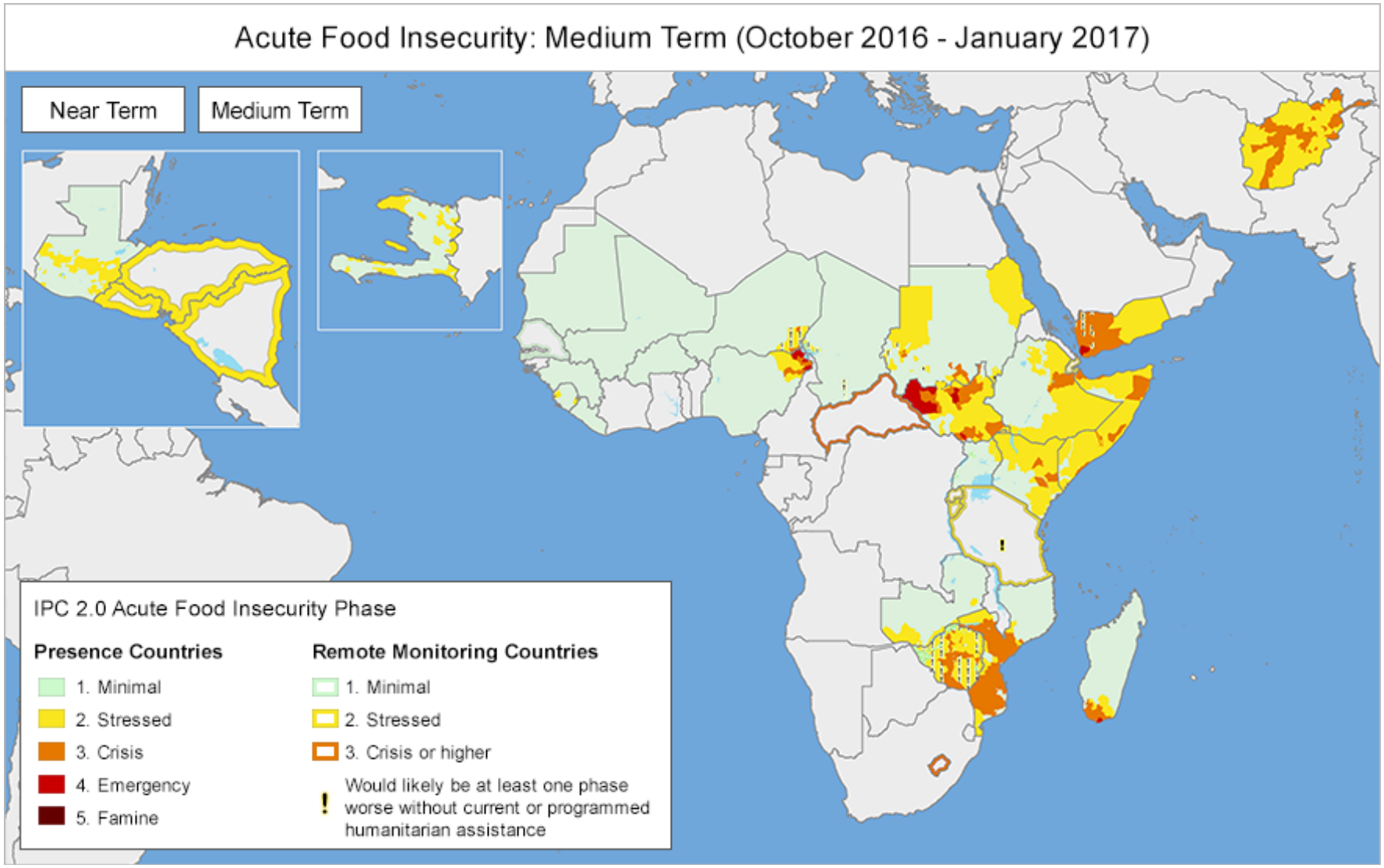
Sequelae of stunting

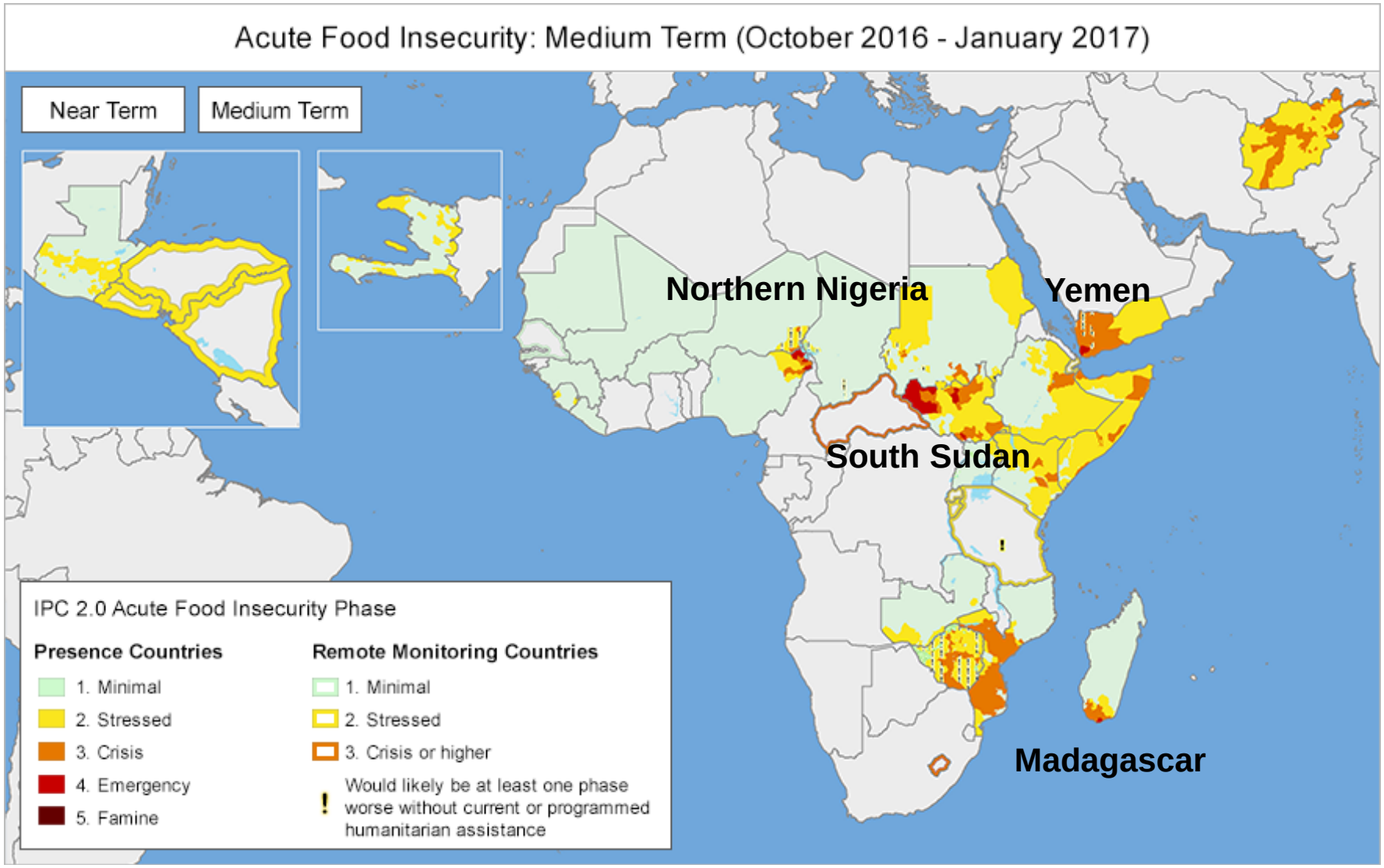
- Long-term loss of developmental potential
  - Irreversible **height**-potential loss after 2 years
  - Less time in **education** and poorer attainment
  - Impaired **neurocognitive** development
  - Less **economic** productivity in adulthood
  - Low birthweight in the **next generation**

Causes of SAM/Stunting



- Food security is compromised by natural disasters and conflict
- Long-term food insecurity is driven agricultural mismanagement, climatic features, and by political instability or failure

www.fews.net



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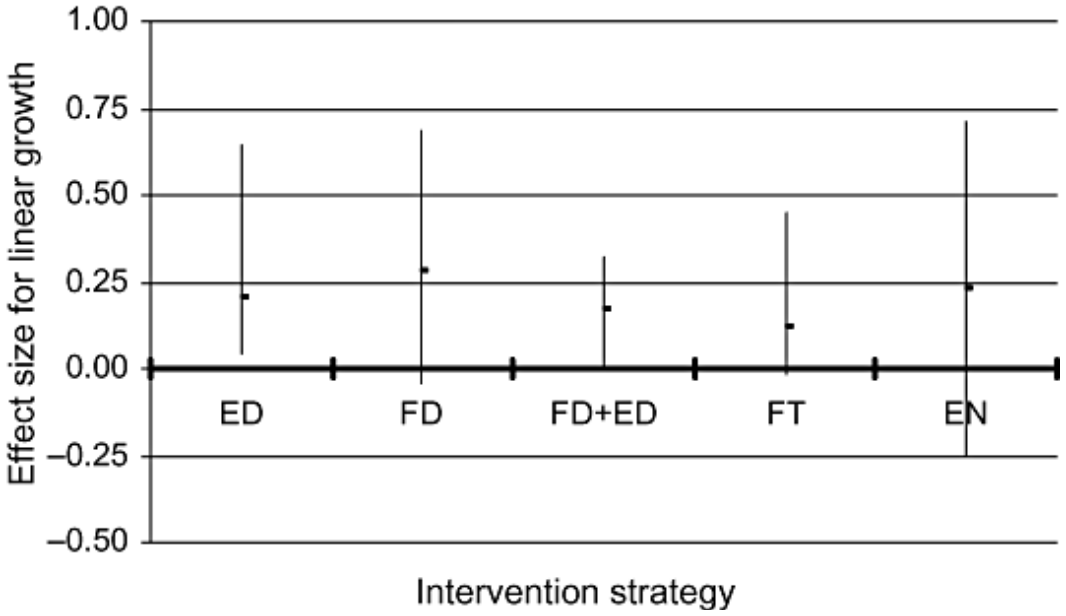
www.fews.net

Causes of stunting

- Chronic undernutrition?
  - Dietary improvements reduce stunting but do not eradicate it
  - Impact is equivalent to 0.7 z-scores (deficit is >2)



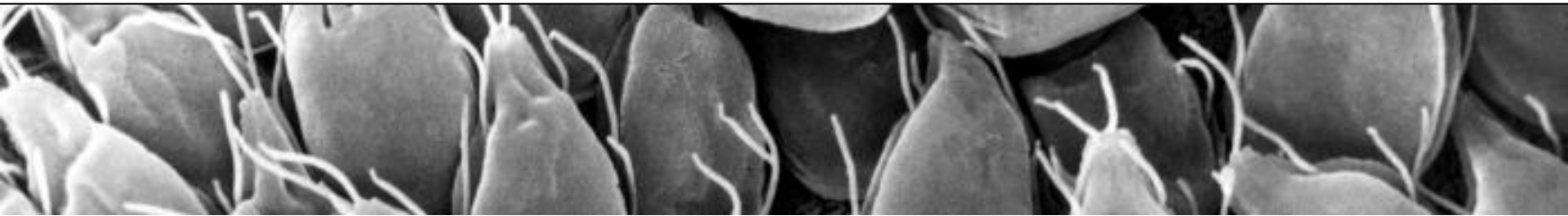
ED: Nutrition education
FD: Complementary foods
FT: Fortification
EN: Increasing energy density

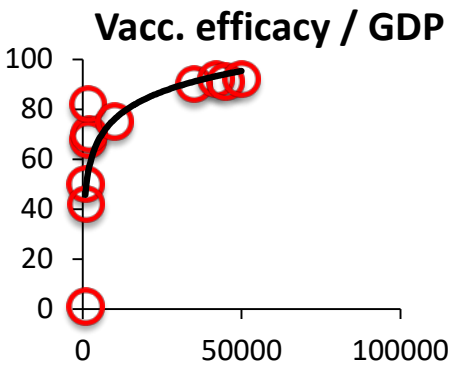
Dewey, Matern Child Nutr 2008

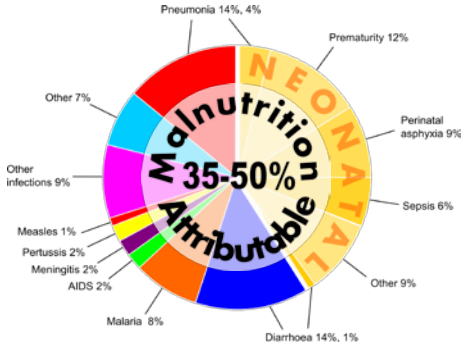
Causes of stunting

- Chronic undernutrition?
  - Dietary improvements reduce stunting but do not eradicate it
  - Impact is equivalent to 0.7 z-scores (deficit is >2)
- Burden of diarrhoeal disease?
  - Scale-up of all current recognised anti-diarrhoeal interventions would reduce diarrhoea by 30% but stunting by just 2.4%

Humphrey, Lancet 2009




Vacc. efficacy / GDP
100
80
60
40
20
0
0
50000
100000


Pneumonia 14%, 4%
Prematurity 12%
Other 7%
Perinatal asphyxia 9%
Other infections 9%
Sepsis 6%
Measles 1%
Pertussis 2%
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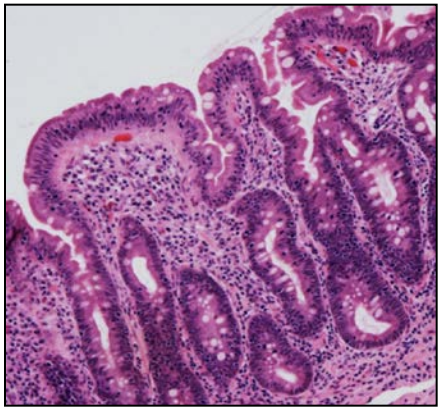
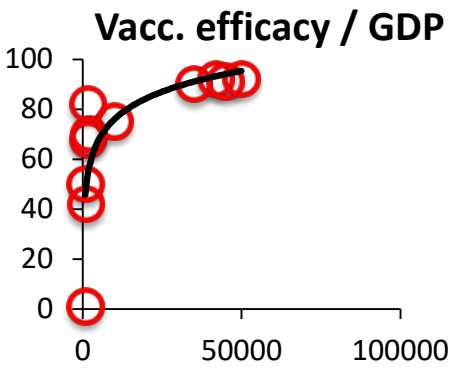
Malaria 8%
Diarrhoea 14%, 1%
NEONATAL
Malnutrition
35-50%
Attributable

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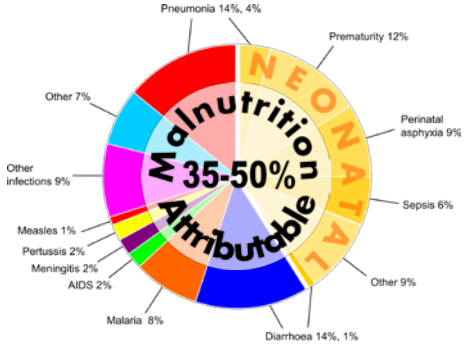
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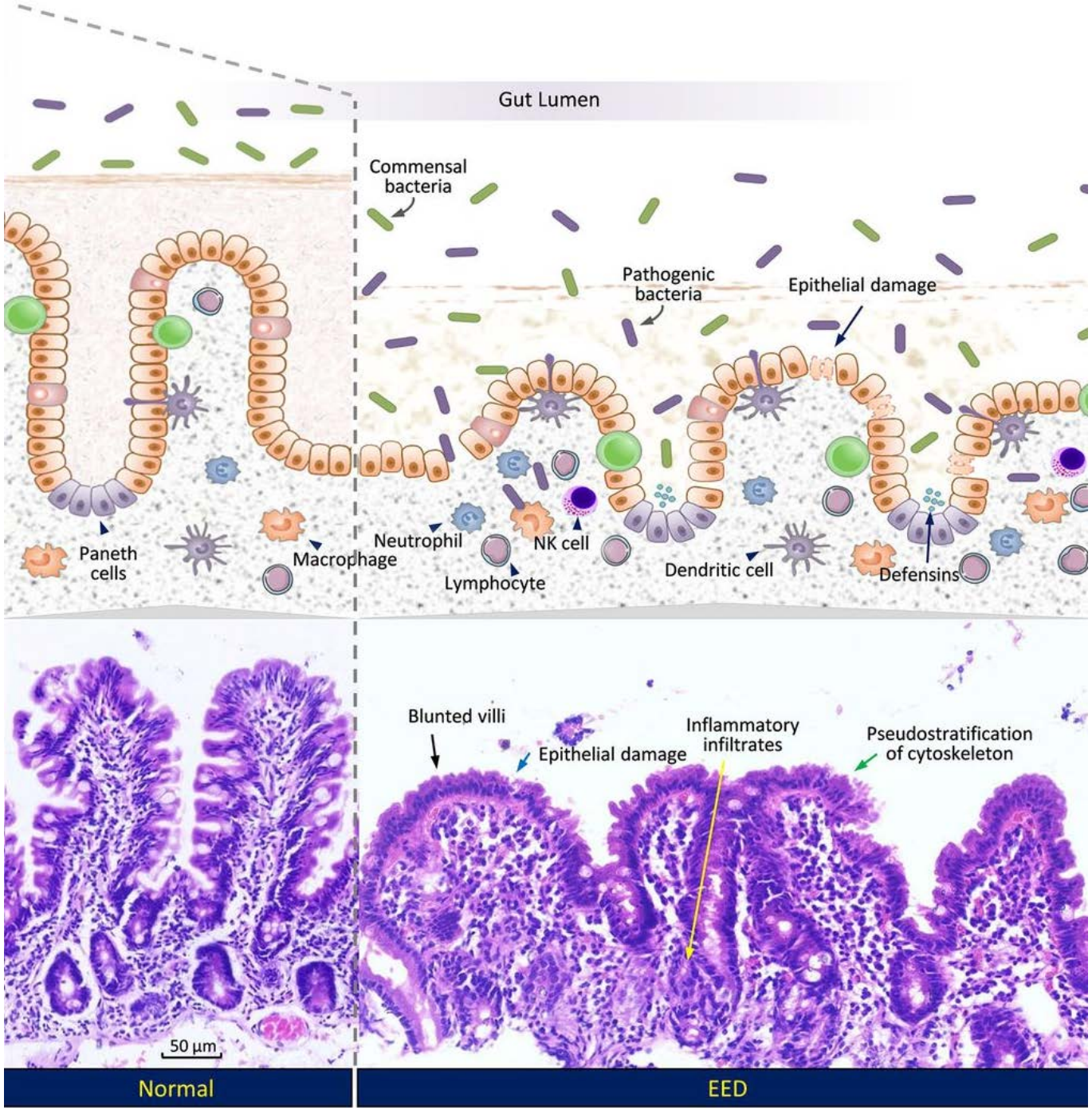
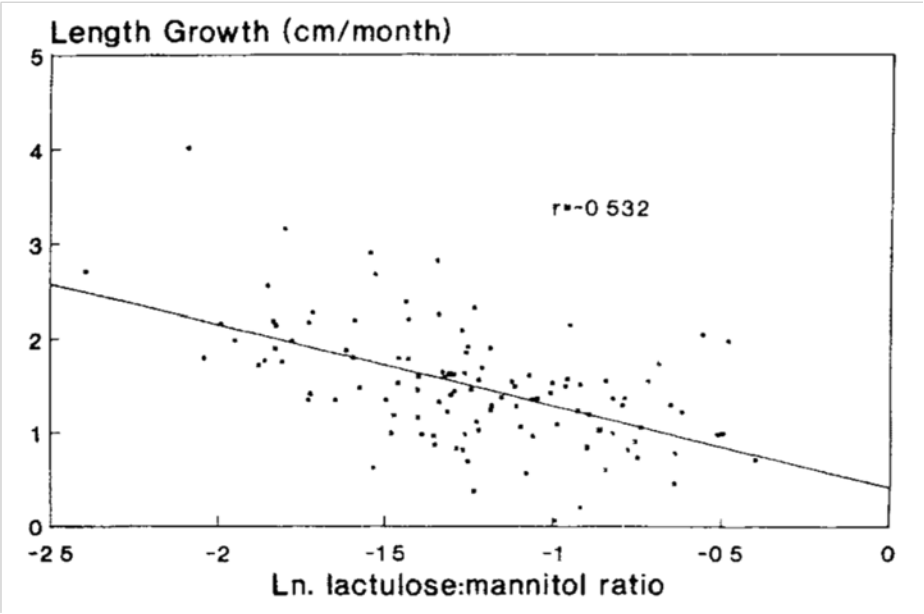
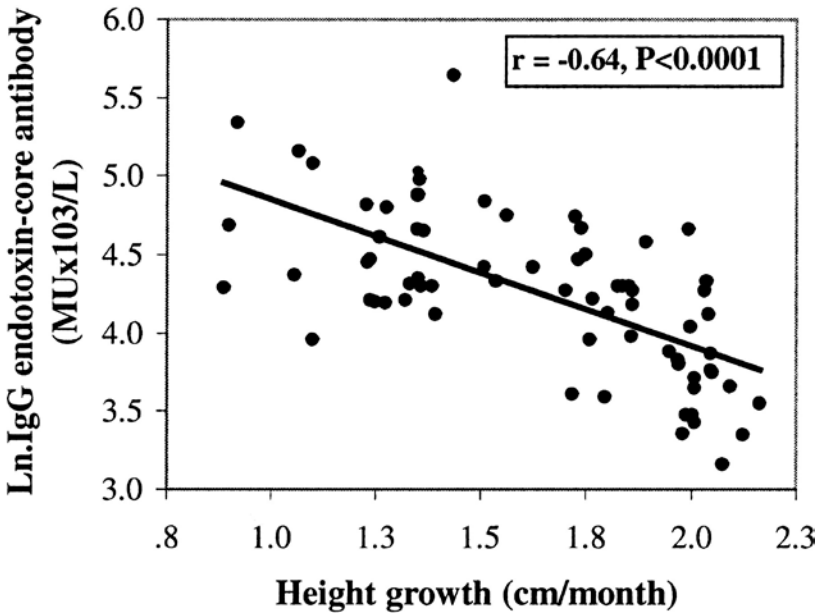
1960s, US Peace Corp Volunteers
Returning from Pakistan
Malabsorption, jejunitis, *without diarrhoea*



Trehan,
ADC 2016

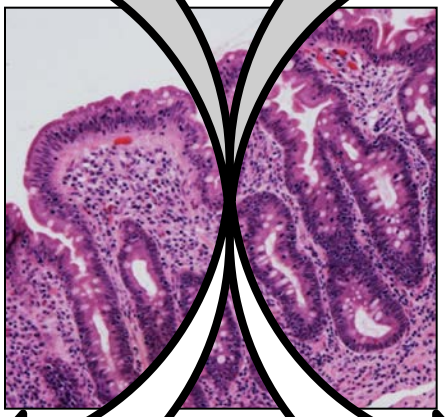
Growth failure and intestinal permeability

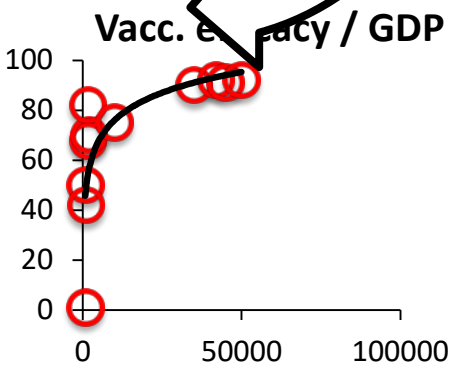




- Work initially in the Gambia uncovered important negative associations between intestinal permeability and linear growth
- Similar relationships exist for indices of enteric inflammation

Lunn, Lancet 1991; Campbell, J Nutr 2003

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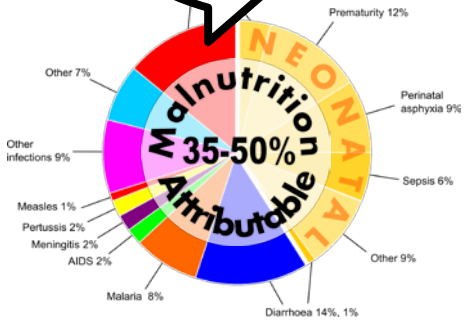
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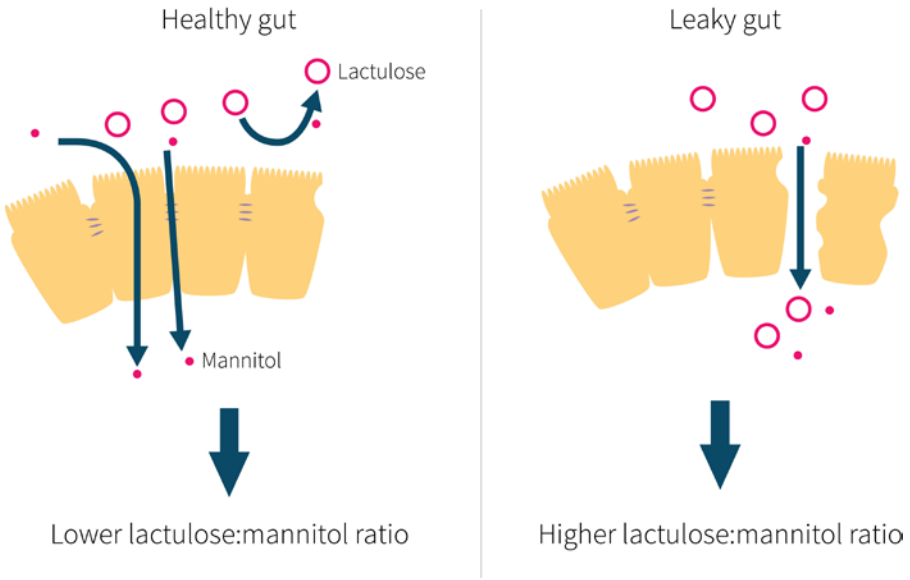
Other 7%


From
epidemiology
to clinical care

EED Diagnosis

- Gold standard is small intestinal biopsy
  - To date, impractical, unethical(?)
- L:M dual sugar absorption test
  - Technically tricky
  - Labourious
  - Requires mass spec
  - Many assumptions



EED Diagnosis

- New range of tests are being verified against linear growth (risk of incident stunting)
  - Faecal markers of inflammatory response (calprotectin, neopterin, MPO, host mRNA)
  - Faecal markers of protein loss (α1AT)
  - Bacterial translocation (EndoCAb, LPS, 16S)
  - Others (kyneurinine/tryptophan ratio)
- Combinatorial approaches required
- Lack of real gold standard is a major problem


UNITED STATES OF AMERICA
QUARTER DOLLAR

EED: Treatment

1. Remove the cause: tackle undernutrition, unsafe water, poor sanitation
2. Antimicrobials
3. Microbiota-modulating therapies
4. Host-directed therapies

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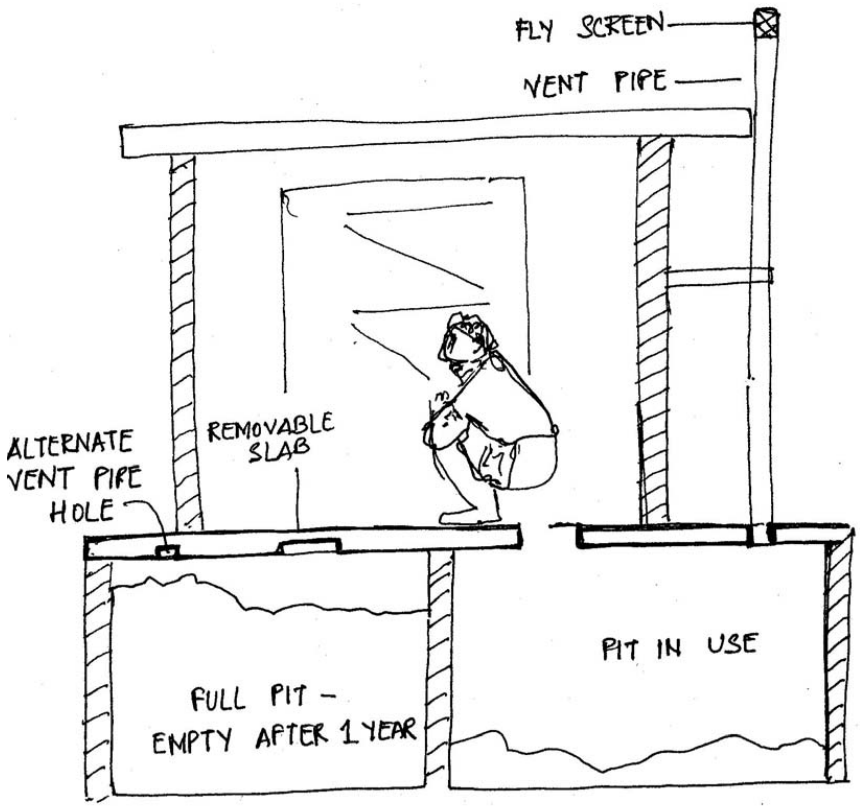

- **WASH-Benefits** (Kenya and Bangladesh); **SHINE** (Zimbabwe)
- Cluster-RCTs of WASH/Nutrition interventions – stunting endpoint
- c. 20,000 newborns
- Recruitment ongoing
- *Efficacy*, and not *effectiveness* trials

Overall mean and no. samples (%) in each category of other bacteria counts for selected vectors, Shurugwi District, Midlands Province, Zimbabwe

Vector	No. samples	Mean (95% CI) *	No. samples under each category of counts (%)			
			< 100	100–10,000	10,000–1,000,000	> 1,000,000
Coliforms						
Food (porridge)	15	2 (0–6)	14 (93)	1 (7)	0 (0)	0 (0)
Water	43	18 (10–33)	36 (84)	7 (16)	0 (0)	0 (0)
Kitchen floor	42	658 (324–1,340)	9 (21)	29 (69)	4 (10)	0 (0)
Trodden path to pit	43	274 (126–596)	12 (28)	28 (65)	3 (7)	0 (0)
Kitchen door step	43	639 (294–1,390)	9 (21)	29 (70)	6 (4)	0 (0)
Laundry area	43	1,880 (718–4,950)	5 (12)	22 (51)	16 (37)	0 (0)
Chicken feces	42	23.2 (10.1–53.4) m	0 (0)	0 (0)	5 (12)	37 (88)
Enterobacteriaceae						
Food (porridge)	15	4 (1–13)	14 (93)	1 (7)	0 (0)	0 (0)
Water	43	52 (27–100)	29 (67)	13 (30)	1 (2)	0 (0)
Kitchen floor	42	1,850 (1,030–3,340)	2 (5)	35 (83)	5 (12)	0 (0)
Trodden path to pit	43	1,290 (623–2, 690)	3 (7)	34 (79)	6 (14)	0 (0)
Kitchen door step	43	2,970 (1,390–6,350)	3 (7)	28 (64)	13 (30)	0 (0)
Laundry area	43	5,750 (2,560–12,900)	2 (5)	24 (56)	16 (37)	1 (2)
Chicken feces	42	29.5 (14.3–60.7) m	0 (0)	0 (0)	3 (7)	39 (93)
Aerobic counts						
Food (porridge)	15	1,420 (168–12,000)	3 (20)	8 (53)	2 (13)	2 (13)
Water	43	21,400 (10,200–45,100)	0 (0)	19 (44)	19 (44)	5 (12)
Kitchen floor	42	105,000 (94,600–117,000)	0 (0)	0 (0)	42 (100)	0 (0)
Trodden path to pit	43	1.89 (1.23–2.92) m	0 (0)	0 (0)	13 (30)	30 (70)
Kitchen door step	43	4.44 (2.49–7.93) m	0 (0)	0 (0)	8 (18)	35 (81)
Laundry area	43	20.3 (11.6–35.5) m	0 (0)	0 (0)	2 (5)	41 (95)
Chicken feces	42	1.30 b (474 m–3.58 b)	0 (0)	0 (0)	1 (2)	41 (98)

*CI = confidence interval. Mean counts are geometric means (95% confidence interval) 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; b = billion.

3000 hours of child observation

Chicken faeces (20g) ingested on average every 2h!

Ngure, AJTMH 2013

Play mats and play ‘yards’ given to families in WASH arms – *extremely controversial*…


9208

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Antimicrobials?

- Evidence from animal husbandry that antimicrobials improve growth
- Equivalent data from use of co-trimoxazole in children with HIV

Variable	All	TMP-SMX group		Placebo group		
	Baseline value (mean, SD)	Weeks to last measurement (median, IQR)	Change per year (mean, 95% CI)	Weeks to last measurement (median, IQR)	Change per year (mean, 95% CI)	P [a]
CD4 cell percentage	12.3 (7.0)	50 (26, 80)	+.14 (−.55, +.83)	41 (5, 71)	−.37 (−1.18, +.44)	0.33
Weight-for-age Z score	−2.84 (1.63)	64 (34, 96)	−.15 (−.28, −.03)	48 (18, 74)	−.35 (−.49, −.21)	0.04
Height-for-age Z score	−3.25 (1.48)	64 (34, 96)	−.07 (−.15, +.01)	48 (18, 74)	−.22 (−.30, −.13)	0.01
Hemoglobin level, g/dL	9.44 (1.27)	51 (25, 91)	+.33 (+.20, +.47)	47 (15, 72)	+.08 (−.08, +.24)	0.01
Neutrophil count, $\times 10^9$ cells/L	3.21 (1.62)	51 (25, 91)	+.47[b] (+.25, +.69)	47 (15, 72)	+.46 (+.25 +.67)	0.97
Platelet count, $\times 10^9$ cells/L	296 (116)	51 (25, 91)	−13 (−25, −1)	47 (15, 72)	−14 (−28, −1)	0.89

Prendergast, CID, 2011

Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial

James A Berkley, Moses Ngari, Johnstone Thitiri, Laura Mwalekwa, Molline Timbwa, Fauzat Hamid, Rehema Ali, Jimmy Shangala, Neema Mturi, Kelsey D J Jones, Hassan Alphan, Beatrice Mutai, Victor Bandika, Twahir Hemed, Ken Awuondo, Susan Morpeth, Samuel Kariuki, Gregory Fegan

Summary

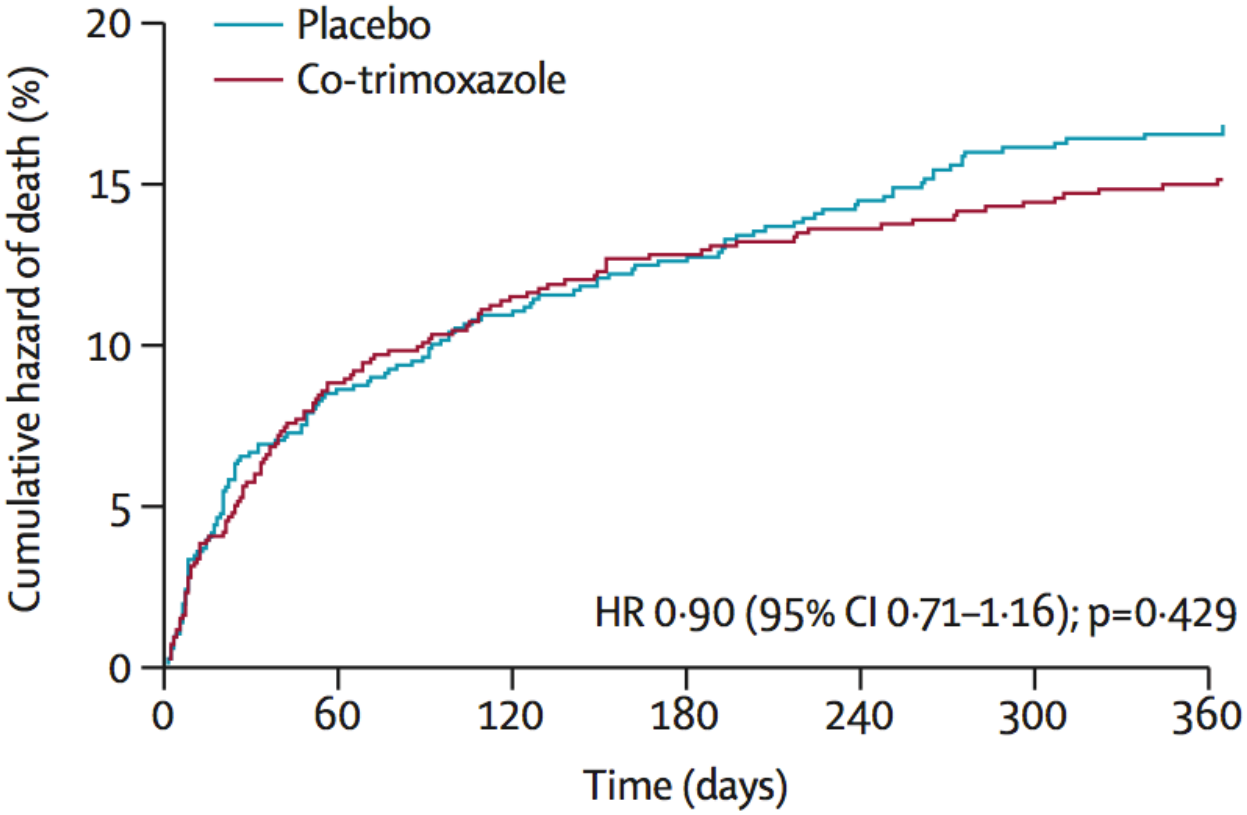
Background Children with complicated severe acute malnutrition (SAM) have a greatly increased risk of mortality from infections while in hospital and after discharge. In HIV-infected children, mortality and admission to hospital are prevented by daily co-trimoxazole prophylaxis, despite locally reported bacterial resistance to co-trimoxazole. We aimed to assess the efficacy of daily co-trimoxazole prophylaxis on survival in children without HIV being treated for complicated SAM.

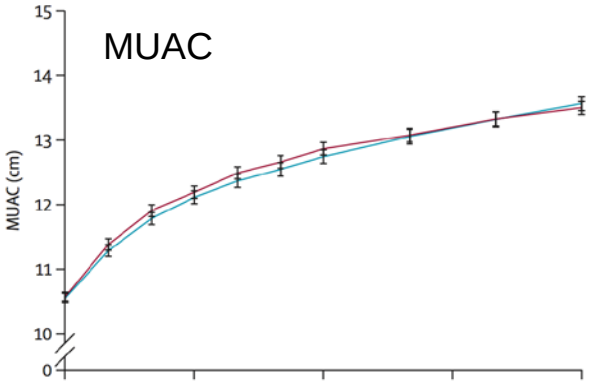
Lancet Glob Health 2016; 4: e464–73

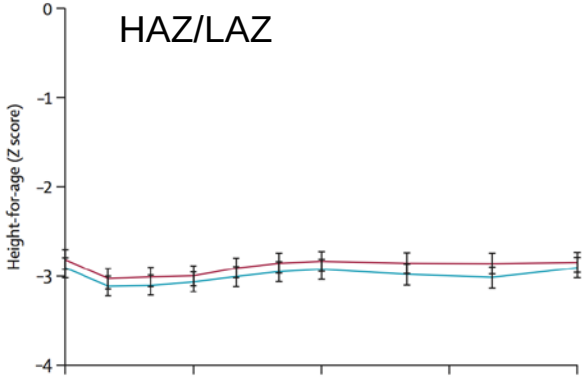
Published Online June 2, 2016 http://dx.doi.org/10.1016/S2214-109X(16)30096-1

- Double-blind RCT
- 6m treatment, 12m follow-up
- Complicated SAM (HIV-ve)
- Clinical and laboratory evidence of EED

Berkley, Lancet Global Health, 2016







Berkley, Lancet Global Health, 2016

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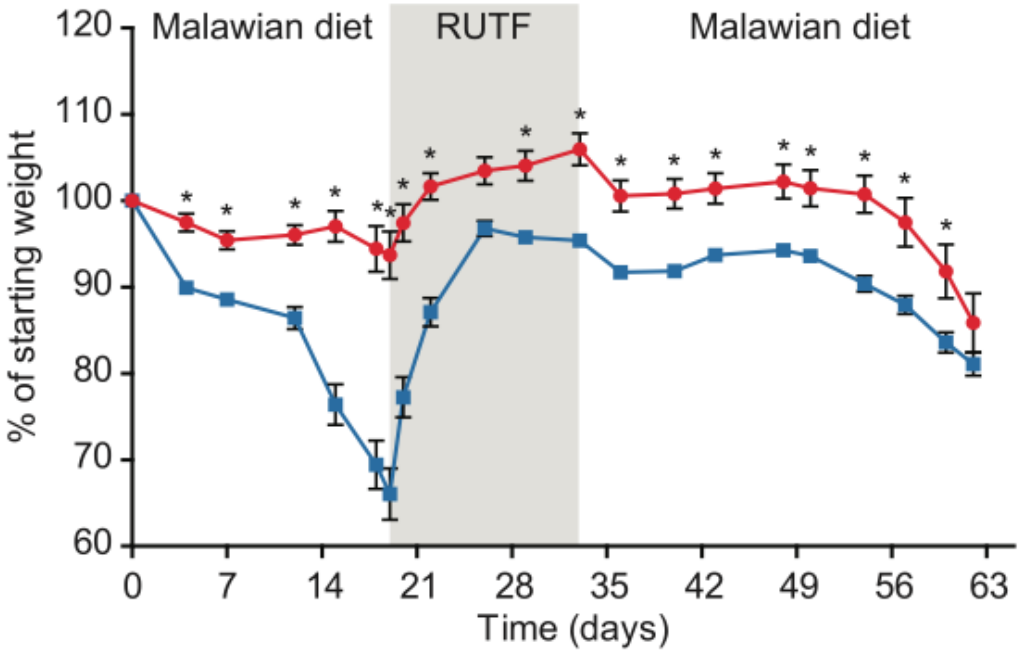
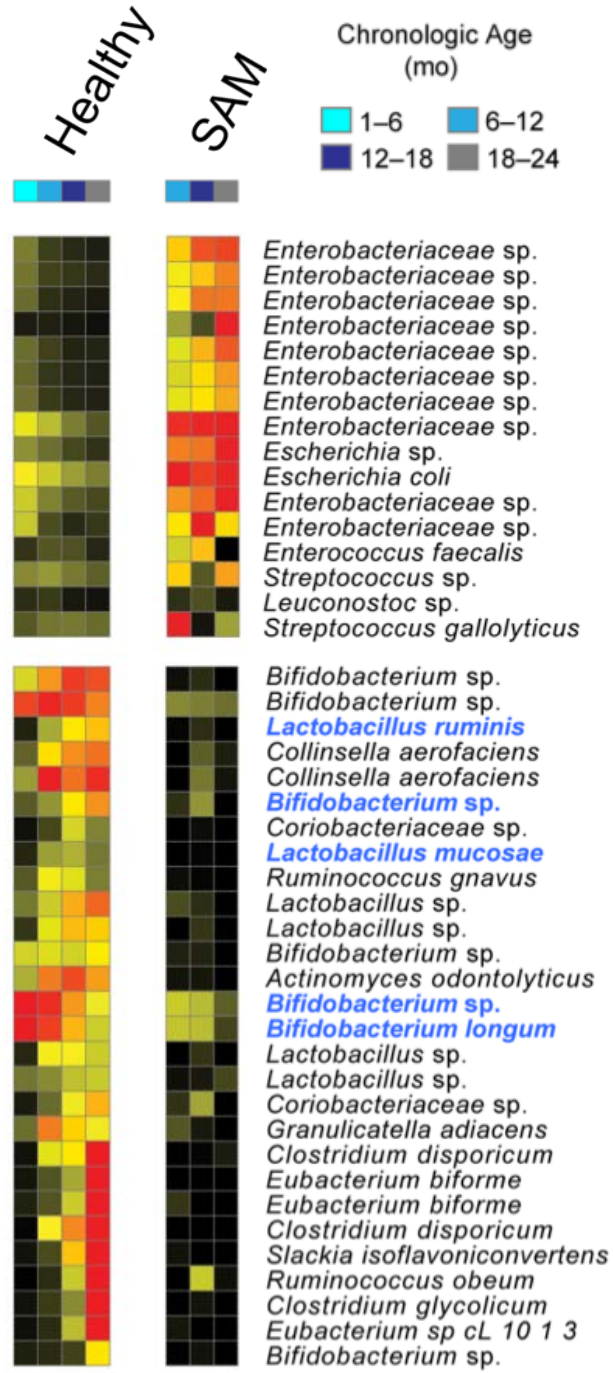
A role for the intestinal microbiome?

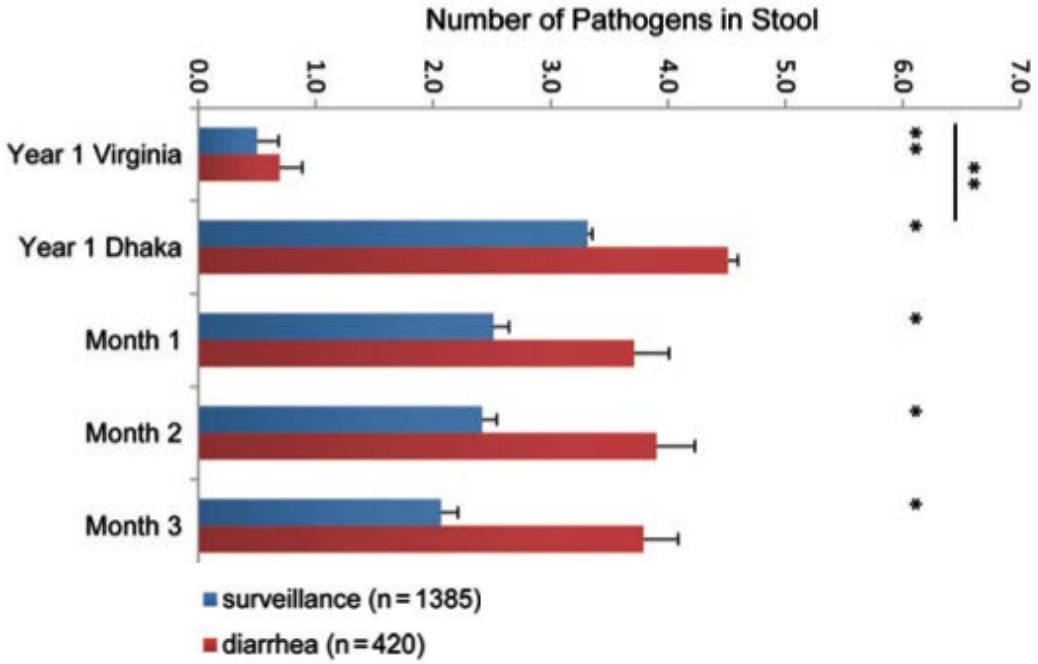


- Stool from malnourished or non-malnourished children Malawian twins implanted into previously germ-free (gnotobiotic) mice, who they then fed a typical Malawian diet.
- Mice with the 'malnourished' microbiome (blue) lost weight on the Malawian diet, and regained it when they were fed Plumpy'nut®, whereas those with the 'healthy' microbiome did not lose weight.
- Provided clear evidence that altered microbiome could play a **causal** role in the development of malnutrition.

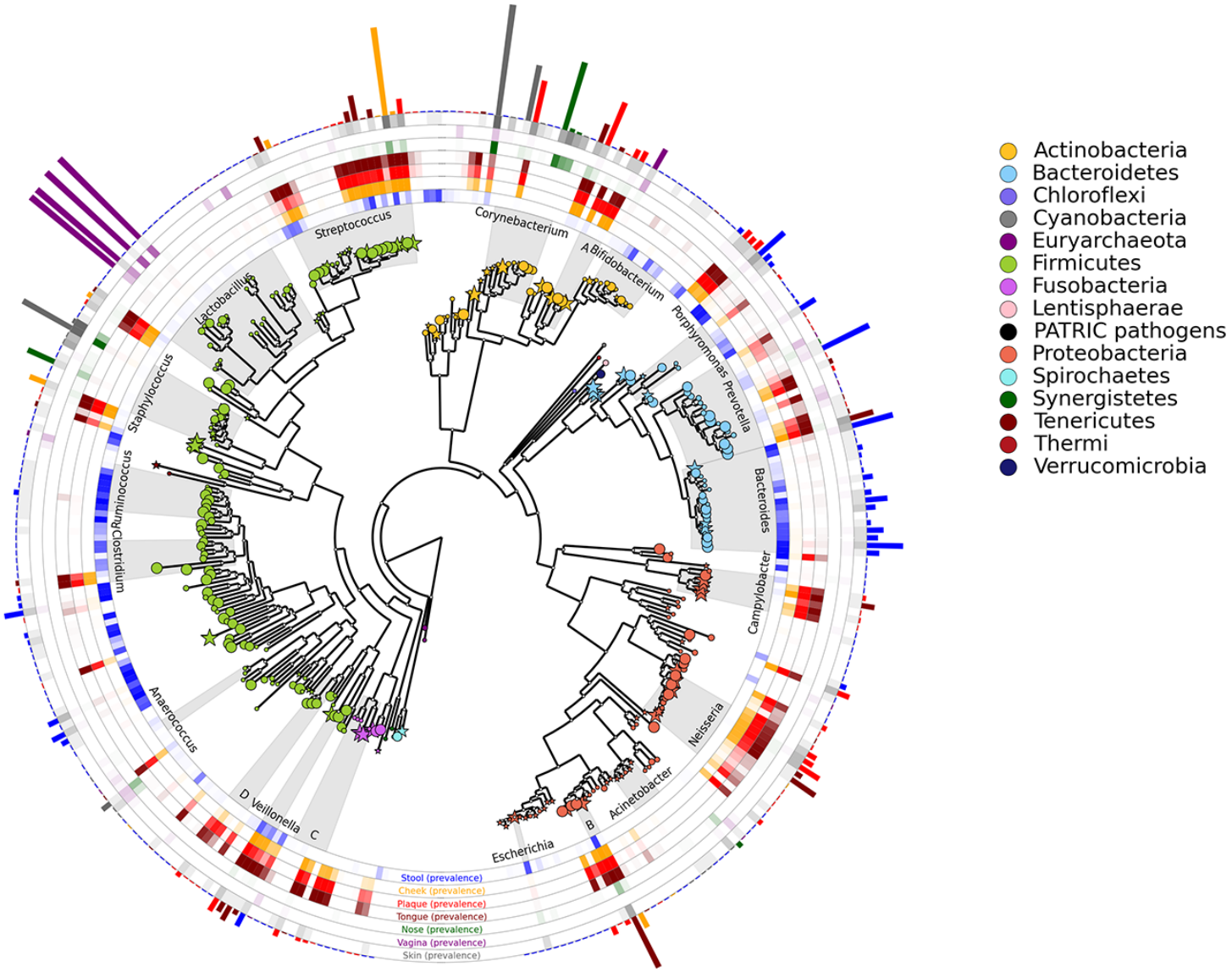
Smith, Science 2013



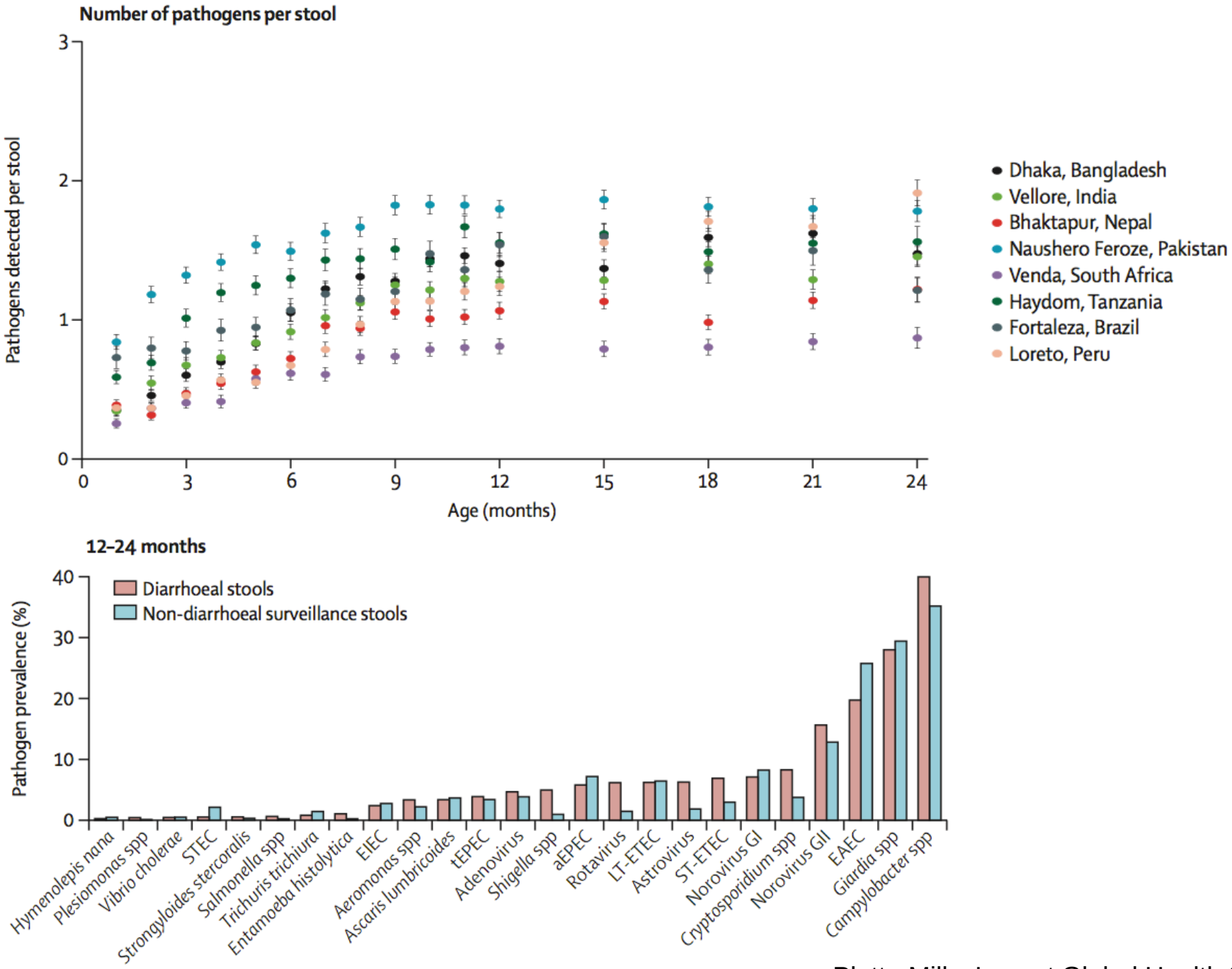
- Growth failure is associated with microbiome abnormalities (left)
- Children living in poverty have very high enteric pathogen exposure (below)



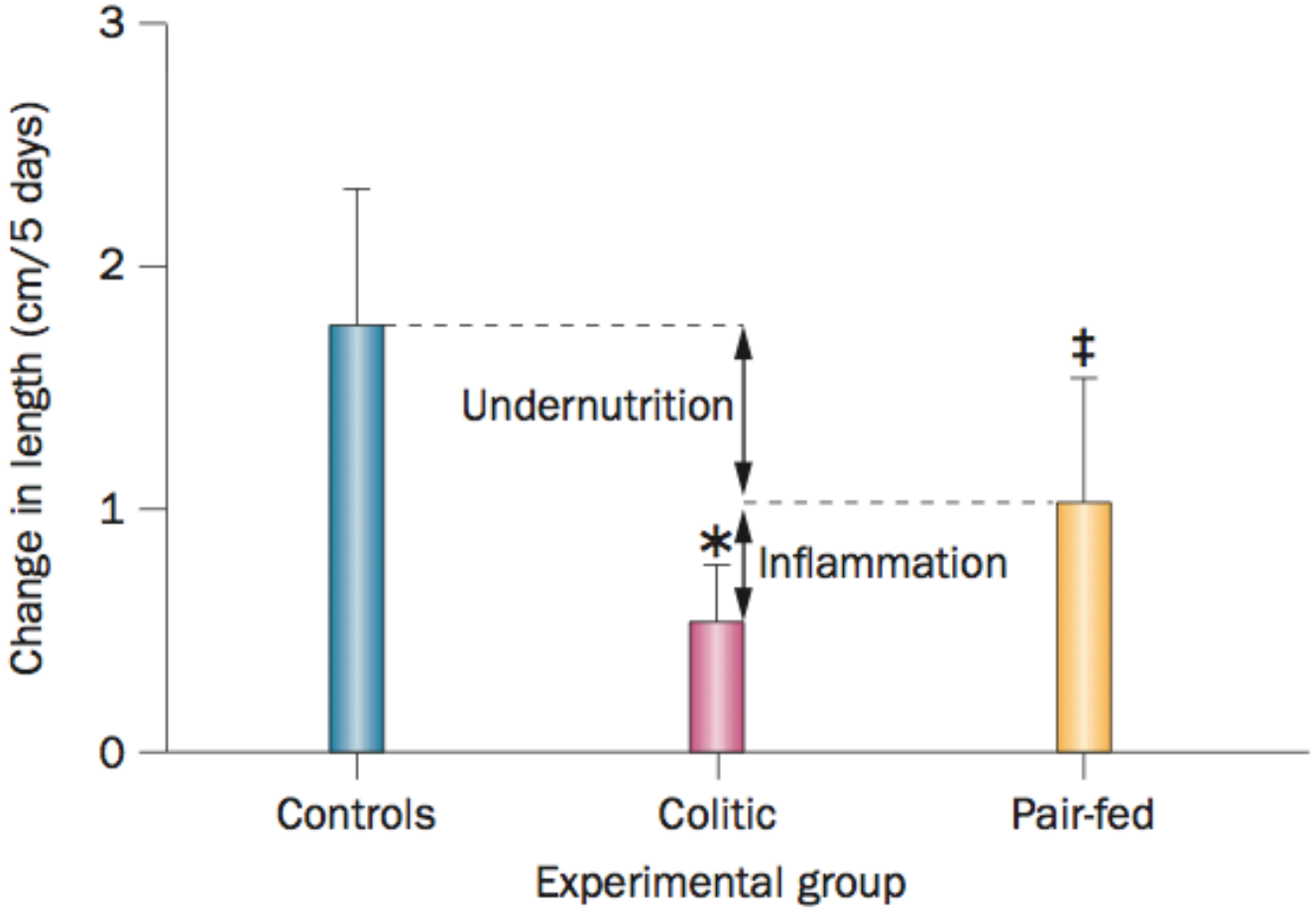
Subramaniam, Nature 2014; Taniuchi JID 2012



Will complex communities outperform ‘probiotics’?



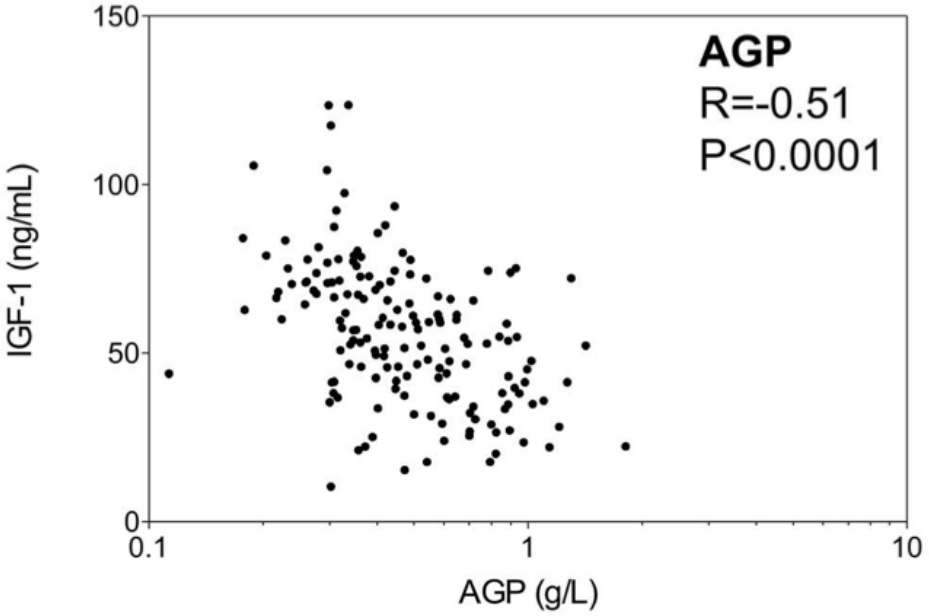
Platts-Mills, Lancet Global Health 2016

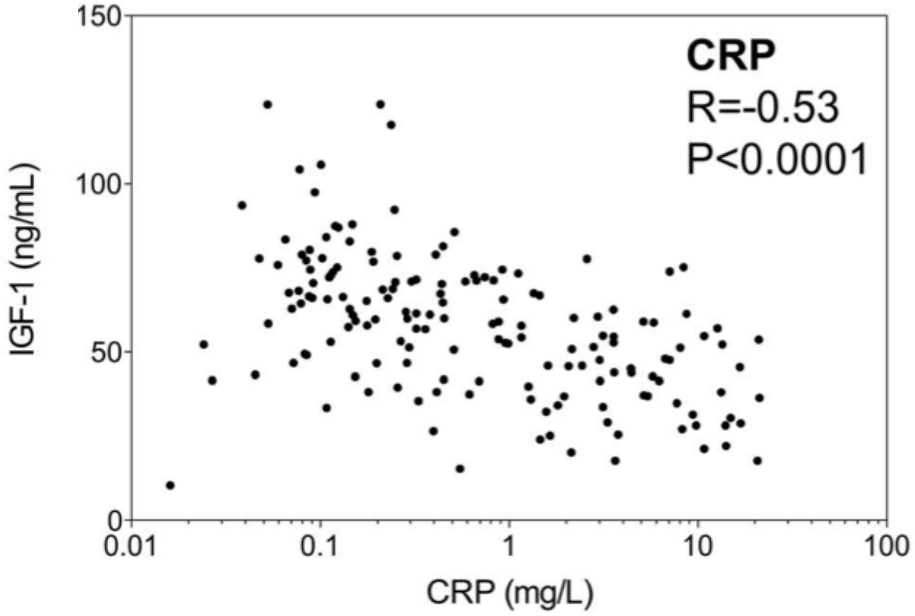


- Enteric inflammation itself causes linear growth failure
  - Inflammatory cytokines interfere with the GH-IGF-1 axis
  - IL-6 acts directly on chondrocytes at growth plates

Ballinger, Gut 2000 (via Sanderson, Nat Rev Gastro Nutr 2014)

In populations with incident stunting and EED you see exactly the expected relationships between linear growth, GH-IGF-1 axis and inflammation



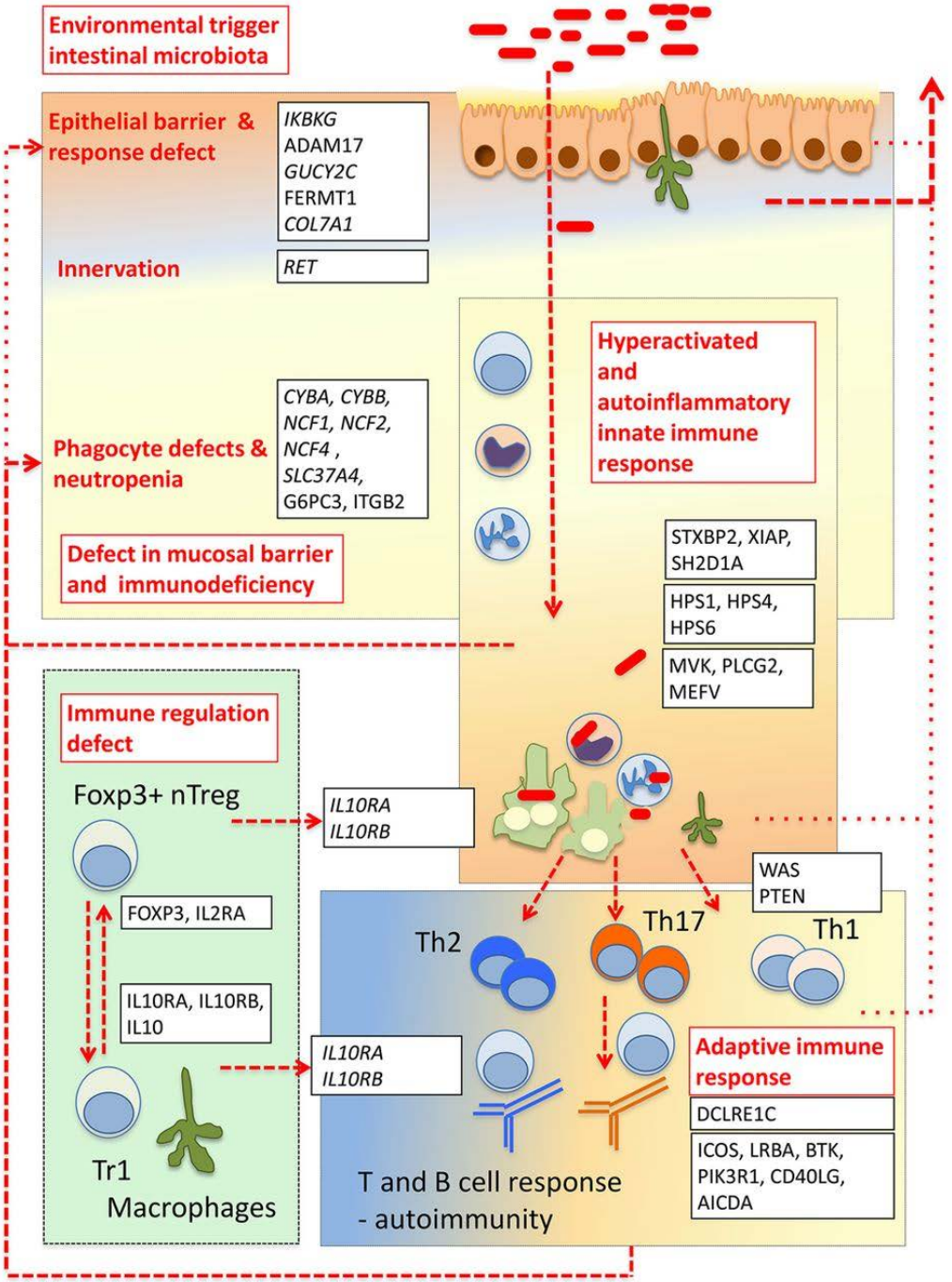


Biomarker*	Adjusted OR for stunting (95%CI) [n]**	P value
IGF-1	0.88 (0.84, 0.92) [185]	<0.001
Log_{10} CRP	3.06 (1.34, 6.99) [180]	0.008
Log_{10} AGP	7.87 (0.74, 83.74) [173]	0.087

Prendergast, CID 2013

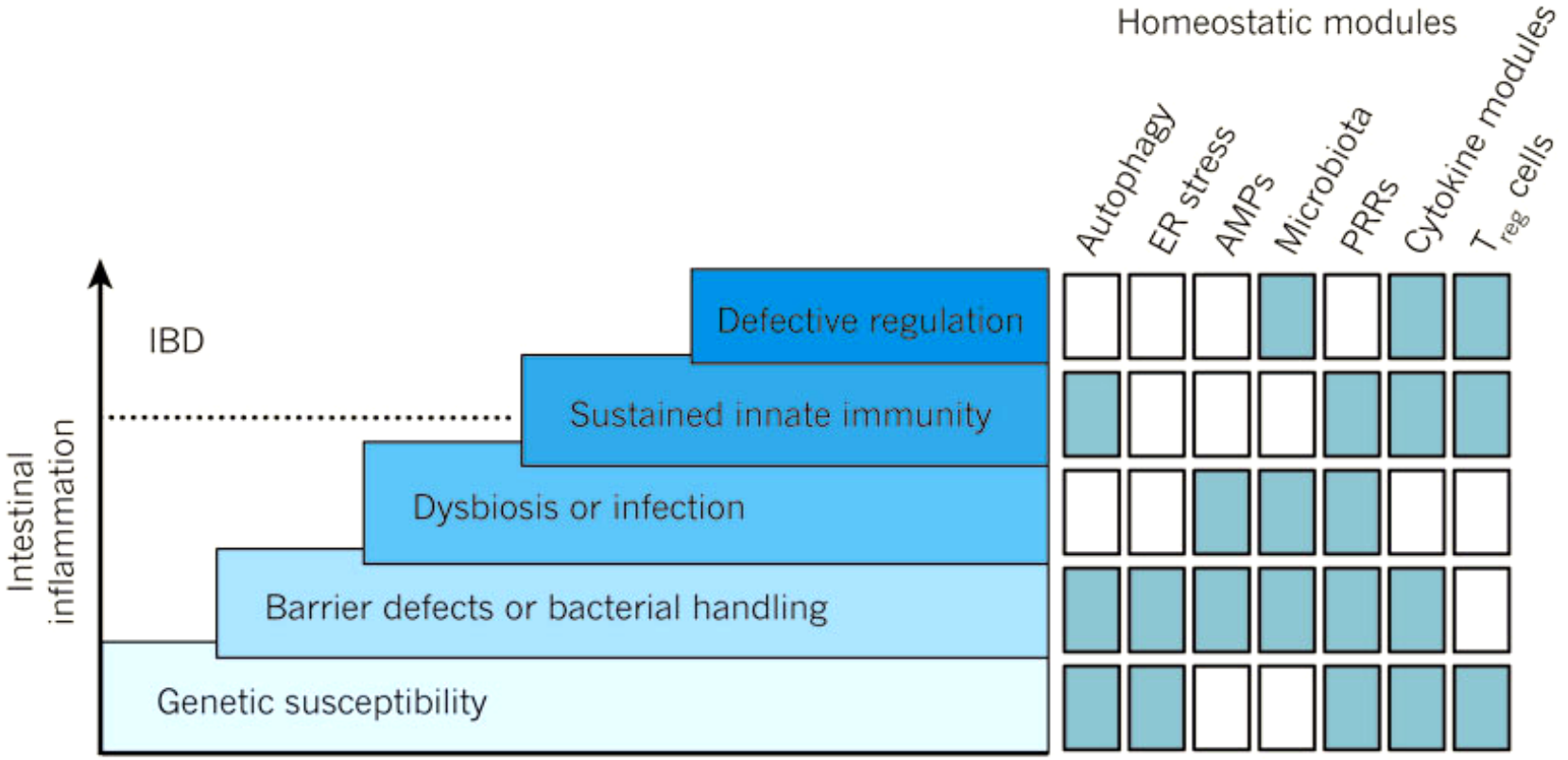
IBD Aetiology

- Early-onset IBD is often caused by single-gene defects
- Diversity in genetic aetiology indicates that involvement of many different pathways can give rise to similar pathology (clinical/macro/micro)
- Later-onset IBD arises in the context of ‘multiple hits’ with less severe involvement across several pathways



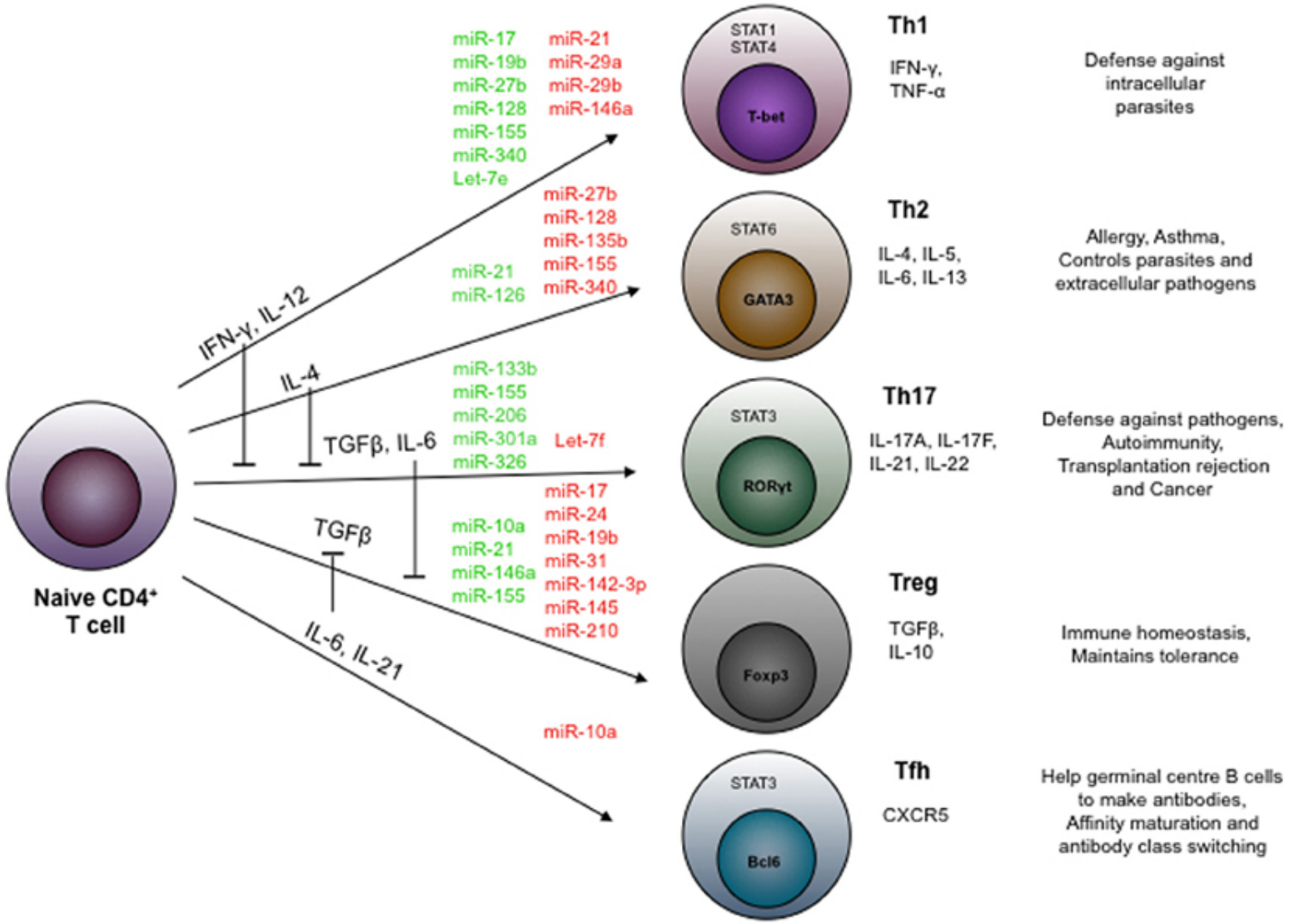
Uhlig, Gut 2013

IBD Aetiology

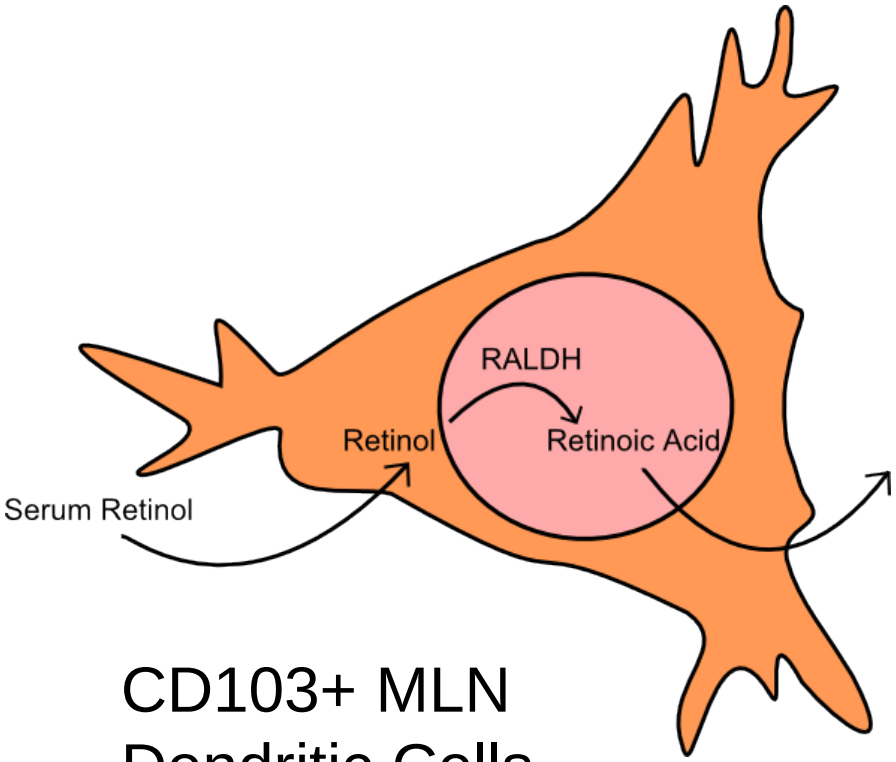


In the multi-hit model, an accumulation of low-level defects in pathways important for mucosal immune homeostasis can lead to chronic inflammatory activation in the gut

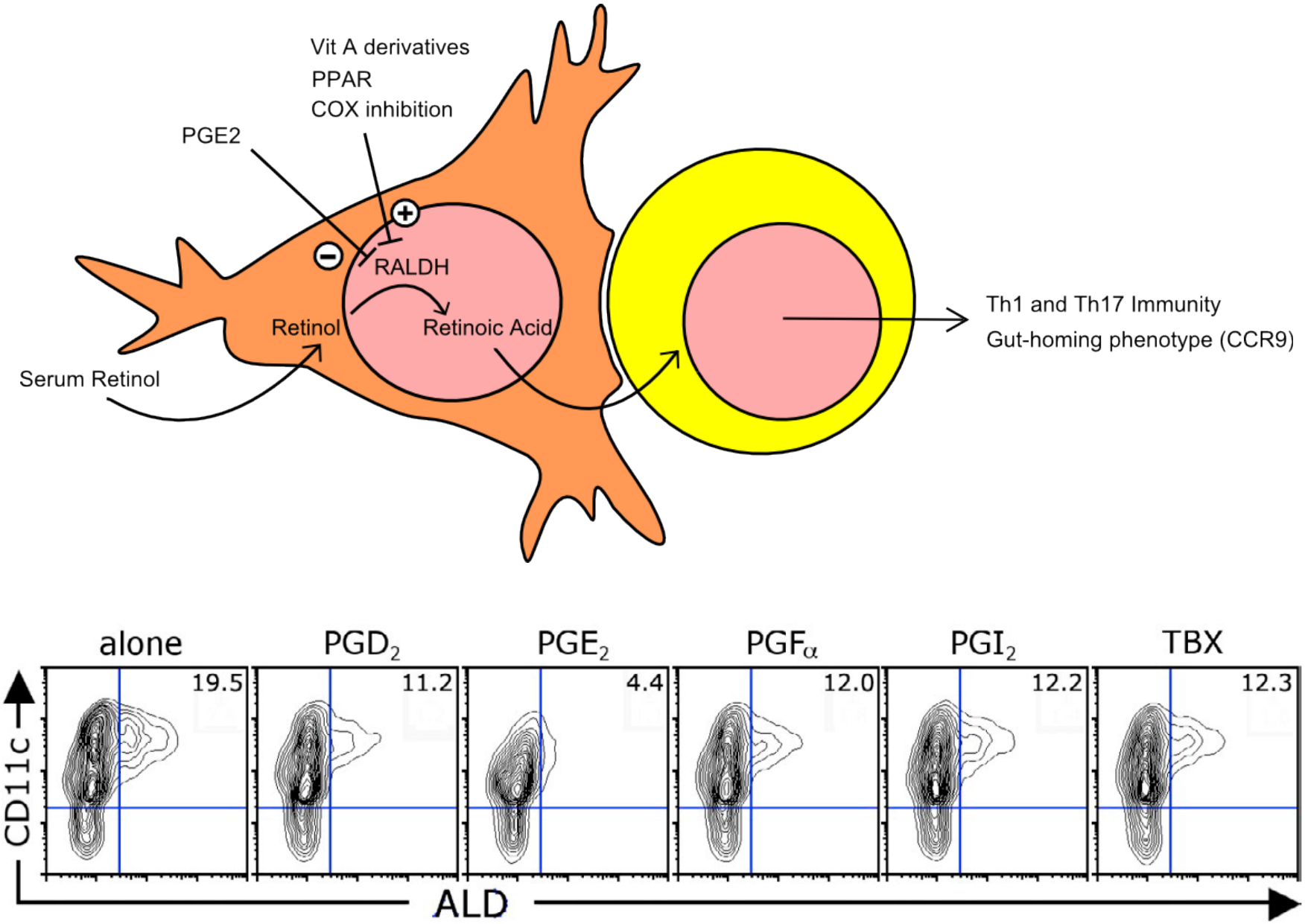
Maloy, Nature 2011



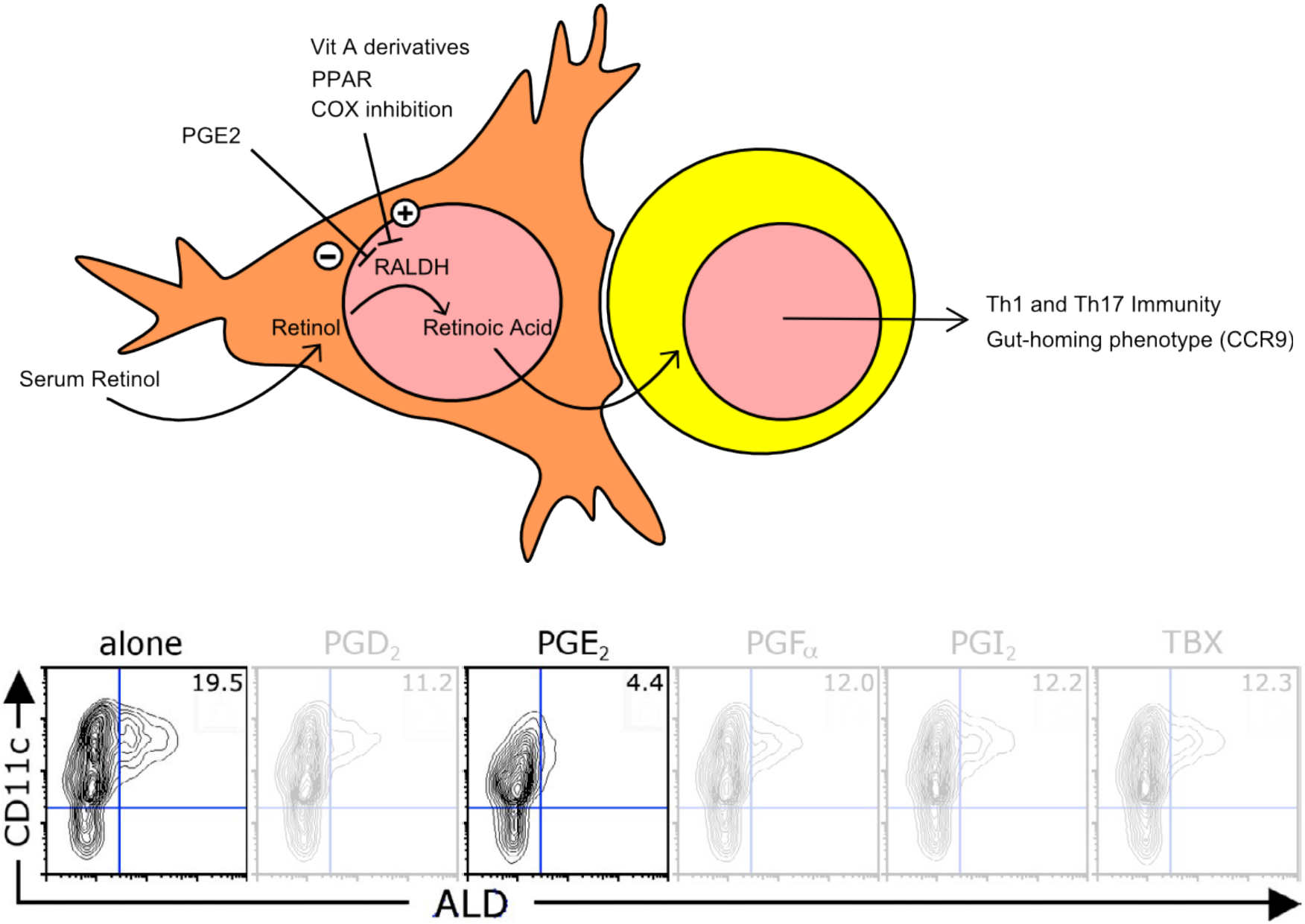
There are many different types of inflammation, which negatively regulate each other: e.g. T cell lineage commitment



CD103+ MLN
Dendritic Cells



Stock, J Exp Med 2011



Stock, J Exp Med 2011

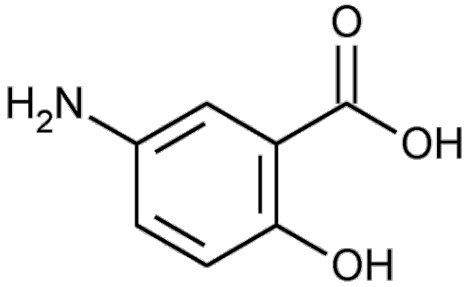

0
HARVARD
TRIP
1400/1500 SERIES
OHAUS
2kg-5lb Capacity
6002098/1010

Inflammation is adaptive response to high pathogen burden, and is a necessary evil

Inflammation is adaptive response to high pathogen burden, and is a necessary evil

Inflammation is maladaptive, unhelpful, and a rational target for treatment

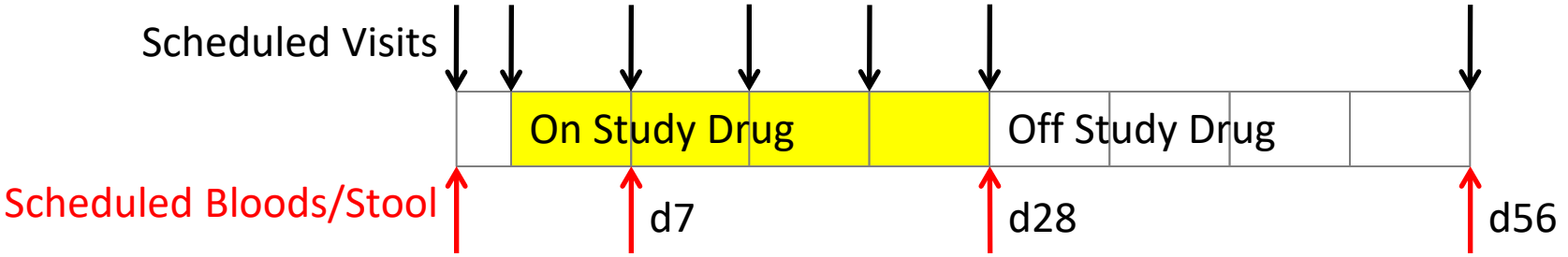
Mesalazine



- Atypical immunomodulator
  - Agonist to PPAR-γ
  - Impairs eicosanoid production
  - Interferes with IL-1, IL-2, TNFα production
  - Reduces antibody production by plasma cells
  - Potent antioxidant
- Activity confined to the gut
- Available as child-friendly granules
- Commonly used in paediatric IBD
- Off-patent

- 44 Children
  - Severe Acute Malnutrition *and* Stunting
  - No HIV or current major infection
  - ESR >20
- Presenting to Baraka Clinic, Mathare Valley Nairobi, or identified during community screening for SAM

Study Procedures



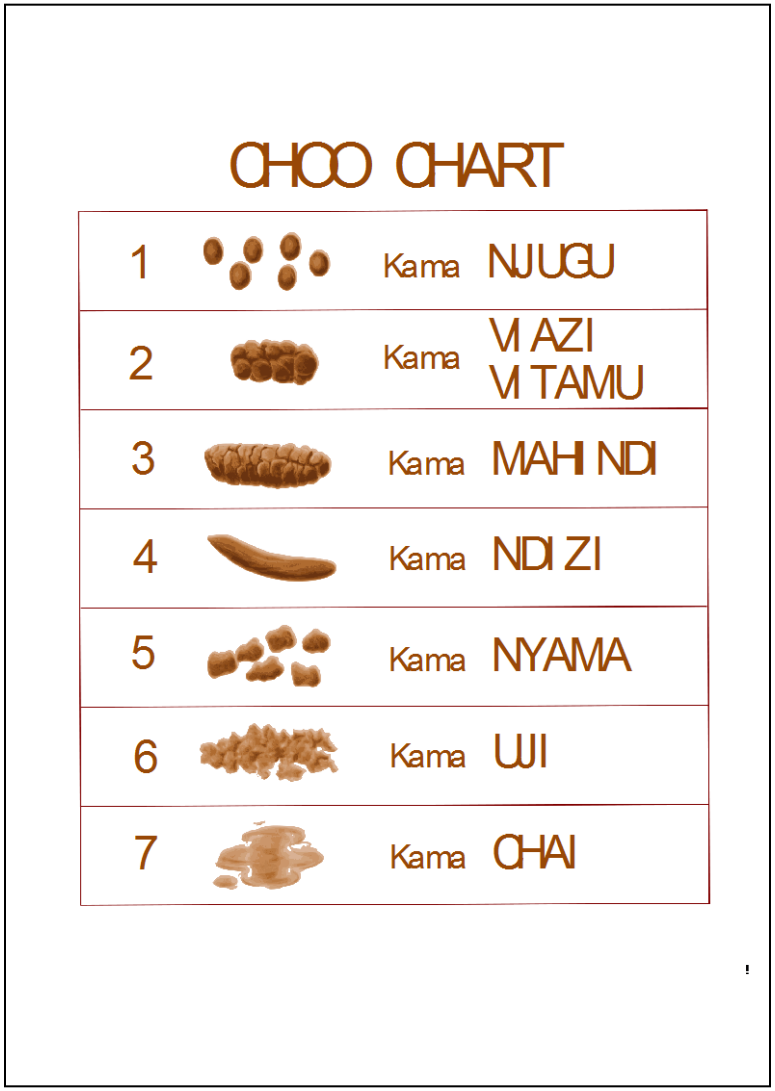
- All participants received nutritional rehabilitation, a week of oral amoxicillin and empiric deworming
- Randomised to mesalazine granules 30mg/kg/day orally for 7 days then 50mg/kg/day for 21 days (three divided doses)
- Follow-up until 28 days after cessation of the study drug
- Scheduled visits and bloods/stool as above

Results: safety/toxicity

Safety Outcome		Mesalazine	Placebo	P
Mortality (Kwashiorkor/dehydration/sepsis)		0	1	
SAEs	Sepsis requiring hospital treatment	0	1	
	Diagnosed Tuberculosis	1	1	
	Diagnosed Sickle Cell Disease	0	1	
Total adverse events		35	27	0.53
Total 'gastrointestinal' adverse events		20	16	0.52
Total 'diarrhoeal' adverse events		9	11	0.70
Total pre-defined Grade 3 Toxicity		0	0	
# participants not able to escalate dose at d7*		1	7	0.02

* Most of those who did not escalate were held on the low dose due to elevation in transaminases, which was more common in the placebo arm

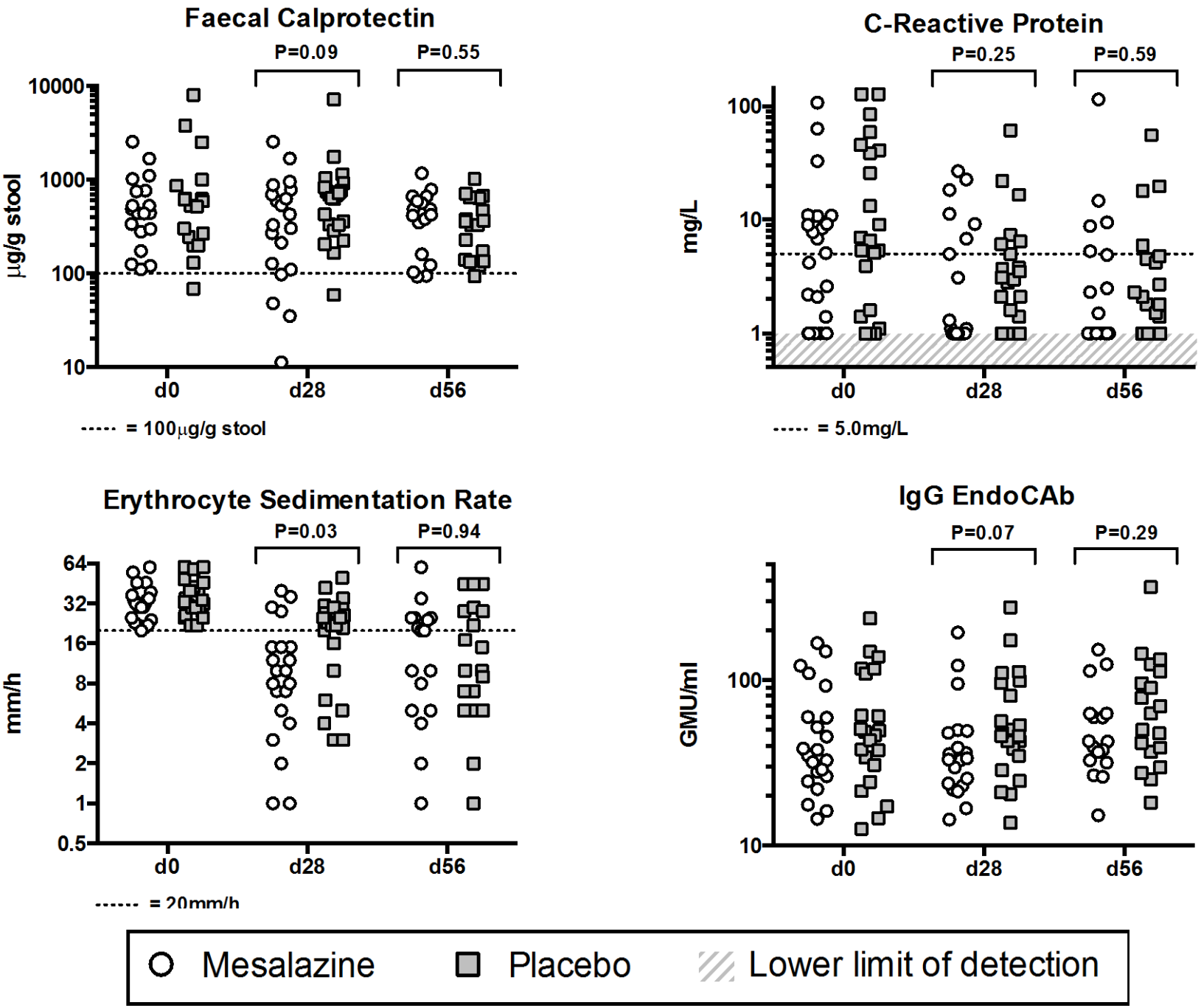
Jones, BMC Med 2014



		1	2	3	4	5	6	7	P
E	M	0	0	1	2	5	12	1	0.65
	P	0	0	0	4	3	13	2	
d7	M	1	2	2	7	0	9	0	**0.03**
	P	0	0	3	1	3	11	3	
d28	M	0	1	0	3	4	10	2	0.24
	P	1	0	2	4	5	6	2	
d56	M	0	0	0	5	3	8	1	0.49
	P	0	1	0	5	5	8	0	

Mesalazine was associated with more-formed stool at day 7 (no difference in stool frequency throughout)

Jones, BMC Med 2014



Jones, BMC Med 2014

EED: Future scientific perspectives

- Point-of-care diagnostics
- Increased understanding of the mechanism of inflammation via small animal models
- Targeted therapeutics: Microbial/Immune
- *Perhaps* an increased focus on WASH delivery
- Immunonutrition?
  - Aryl-hydrocarbon receptor agonists
  - Optimisation of amino acid composition/delivery

Take-home messages

- EED may be a leading cause of stunting, which has important long term impacts on growth and development
- Improving nutrition is not sufficient to prevent or cure stunting
- Stunting may occur via a direct effect of intestinal and systemic inflammatory activation on linear growth
- Targeting aberrant inflammatory activation and the microbiota may be viable approaches to treatment of environmental enteropathy

Thank-you

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