The link between infection, immunity and malnutrition

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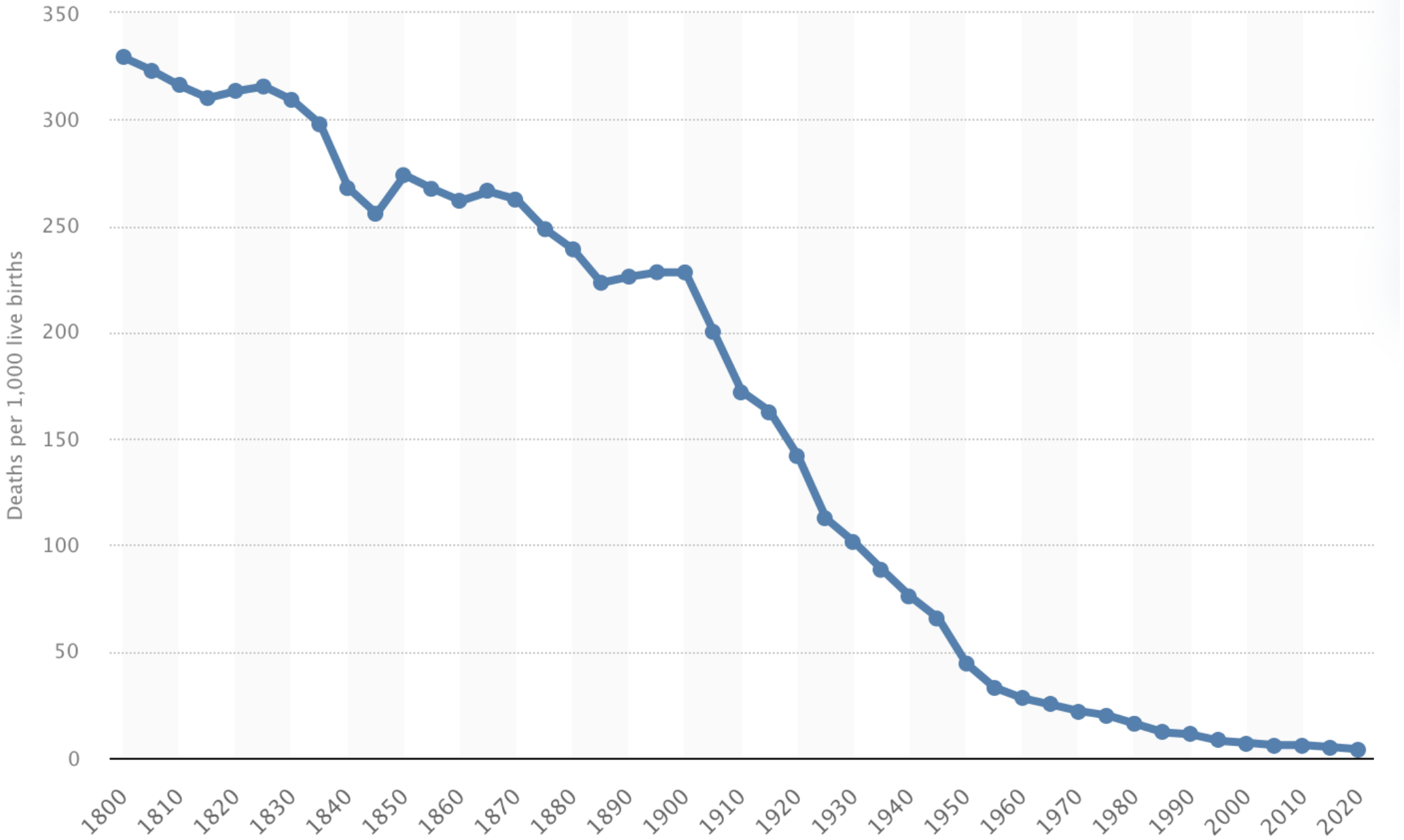
Queen Mary University of London

ZVITAMBO
HELPING CHILDREN SURVIVE AND THRIVE


Deaths per 1,000 live births
350
300
250
200
150
100
50
0
1800
1810
1820
1830
1840
1850
1860
1870
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020

Blowing in the wind: why do so many cities have poor east ends?

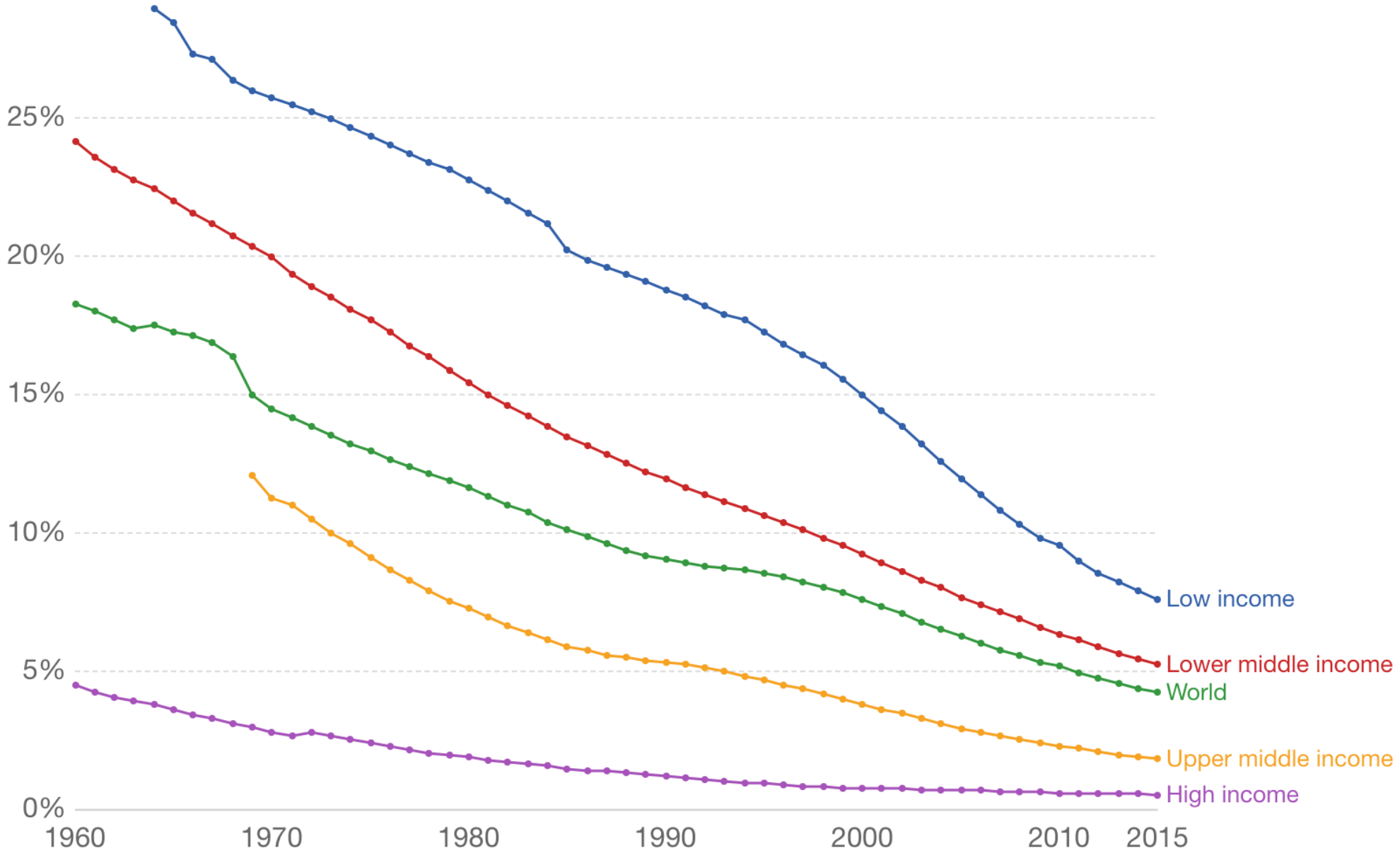
THE "SILENT HIGHWAY"-MAN.

"Your **MONEY** or your **LIFE**!"

Child mortality by income level of country

The child mortality rate measures the share of children that die before reaching the age of 5.

Our World in Data



Source: World Bank – WDI


ORAL
REHYDRATION SALTS
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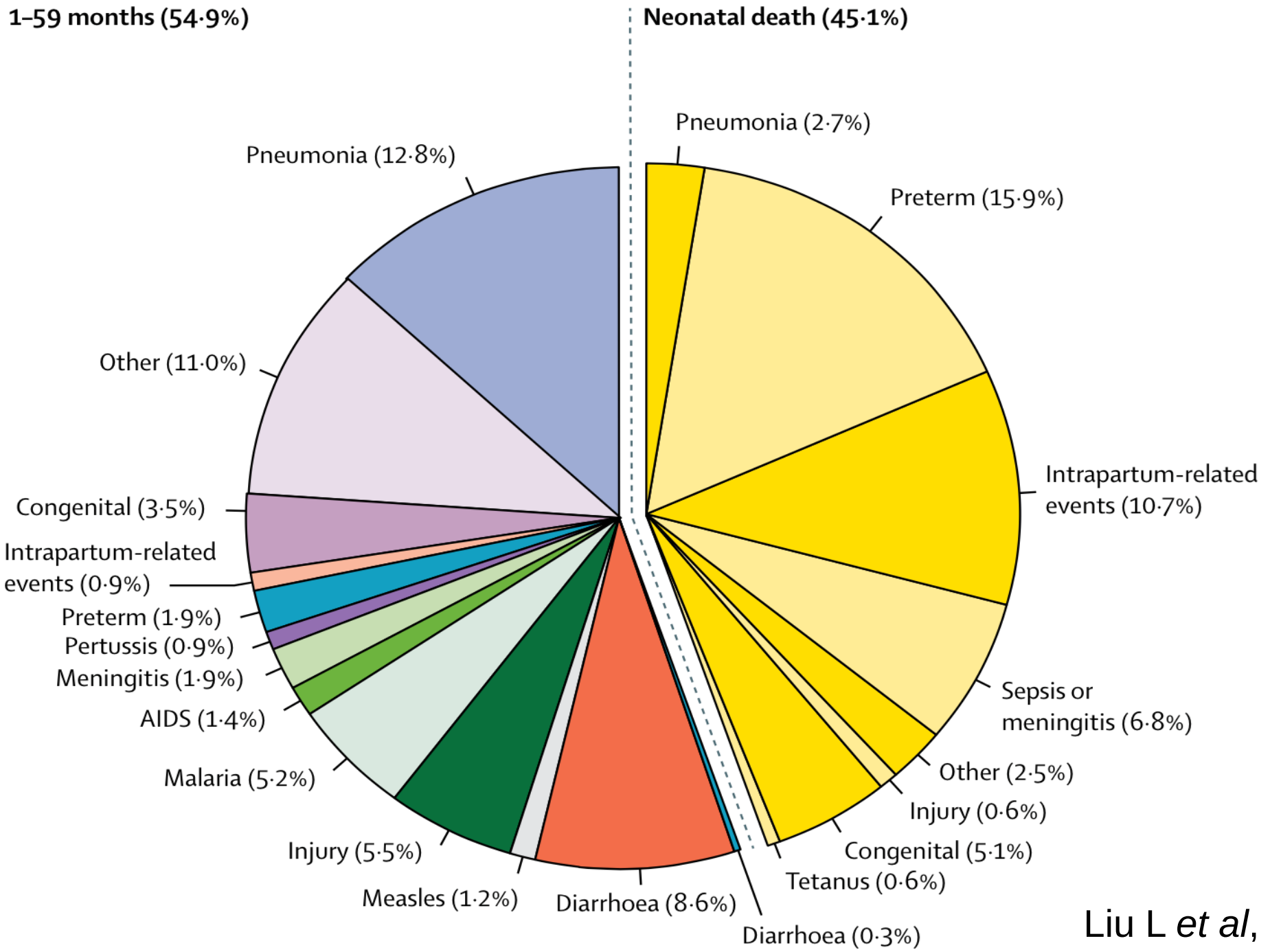
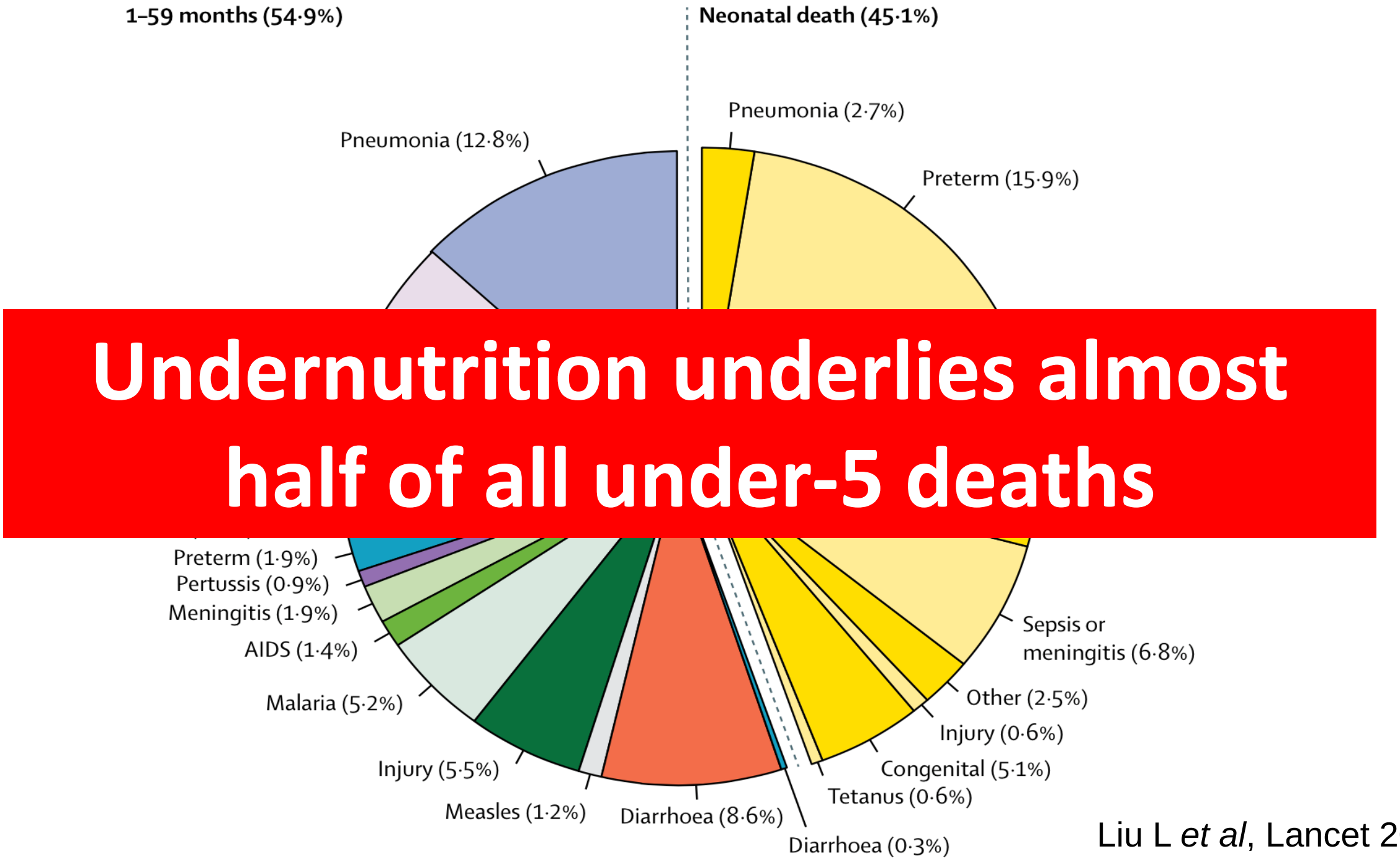
REHYDRATION SALTS

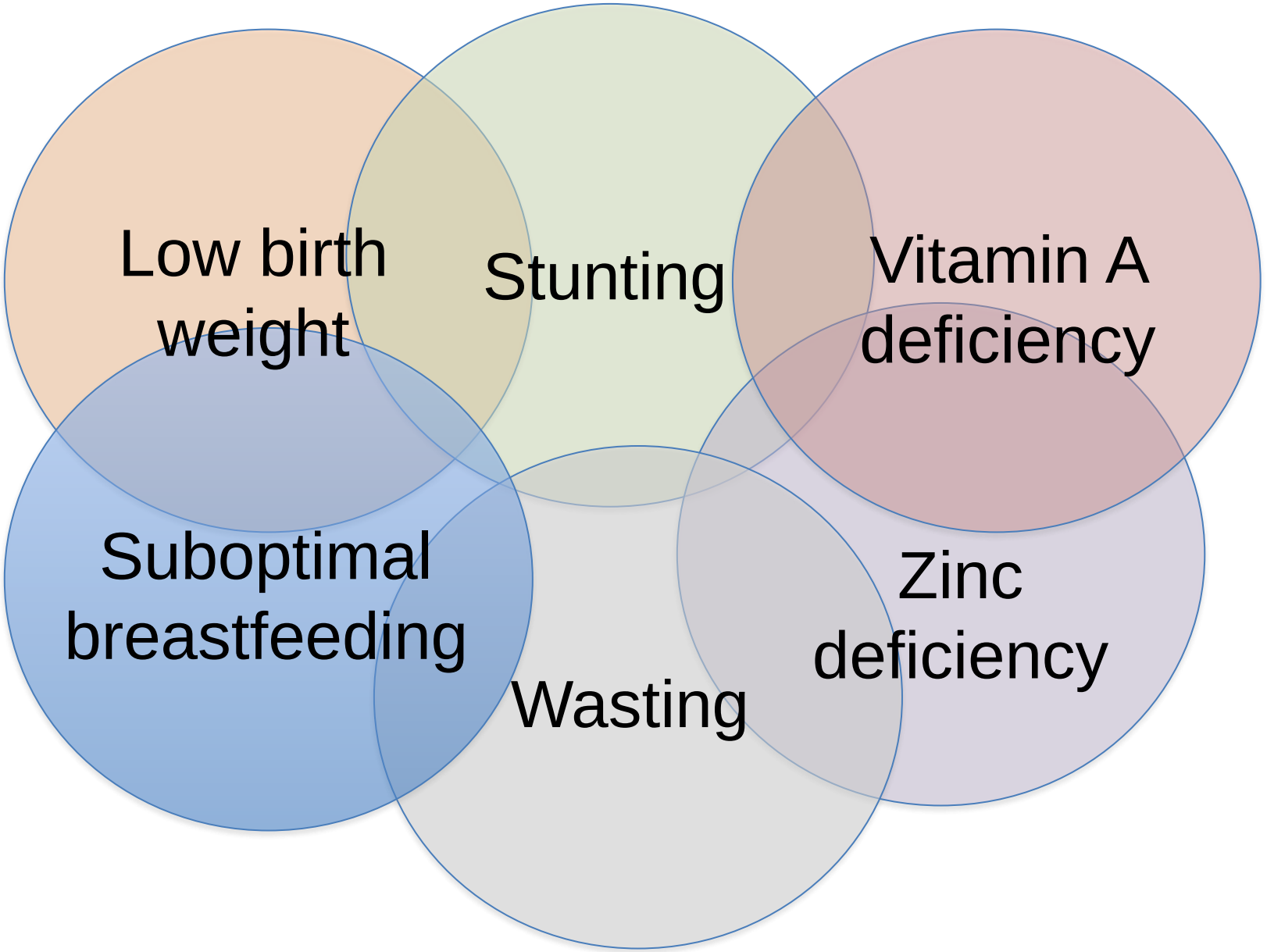


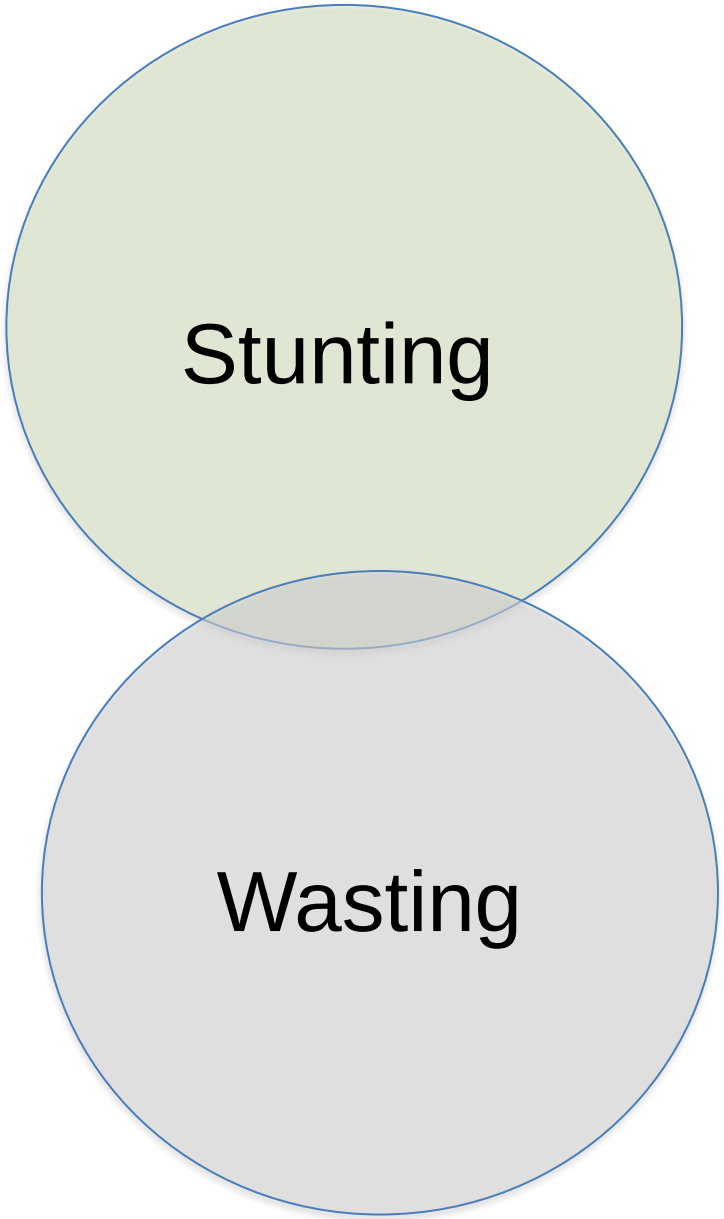
Liu L *et al*, Lancet 2016



Undernutrition underlies almost half of all under-5 deaths

Liu L *et al*, Lancet 2016


Low birth weight
Stunting
Vitamin A deficiency
Suboptimal breastfeeding
Wasting
Zinc deficiency


Stunting
Wasting

Stunting
Low height-for-age

Wasting
Low weight-for-height

TIME Subscribe

WORLD

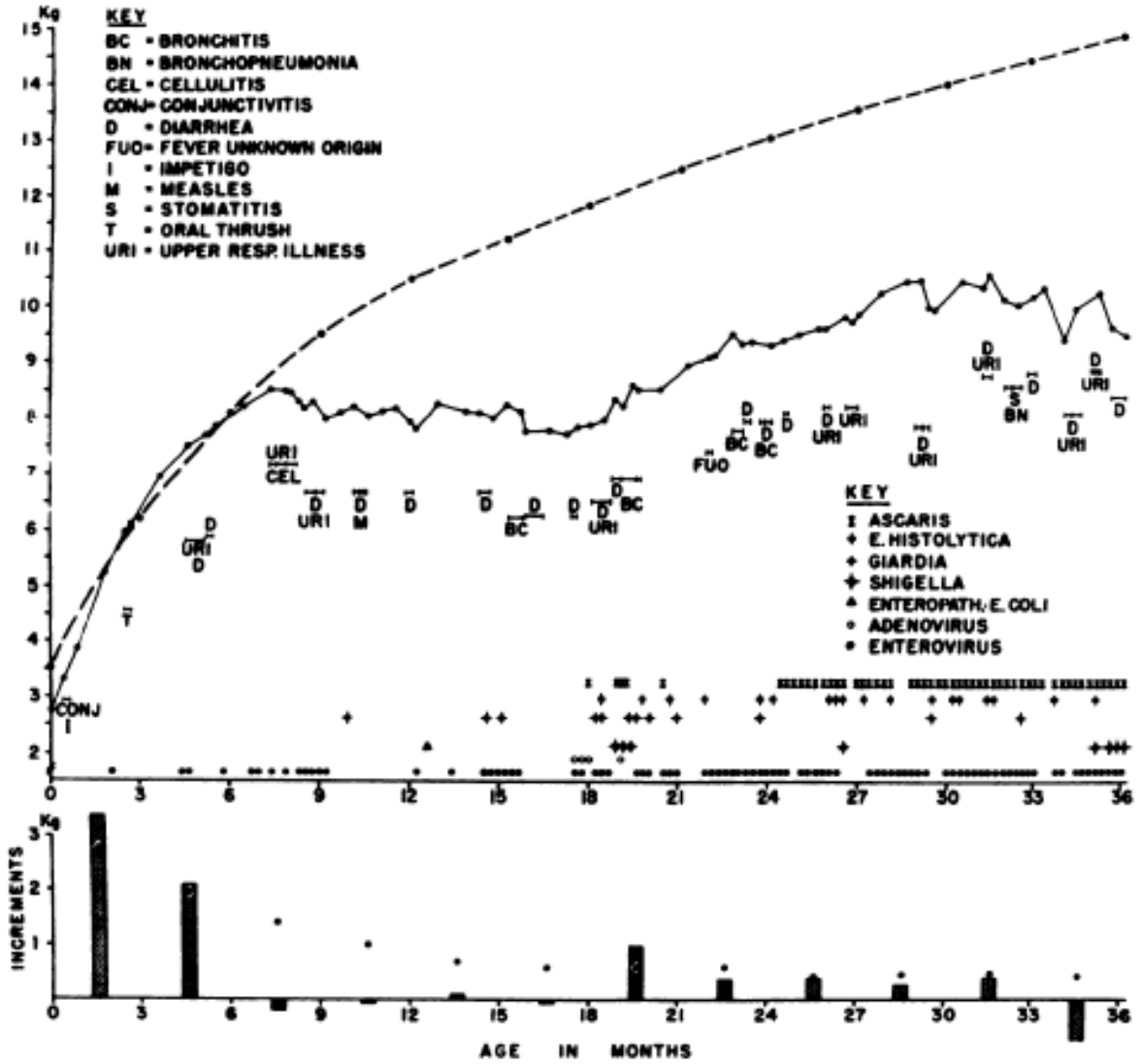
The Global Crisis You've Never Heard Of: Stunting

Chronic malnutrition affects children's bodies and brains and has received far too little attention for too long

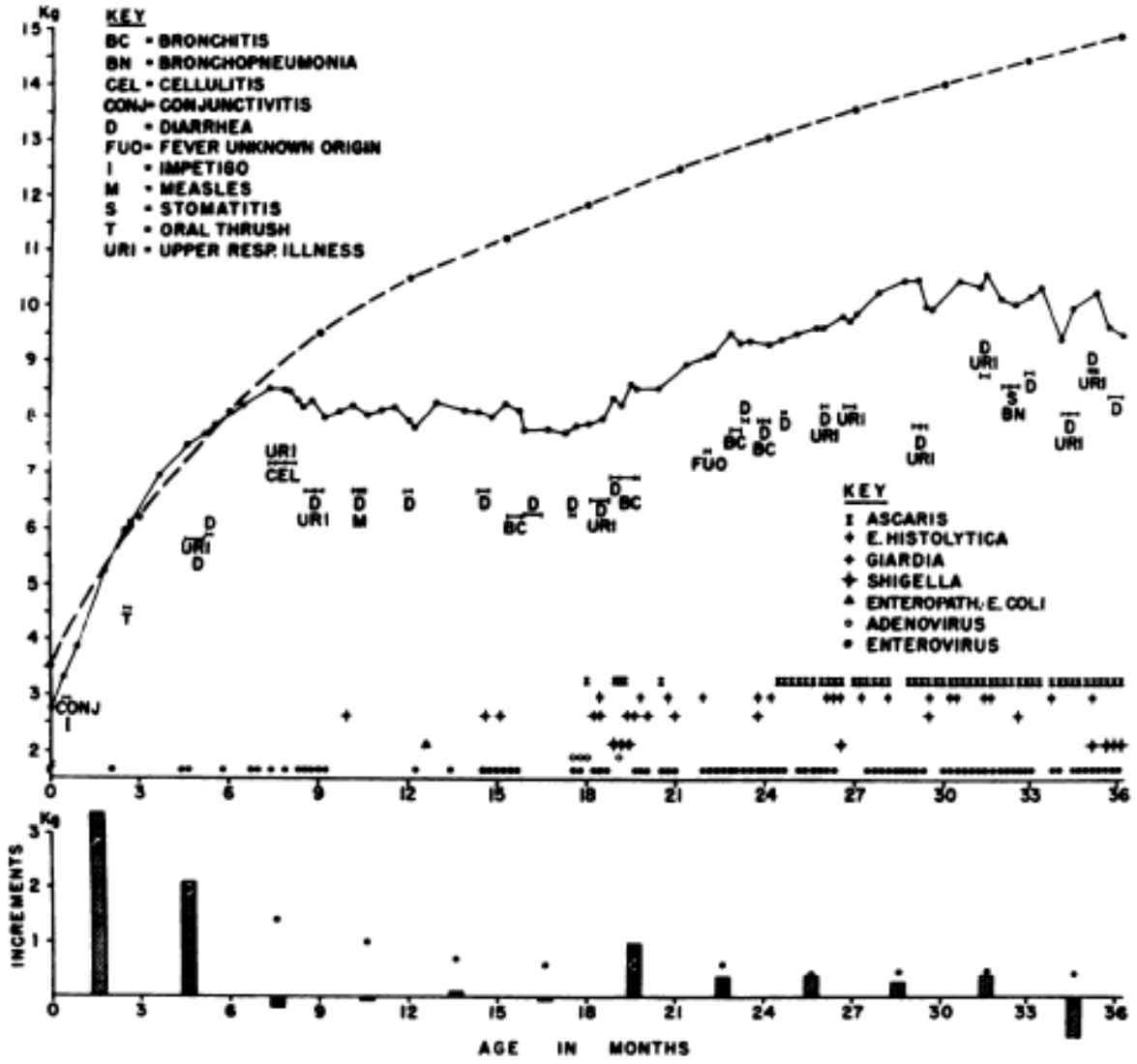
Sustainable Development Goal 2

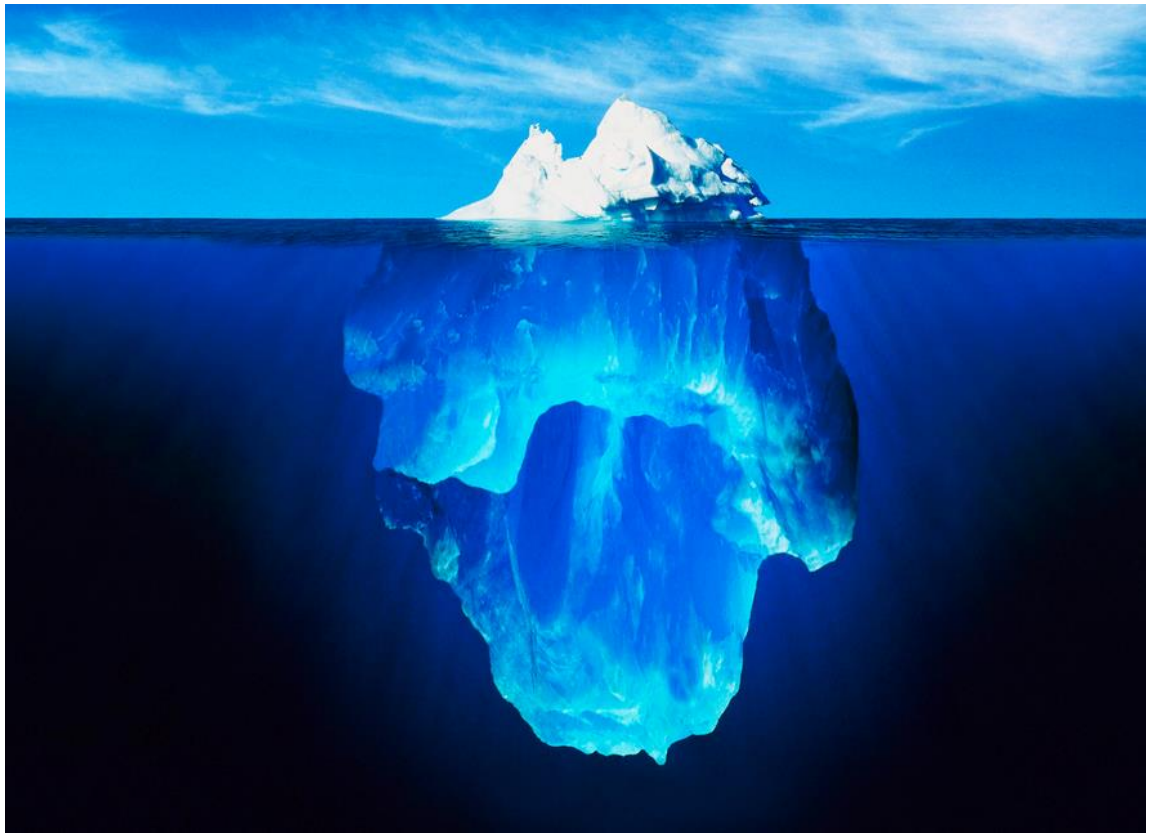
"Ending malnutrition in all its forms by 2030…"

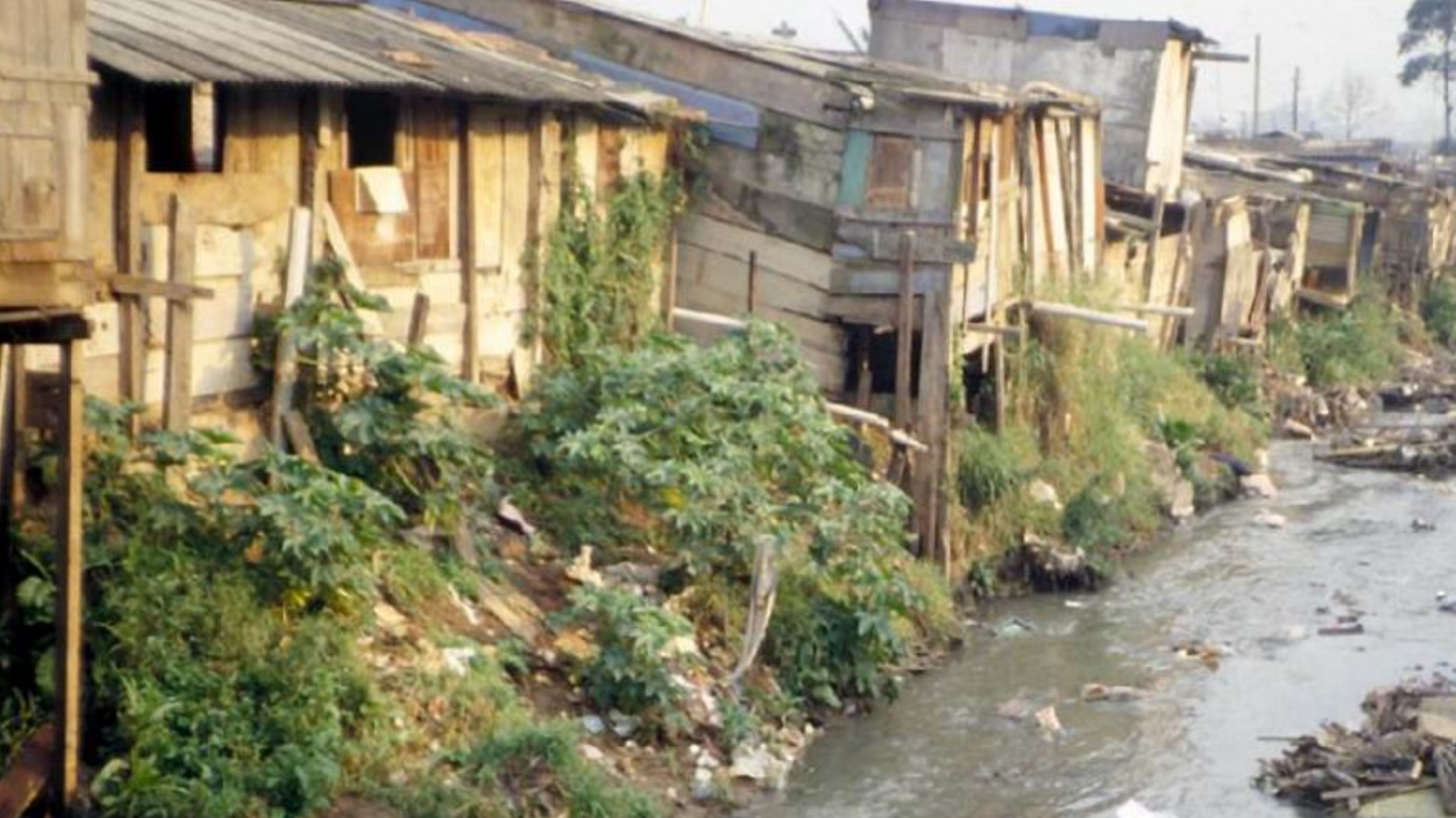
Infections contribute to malnutrition

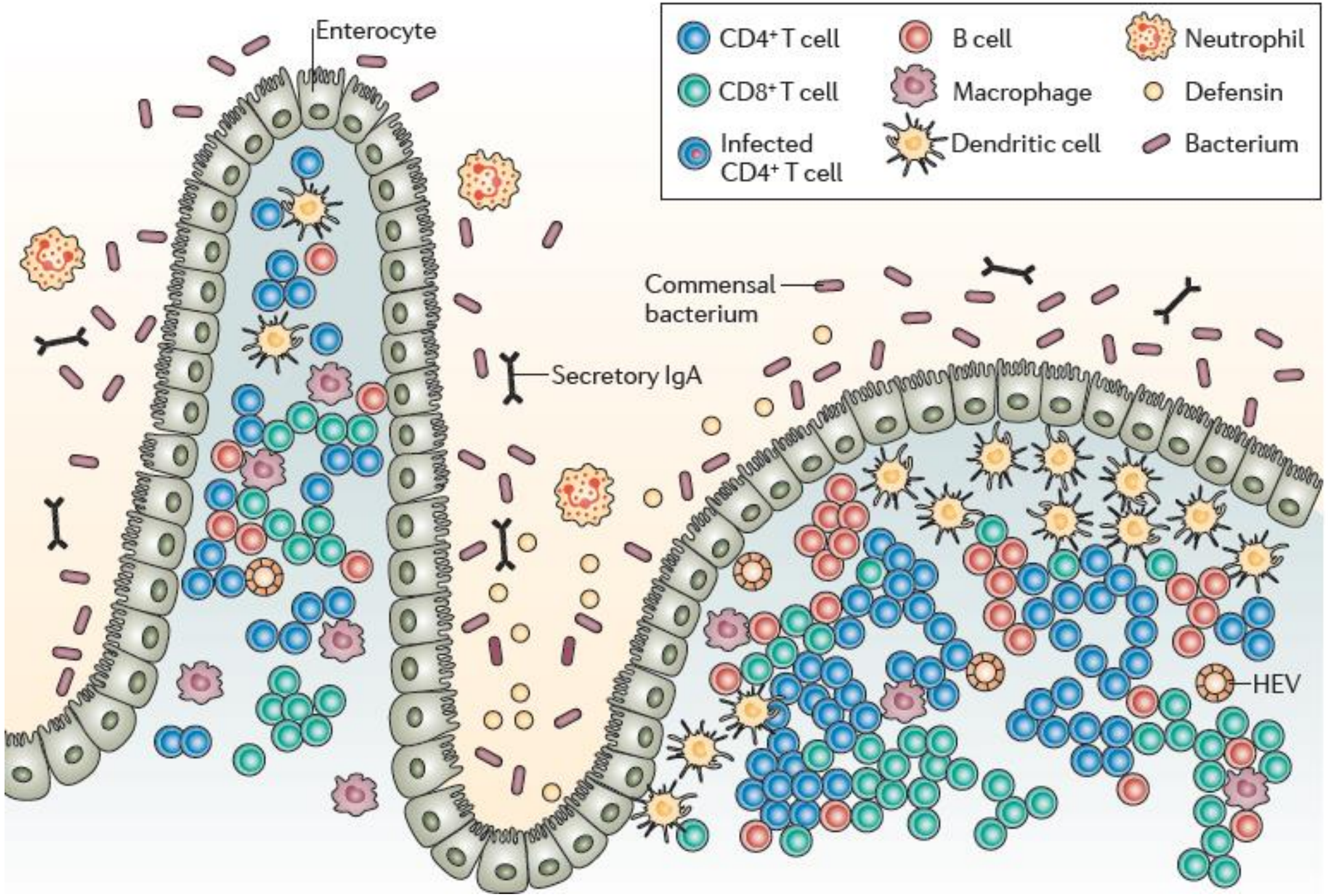


Infections contribute to malnutrition

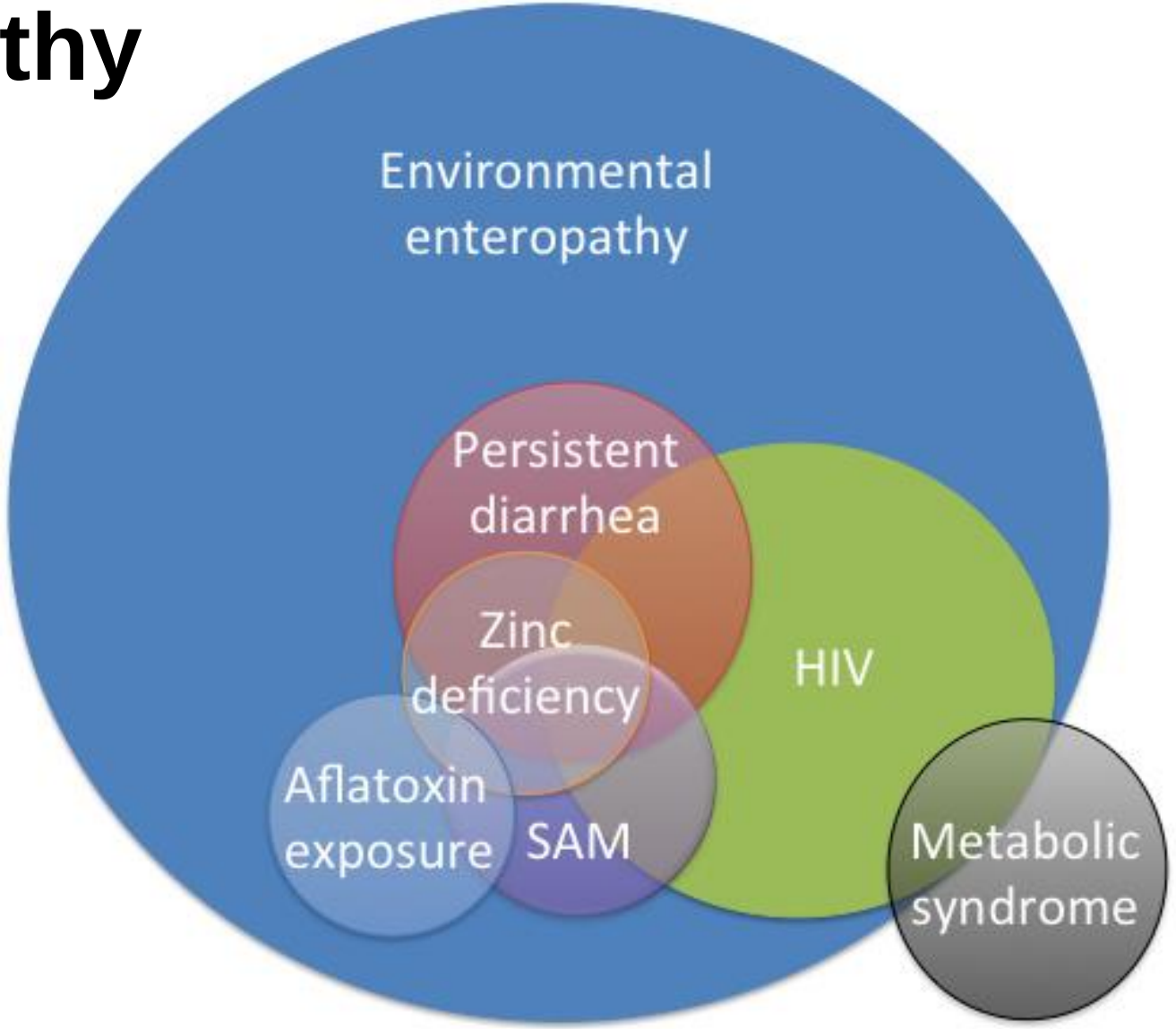







Enterocyte
CD4+ T cell
CD8+ T cell
Infected CD4+ T cell
B cell
Macrophage
Dendritic cell
Neutrophil
Defensin
Bacterium
Commensal bacterium
Secretory IgA
HEV

Overlapping and interacting causes of enteropathy



Prendergast and Kelly, *Am J Trop Med Hyg* 2012

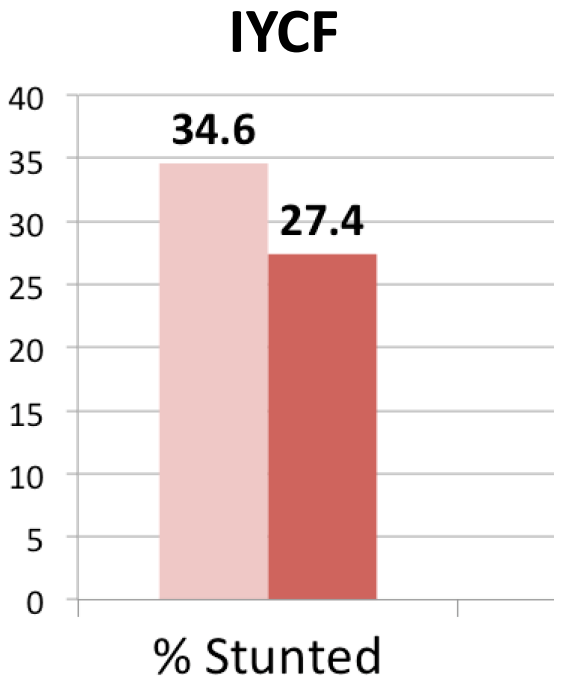
Could this be the answer to stunting?

Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial

Control Standard of Care	**IYCF** Infant and Young Child Feeding
WASH Water and Sanitation Hygiene	**WASH + IYCF**

Primary outcome: Stunting and anaemia at 18 months of age

Effects of IYCF and WASH on stunting and diarrhoea at 18 months of age

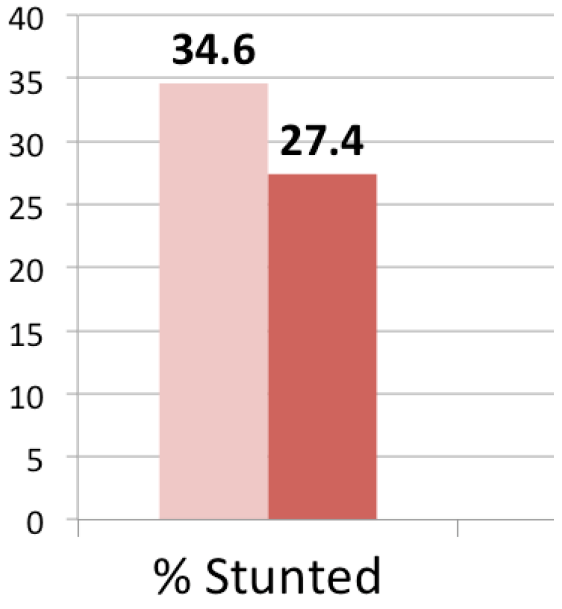


	RR (95%CI)
Unadjusted	**0.79** (0.72, 0.87)
Adjusted	**0.81** (0.74, 0.88)

Humphrey JH et al., Lancet Glob Health 2019

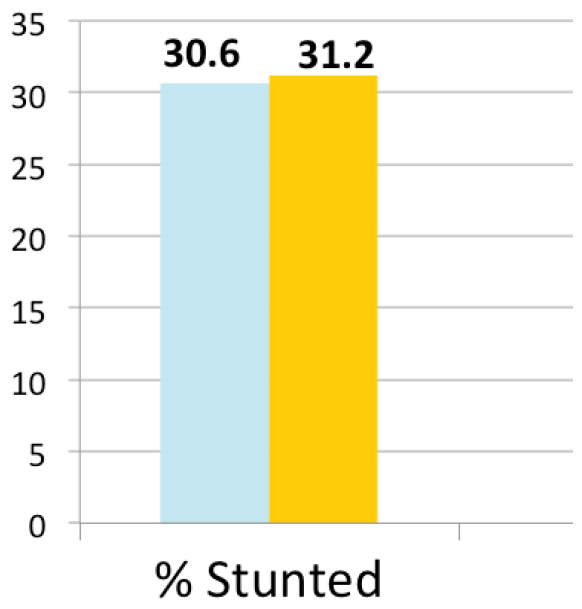
Effects of IYCF and WASH on stunting and diarrhoea at 18 months of age

IYCF



	RR (95%CI)
Unadjusted	**0.79** (0.72, 0.87)
Adjusted	**0.81** (0.74, 0.88)

WASH

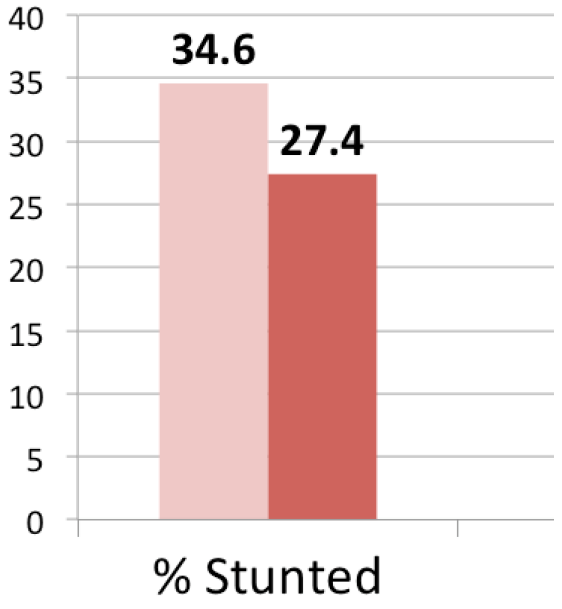


	RR (95%CI)
Unadjusted	**1.03** (0.93, 1.13)
Adjusted	**1.00** (0.91, 1.10)

Humphrey JH et al., Lancet Glob Health 2019

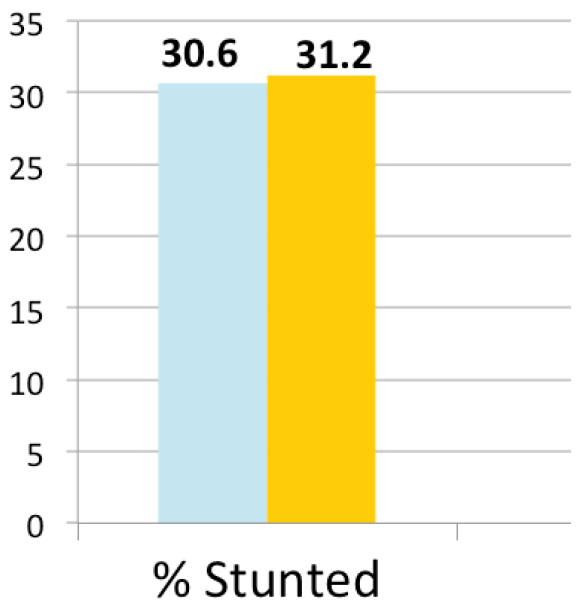
Effects of IYCF and WASH on stunting and diarrhoea at 18 months of age

IYCF



	RR (95%CI)
Unadjusted	**0.79** (0.72, 0.87)
Adjusted	**0.81** (0.74, 0.88)

WASH



	RR (95%CI)
Unadjusted	**1.03** (0.93, 1.13)
Adjusted	**1.00** (0.91, 1.10)

Diarrhoea at 18 months

Main Effects	Prevalence (%)	Difference (95%CI)	p
NO IYCF	9.9	1.0 (Ref)	
IYCF	9.4	**0.94** (0.77,1.16)	0.82
NO WASH	8.4	Ref	
WASH	10.7	**1.28** (1.04,1.57)	0.02

Humphrey JH et al., Lancet Glob Health 2019

3 trials globally of WASH and IYCF for stunting

		Bangladesh	Kenya	SHINE
Stunting	IYCF	YES	YES	YES
	WASH	NO	NO	NO
Anemia	IYCF	YES	YES	YES
	WASH	NO	NO	NO
Diarrhea	IYCF	YES	NO	NO
	WASH	YES	NO	NO

Pickering AJ et al., Lancet Glob Health 2019

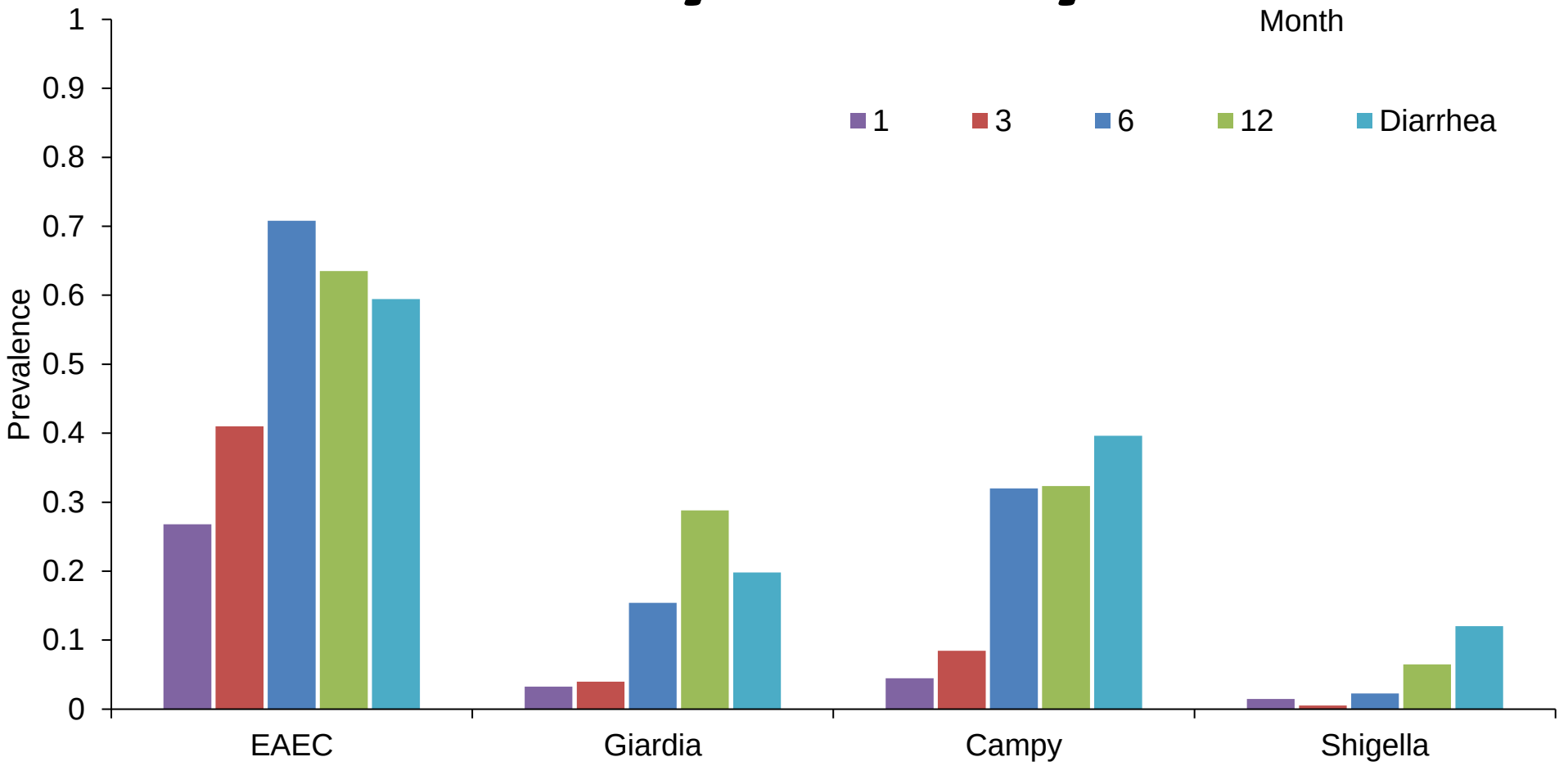
3 trials globally of WASH and IYCF for stunting

		Banglade		SHINE
Stunting	IYCF			YES
	WASH		NO	NO
Anemia	IYCF		YES	YES
			NO	NO
Diarrhea		YES	NO	NO
		YES	NO	NO

Why was there no impact of WASH on child growth?

Pickering AJ et al., Lancet Glob Health 2019

Carriage of enteric pathogens from early infancy



Rogawski-McQuade *et al.,* J Infect Dis 2019

Transformative WASH is needed

WASH needs a transformational shift to be truly beneficial for child health

Cumming *et al. BMC Medicine* (2019) 17:173
https://doi.org/10.1186/s12916-019-1410-x

BMC Medicine

OPINION Open Access

The implications of three major new trials for the effect of water, sanitation and hygiene on childhood diarrhea and stunting: a consensus statement

Oliver Cumming[1*], Benjamin F. Arnold[2], Radu Ban[3], Thomas Clasen[4], Joanna Esteves Mills[1], Matthew C. Freeman[4], Bruce Gordon[5], Raymond Guiteras[6], Guy Howard[7], Paul R. Hunter[8], Richard B. Johnston[5], Amy J. Pickering[9], Andrew J. Prendergast[10], Annette Prüss-Ustün[5], Jan Willem Rosenboom[3], Dean Spears[11], Shelly Sundberg[3], Jennyfer Wolf[6], Clair Null[12], Stephen P. Luby[13], Jean H. Humphrey[14] and John M. Colford Jr.[2]

Abstract

Background: Three large new trials of unprecedented scale and cost, which included novel factorial designs, have found no effect of basic water, sanitation and hygiene (WASH) interventions on childhood stunting, and only mixed effects on childhood diarrhea. Arriving at the inception of the United Nations' Sustainable Development Goals, and the bold new target of safely managed water, sanitation and hygiene for all by 2030, these results warrant the attention of researchers, policy-makers and practitioners.

Main body: Here we report the conclusions of an expert meeting convened by the World Health Organization and the Bill and Melinda Gates Foundation to discuss these findings, and present five key consensus messages as a basis for wider discussion and debate in the WASH and nutrition sectors. We judge these trials to have high internal validity, constituting good evidence that these specific interventions had no effect on childhood linear growth, and mixed effects on childhood diarrhea. These results suggest that, in settings such as these, more comprehensive or ambitious WASH interventions may be needed to achieve a major impact on child health.

Conclusion: These results are important because such basic interventions are often deployed in low-income rural settings with the expectation of improving child health, although this is rarely the sole justification. Our view is that these three new trials do not show that WASH in general cannot influence child linear growth, but they do demonstrate that these specific interventions had no influence in settings where stunting remains an important public health challenge. We support a call for transformative WASH, in so much as it encapsulates the guiding principle that – in any context – a comprehensive package of WASH interventions is needed that is tailored to address the local exposure landscape and enteric disease burden.

Keywords: Diarrhea, Undernutrition, Stunting, Water, Sanitation, Hygiene

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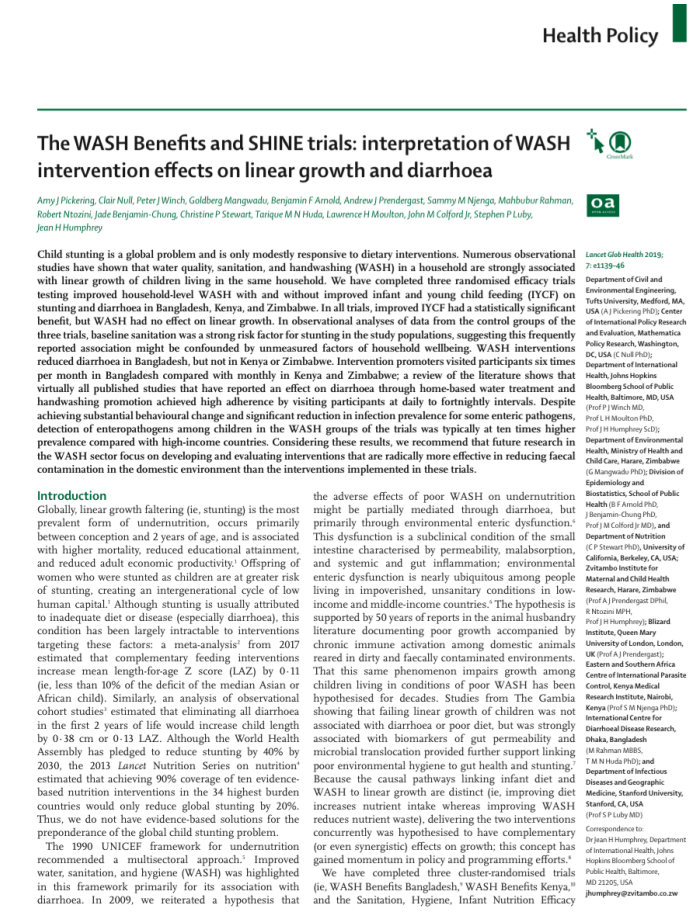
Full list of author information is available at the end of the article

Cumming O et al., BMC Medicine 2019



Health Policy

The WASH Benefits and SHINE trials: interpretation of WASH intervention effects on linear growth and diarrhoea

Amy J Pickering, Clair Null, Peter J Winch, Goldberg Mangwadu, Benjamin F Arnold, Andrew J Prendergast, Sammy M Njenga, Mahbubur Rahman, Robert Ntozini, Jade Benjamin-Chung, Christine P Stewart, Tarique M N Huda, Lawrence H Moulton, John M Colford Jr, Stephen P Luby, Jean H Humphrey

Child stunting is a global problem and is only modestly responsive to dietary interventions. Numerous observational studies have shown that water quality, sanitation, and handwashing (WASH) in a household are strongly associated with linear growth of children living in the same household. We have completed three randomised efficacy trials testing improved household-level WASH with and without improved infant and young child feeding (IYCF) on stunting and diarrhoea in Bangladesh, Kenya, and Zimbabwe. In all trials, improved IYCF had a statistically significant benefit, but WASH had no effect on linear growth. In observational analyses of data from the control groups of the three trials, baseline sanitation was a strong risk factor for stunting in the study populations, suggesting this frequently reported association might be confounded by unmeasured factors of household wellbeing. WASH interventions reduced diarrhoea in Bangladesh, but not in Kenya or Zimbabwe. Intervention promoters visited participants six times per month in Bangladesh compared with monthly in Kenya and Zimbabwe; a review of the literature shows that virtually all published studies that have reported an effect on diarrhoea through home-based water treatment and handwashing promotion achieved high adherence by visiting participants at daily to fortnightly intervals. Despite achieving substantial behavioural change and significant reduction in infection prevalence for some enteric pathogens, detection of enteropathogens among children in the WASH groups of the trials was typically at ten times higher prevalence compared with high-income countries. Considering these results, we recommend that future research in the WASH sector focus on developing and evaluating interventions that are radically more effective in reducing faecal contamination in the domestic environment than the interventions implemented in these trials.

Lancet Glob Health 2019; 7: e1139–46

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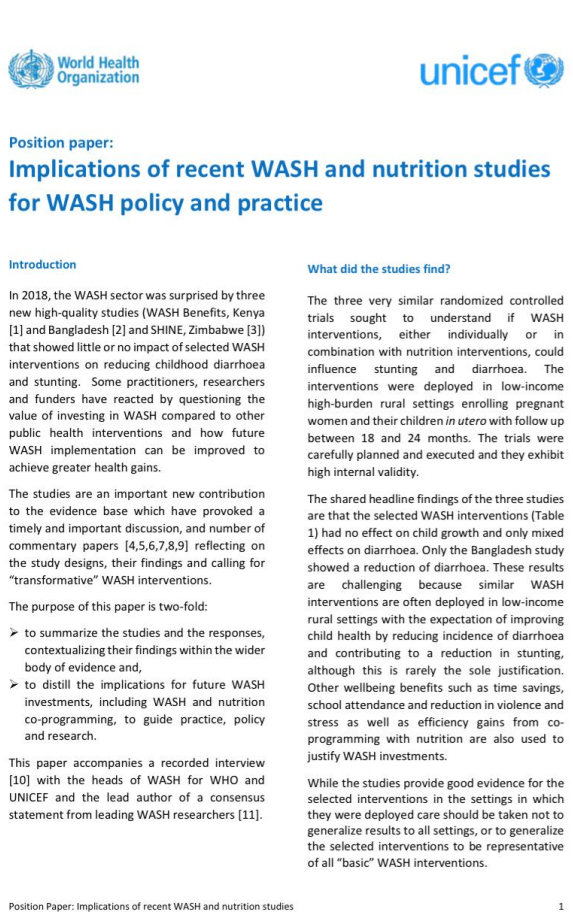
Introduction

Globally, linear growth faltering (ie, stunting) is the most prevalent form of undernutrition, occurs primarily between conception and 2 years of age, and is associated with higher mortality, reduced educational attainment, and reduced adult economic productivity.[1] Offspring of women who were stunted as children are at greater risk of stunting, creating an intergenerational cycle of low human capital.[1] Although stunting is usually attributed to inadequate diet or disease (especially diarrhoea), this condition has been largely intractable to interventions targeting these factors: a meta-analysis[2] from 2017 estimated that complementary feeding interventions increase mean length-for-age Z score (LAZ) by 0·11 (ie, less than 10% of the deficit of the median Asian or African child). Similarly, an analysis of observational cohort studies[3] estimated that eliminating all diarrhoea in the first 2 years of life would increase child length by 0·38 cm or 0·13 LAZ. Although the World Health Assembly has pledged to reduce stunting by 40% by 2030, the 2013 *Lancet* Nutrition Series on nutrition[4] estimated that achieving 90% coverage of ten evidence-based nutrition interventions in the 34 highest burden countries would only reduce global stunting by 20%. Thus, we do not have evidence-based solutions for the preponderance of the global child stunting problem.

The 1990 UNICEF framework for undernutrition recommended a multisectoral approach.[5] Improved water, sanitation, and hygiene (WASH) was highlighted in this framework primarily for its association with diarrhoea. In 2009, we reiterated a hypothesis that the adverse effects of poor WASH on undernutrition might be partially mediated through diarrhoea, but primarily through environmental enteric dysfunction.[6] This dysfunction is a subclinical condition of the small intestine characterised by permeability, malabsorption, and systemic and gut inflammation; environmental enteric dysfunction is nearly ubiquitous among people living in impoverished, unsanitary conditions in low-income and middle-income countries.[6] The hypothesis is supported by 50 years of reports in the animal husbandry literature documenting poor growth accompanied by chronic immune activation among domestic animals reared in dirty and faecally contaminated environments. That this same phenomenon impairs growth among children living in conditions of poor WASH has been hypothesised for decades. Studies from The Gambia showing that failing linear growth of children was not associated with diarrhoea or poor diet, but was strongly associated with biomarkers of gut permeability and microbial translocation provided further support linking poor environmental hygiene to gut health and stunting.[7] Because the causal pathways linking infant diet and WASH to linear growth are distinct (ie, improving diet increases nutrient intake whereas improving WASH reduces nutrient waste), delivering the two interventions concurrently was hypothesised to have complementary (or even synergistic) effects on growth; this concept has gained momentum in policy and programming efforts.[8]

We have completed three cluster-randomised trials (ie, WASH Benefits Bangladesh,[9] WASH Benefits Kenya,[10] and the Sanitation, Hygiene, Infant Nutrition Efficacy

Pickering AJ et al., Lancet Glob Health 2019



World Health Organization unicef

Position paper:

Implications of recent WASH and nutrition studies for WASH policy and practice

Introduction

In 2018, the WASH sector was surprised by three new high-quality studies (WASH Benefits, Kenya [1] and Bangladesh [2] and SHINE, Zimbabwe [3]) that showed little or no impact of selected WASH interventions on reducing childhood diarrhoea and stunting. Some practitioners, researchers and funders have reacted by questioning the value of investing in WASH compared to other public health interventions and how future WASH implementation can be improved to achieve greater health gains.

The studies are an important new contribution to the evidence base which have provoked a timely and important discussion, and number of commentary papers [4,5,6,7,8,9] reflecting on the study designs, their findings and calling for "transformative" WASH interventions.

The purpose of this paper is two-fold:

- to summarize the studies and the responses, contextualizing their findings within the wider body of evidence and,
- to distill the implications for future WASH investments, including WASH and nutrition co-programming, to guide practice, policy and research.

This paper accompanies a recorded interview [10] with the heads of WASH for WHO and UNICEF and the lead author of a consensus statement from leading WASH researchers [11].

What did the studies find?

The three very similar randomized controlled trials sought to understand if WASH interventions, either individually or in combination with nutrition interventions, could influence stunting and diarrhoea. The interventions were deployed in low-income high-burden rural settings enrolling pregnant women and their children *in utero* with follow up between 18 and 24 months. The trials were carefully planned and executed and they exhibit high internal validity.

The shared headline findings of the three studies are that the selected WASH interventions (Table 1) had no effect on child growth and only mixed effects on diarrhoea. Only the Bangladesh study showed a reduction of diarrhoea. These results are challenging because similar WASH interventions are often deployed in low-income rural settings with the expectation of improving child health by reducing incidence of diarrhoea and contributing to a reduction in stunting, although this is rarely the sole justification. Other wellbeing benefits such as time savings, school attendance and reduction in violence and stress as well as efficiency gains from co-programming with nutrition are also used to justify WASH investments.

While the studies provide good evidence for the selected interventions in the settings in which they were deployed care should be taken not to generalize results to all settings, or to generalize the selected interventions to be representative of all "basic" WASH interventions.

WHO/UNICEF Position Paper 2019 https://www.who.int/water_sanitation_health/

https://doi.org/10.1038/s43016-023-00703-2

Benefits of small-quantity lipid-based nutrient supplements for child nutrition and survival warrant moving to scale

	Relative reduction % (95% CI)
Growth[11,12]	
Stunting (LAZ <–2 SD)	12 (9, 15)
Severe stunting (LAZ <–3 SD)	17 (10, 22)
Wasting (WLZ <–2 SD) (cross-sectional prevalence)	14 (7, 20)
Severe wasting (WLZ <–3 SD) (cross-sectional prevalence)	31 (14, 45)
Underweight (WAZ <–2 SD)	13 (9, 17)
Acute malnutrition (WLZ <–2 SD or MUAC <125 mm)	14 (7, 20)
Low MUAC (MUACZ <–2 SD or MUAC <125 mm)	18 (11, 25)
Small head circumference (HCZ <–2 SD)	9 (5, 14)
Development[13]	
Low language development score	16 (8, 24)
Low motor development score	16 (8, 24)
Low social–emotional development score	19 (11, 26)
Anaemia and micronutrient status[14]	
Anaemia (Hb <110 g l^{-1})	16 (13, 19)
Moderate-severe anaemia (Hb <100 g l^{-1})	28 (24, 32)
Iron deficiency (ferritin <12 µg l^{-1})	56 (50, 61)
Iron deficiency anaemia (Hb <110 g l^{-1} and ferritin <12 µg l^{-1})	64 (56, 70)
Vitamin A deficiency (RBP <0.70 µmol l^{-1})	56 (30, 73)
Mortality[15]	27 (11, 41)

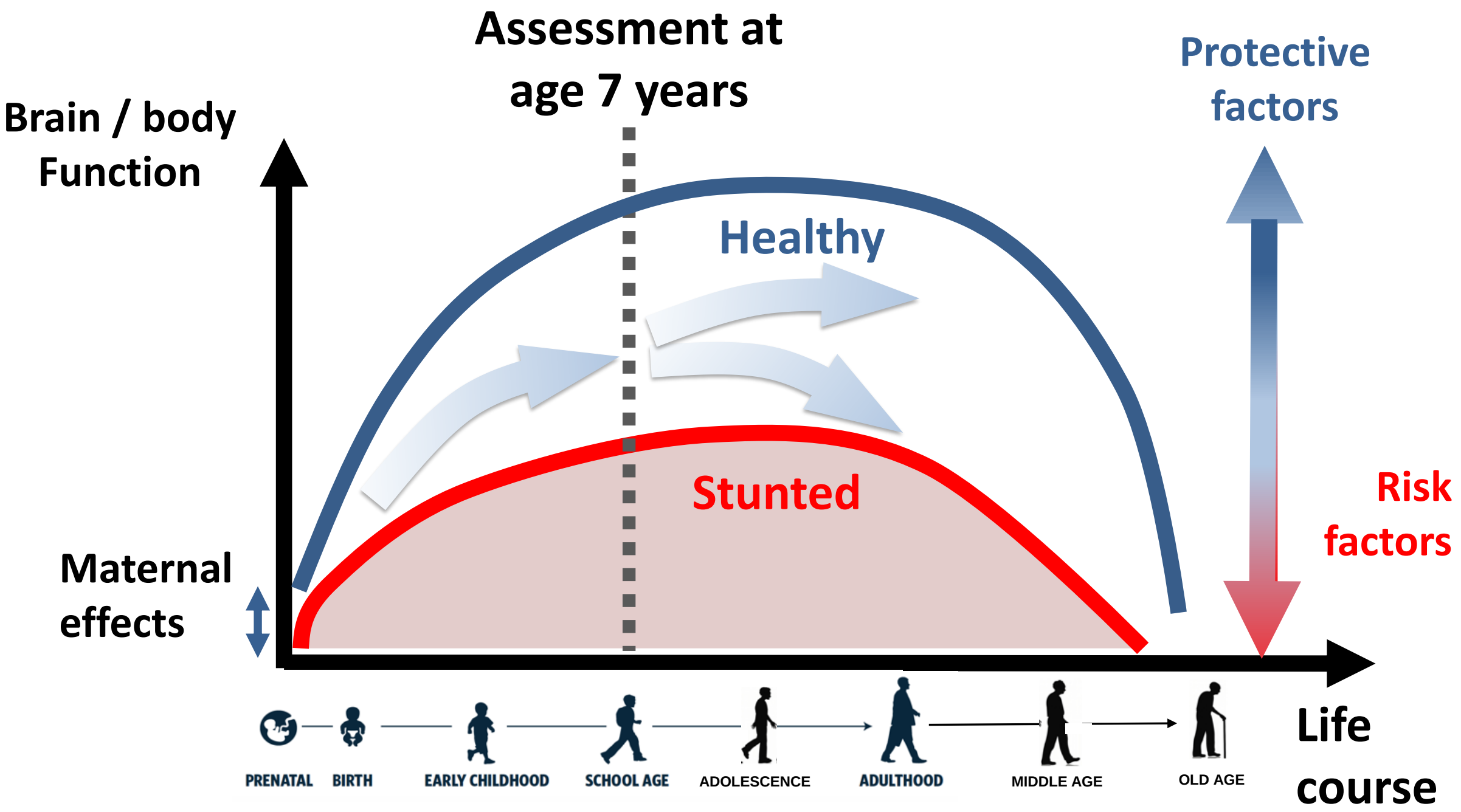
Aguayo VM *et al.*, Nature Food 2023

The importance of long-term follow-up in clinical trials

See Articles page e1086

In *The Lancet Global Health*, Rajshree Thapa and colleagues report the extended 5-year follow-up for the Community-Based Intervention for Control of Hypertension in Nepal (COBIN) cluster trial,[1] in which health workers provided lifestyle advice and blood pressure monitoring every 4 months for 12 months. The COBIN trialists deserve congratulations for an excellently designed and executed study. At 12 months systolic blood pressure was reduced across participants who were normotensive, prehypertensive, and hypertensive (for whom systolic blood pressure [intervention *vs* control] was −4·9 mm Hg [95% CI −7·8 to −2·0]).[2] tends to diminish as missing data increasing over time. COBIN had remarkably good retention, with 83% of randomly assigned participants (and 92% of those with 1-year outcomes) providing 5-year data. However, there are often differences between those participants who do and do not return for follow-up. The missing data might be informative rather than missing at random.[4] In COBIN, fewer than 300 participants (and no clusters) were lost to follow-up, with most of these not found, with 23 deaths, eight migrations, and 29 refusals. No breakdown was given by randomised group; these missing data might not have strongly influenced the

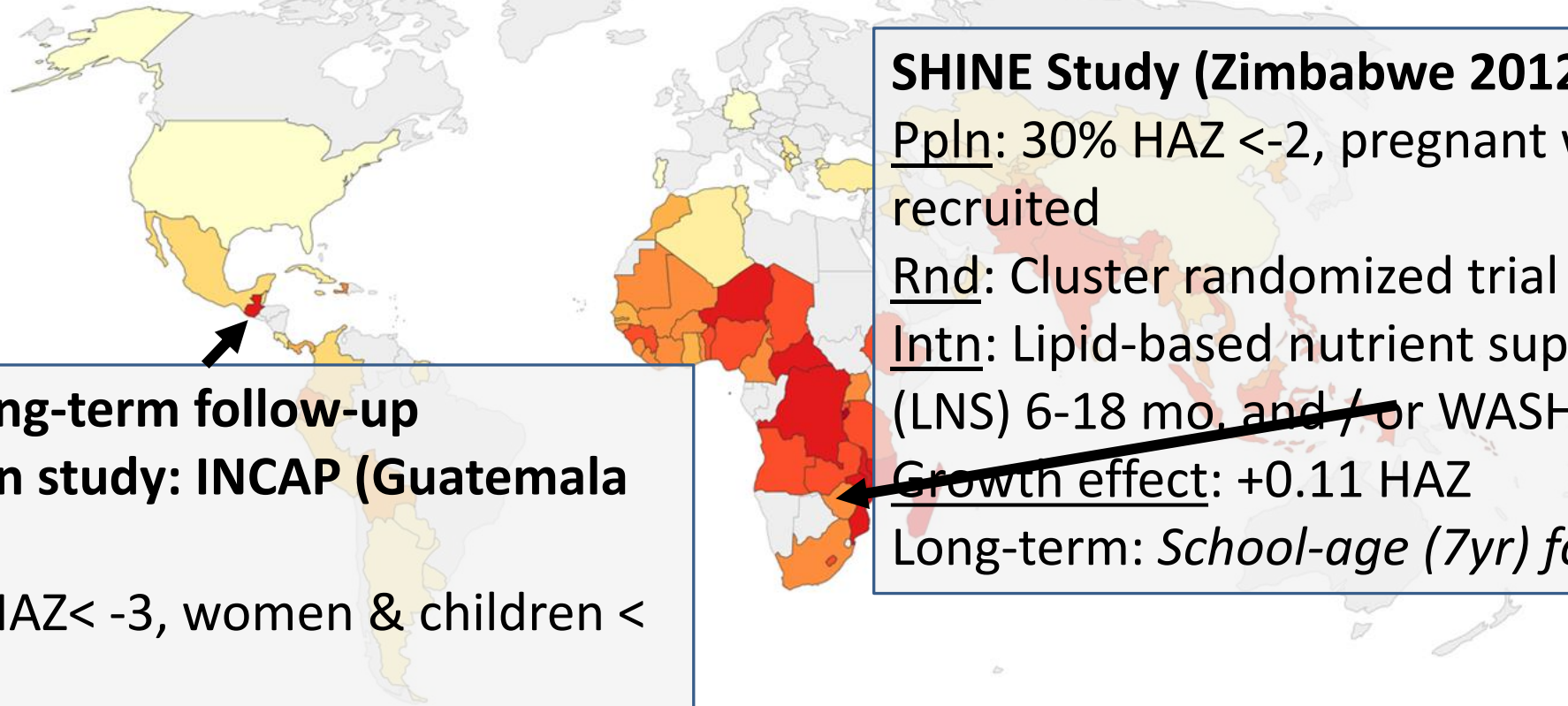
Norrie J, Lancet Glob Health July 202


Assessment at age 7 years
Brain / body Function
Protective factors
Healthy
Stunted
Risk factors
Maternal effects
PRENATAL
BIRTH
EARLY CHILDHOOD
SCHOOL AGE
ADOLESCENCE
ADULTHOOD
MIDDLE AGE
OLD AGE
Life course

Why long-term SHINE follow-up?

→ Modern conditions

→ How well do modern interventions (LNS) work by school-age



SHINE Study (Zimbabwe 2012-23)

Ppln: 30% HAZ <-2, pregnant women recruited

Rnd: Cluster randomized trial

Intn: Lipid-based nutrient supplement (LNS) 6-18 mo, and / or WASH

Growth effect: +0.11 HAZ

Long-term: *School-age (7yr) follow-up*

Previous long-term follow-up intervention study: INCAP (Guatemala 1969-77)

Ppln: 50% HAZ< -3, women & children < 7 yrs

Rnd: Village level randomisation

Intn: Protein vs low-energy drink

Growth effect: +0.62 HAZ

Long-term: Higher IQ, work capacity

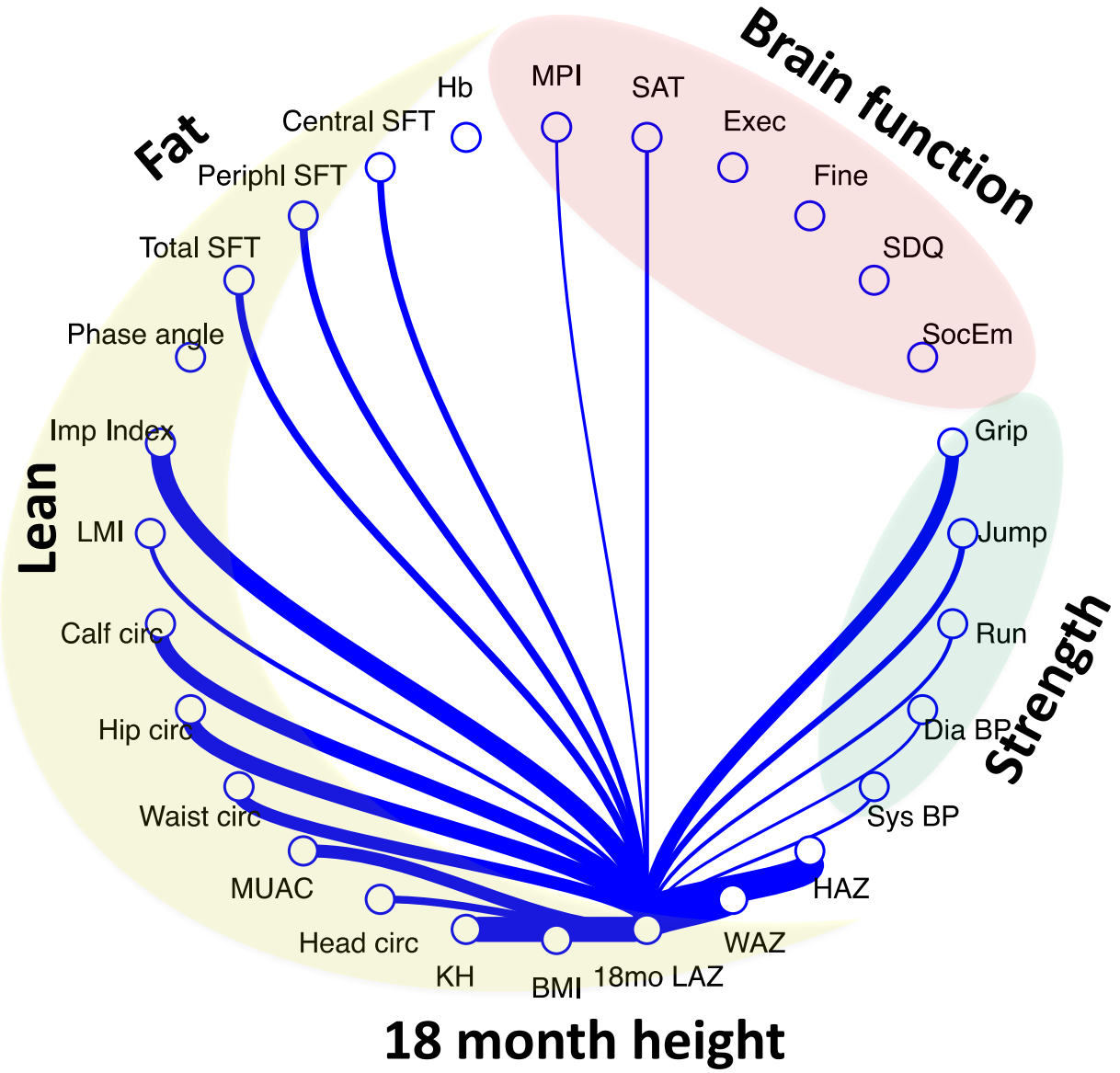

ZVITAMBO
HELPING CHILDREN
SURVIVE AND THRIVE
PRIMARY HEALTH CARE
A HEALTHY NATION
MINISTRY OF HEALTH AND CHILD CARE
ZIMBABWE

1. Early life growth influences child function at age 7 years

Growth in 1st 18 months is strongly associated with 7yr school-age growth, brain function & strength

- **18 mo height**: 7yr cognition, broad jump, body composition
- **18 mo head circumference**: 7yr all child measures of cognition, grip strength, body composition
- **Birth weight:** 7yr growth, Lean mass, peripheral fat, grip strength
- **3 month MUAC**: 7yr growth, Lean & fat mass, grip strength, executive function

The first 18 months' growth associates with 7-year body composition, brain function & strength



2. The current environment of the child influences their function at age 7 years

- **Schooling exposure duration**: cognition, physical function, growth
- **Socioeconomic status**: cognition & physical function
- **Food security:** cognition & physical function
- **Caregiver education**: cognition, handgrip strength, growth
- **Caregiver depression**: cognition & physical function
- **Child-parent relationship**: cognition

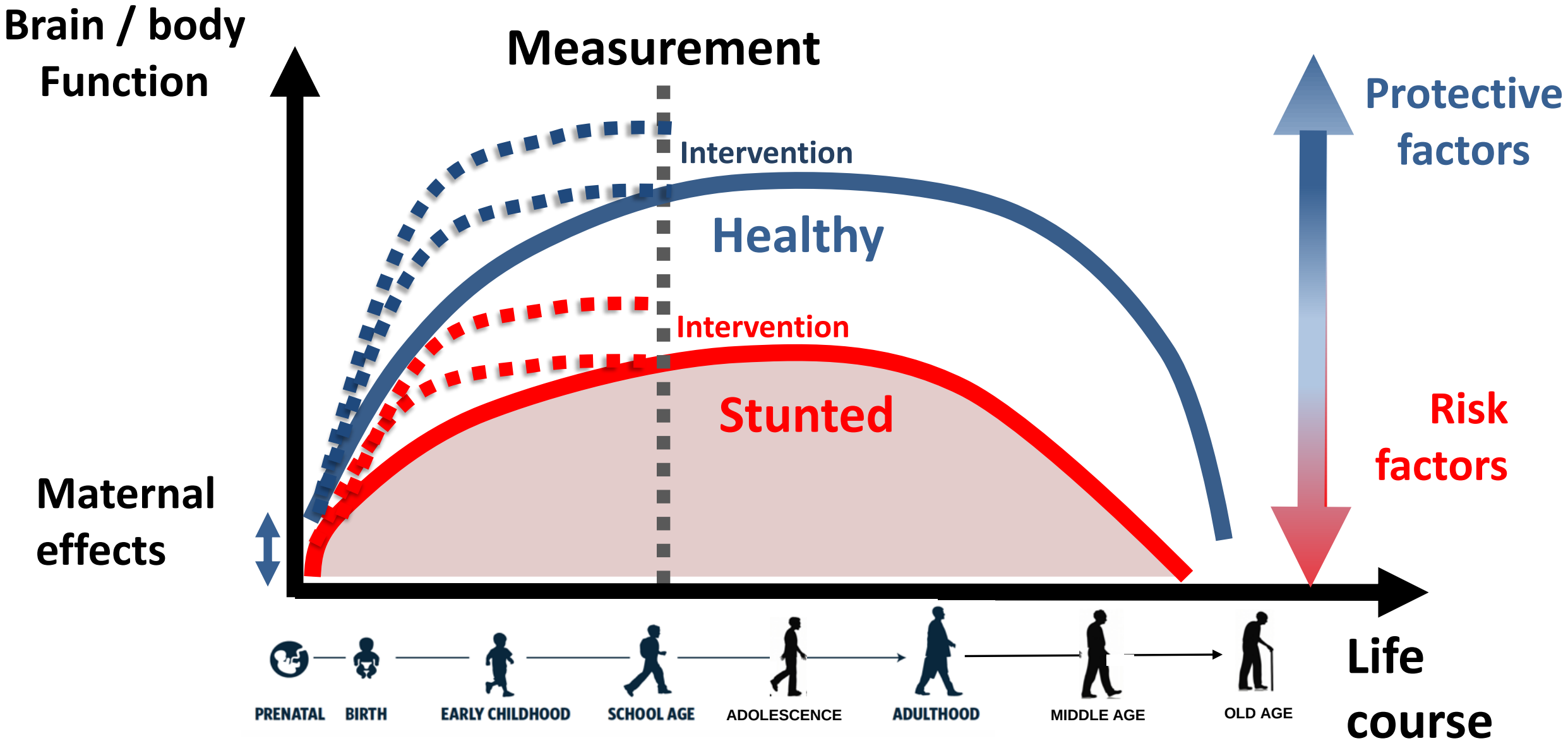
3. Children who are HIV-exposed have reduced cognition, fitness & growth at age 7 years

- Children born to mothers with HIV (children HIV-exposed uninfected, HEU) had **reduced** cognitive function:
  - ↓ Total cognition: "IQ"
  - ↓ Literacy & numeracy
  - ↓ Executive function: *self-control, memory & reasoning*
- Physical function
  - ↓ Cardiovascular fitness
- Growth
  - ↓ Head circumference

4. The SHINE interventions had no long-term effect on growth or cognition

- The early-life growth benefit of IYCF seen at 18 months was **not** significant by 7 years
- No effect of IYCF on cognition at 7 years
- WASH interventions had no consistent effect
- But…
- **IYCF intervention increased grip strength**
  - Small but significant effect: 0.1 standard deviations (2% increase)
- HIV-exposed children showed **no long-term benefit of interventions**

SHINE interventions had minimal long-term impact



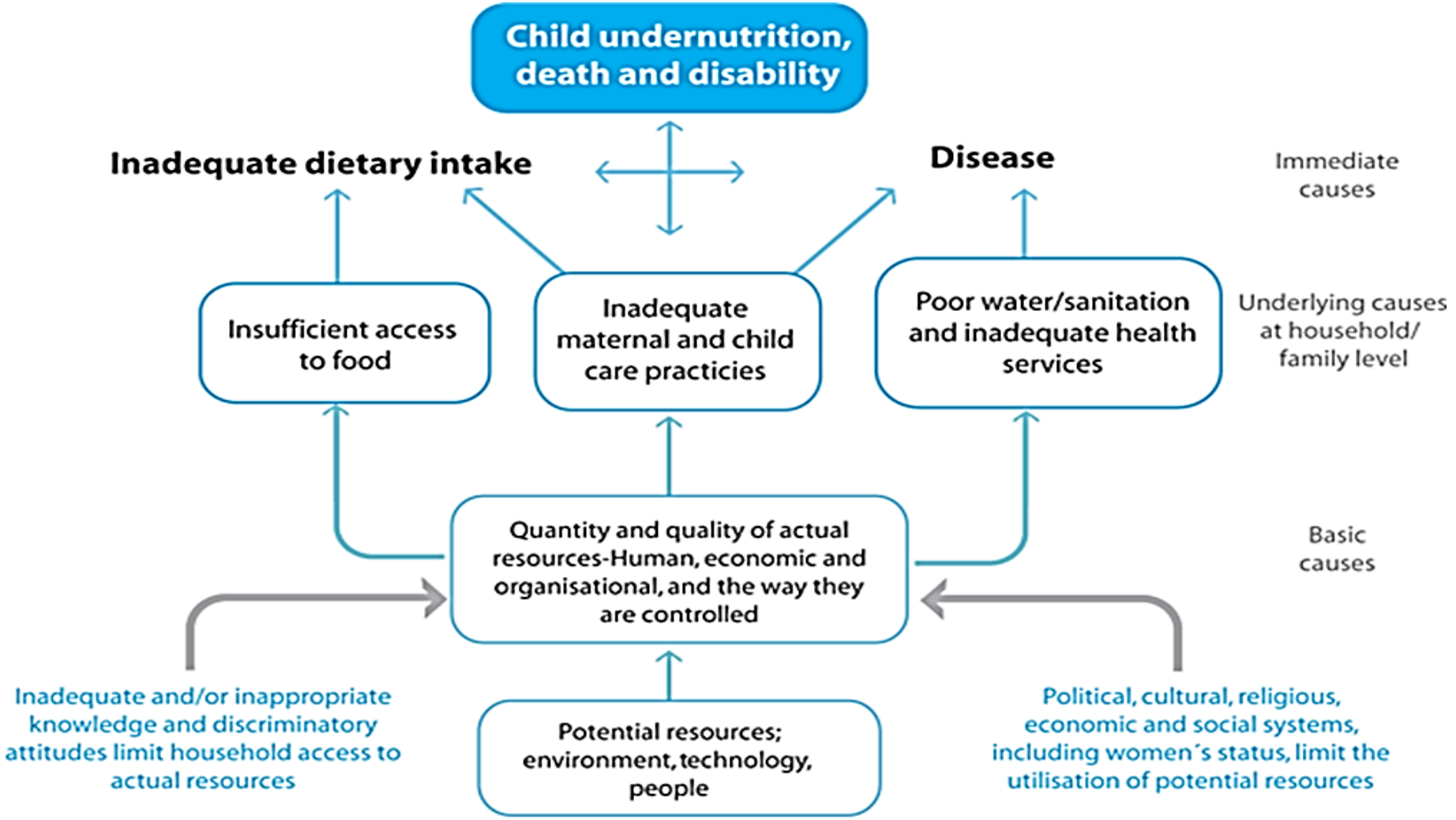
Summary and implications

- Early-life growth is associated with school-age function
- The child's environment shapes their growth and development
- Children born to mothers with HIV have reduced school-age function
- The SHINE IYCF intervention from 6-18mo of age had short-term benefits but no evidence of sustained effects
  - Small effect on grip strength may indicate better muscle quality
- → We need to find **new ways** to promote growth and development

How else can we tackle stunting?

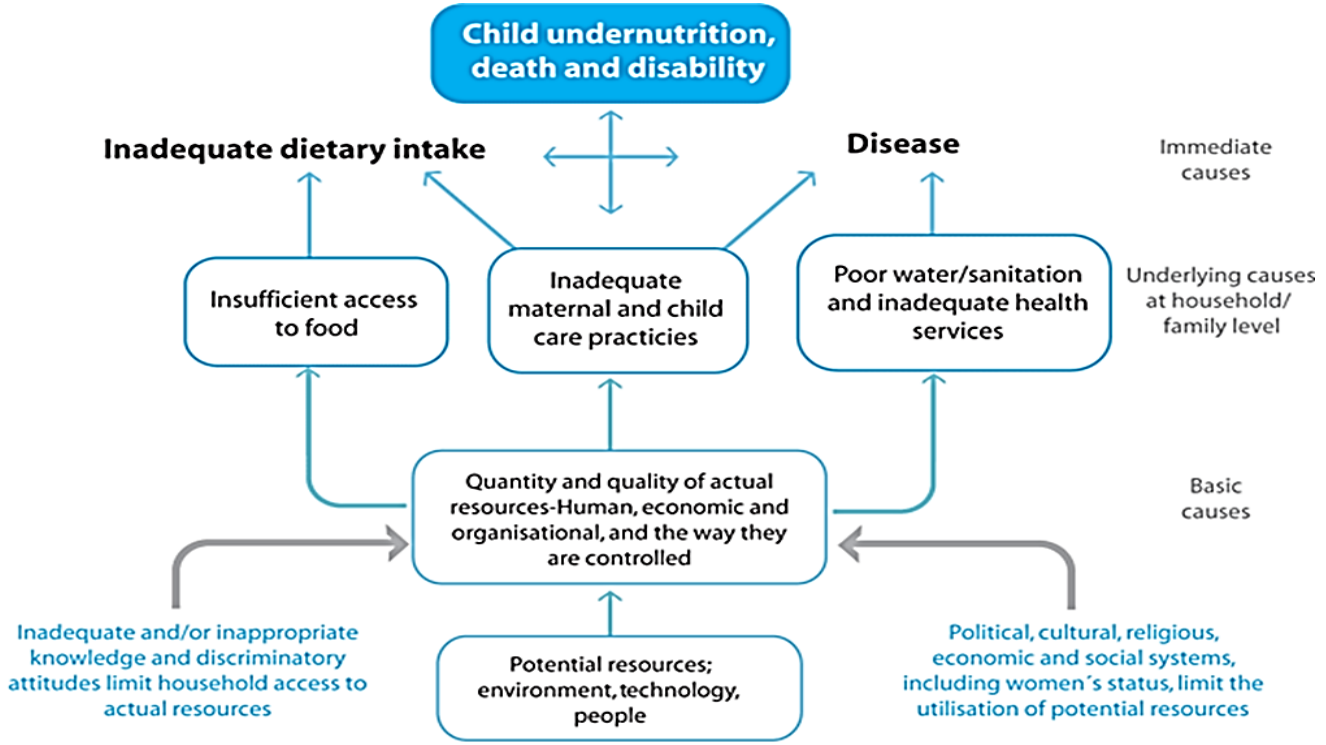
- Deeper
- Broader
- Earlier
- Longer

Undernutrition is multifactorial



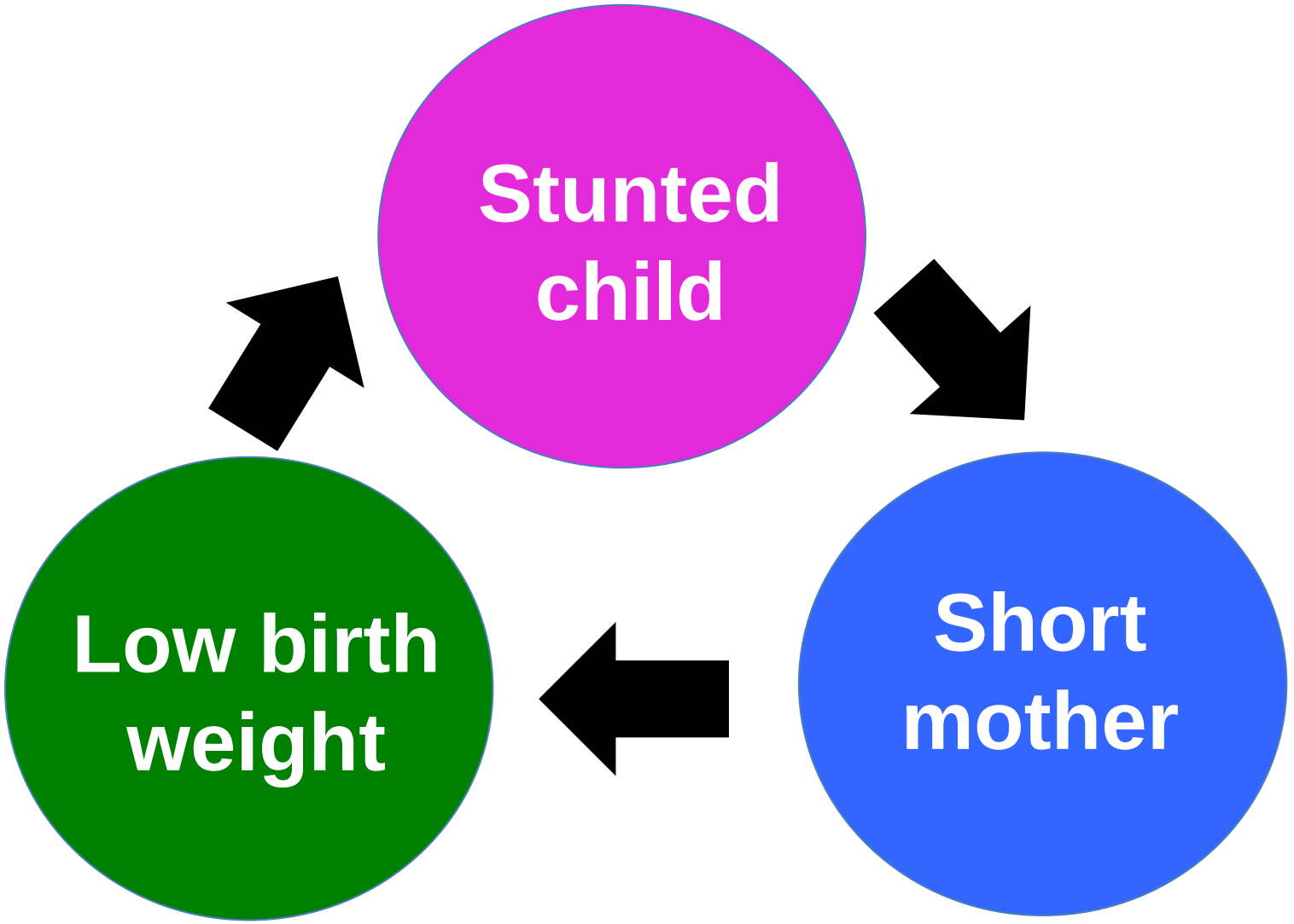
Source: UNICEF, Strategy for Improved Nutrition of Children and Women in Developing Countries, UNICEF, New York, 1990.

Nurturing care to promote child development



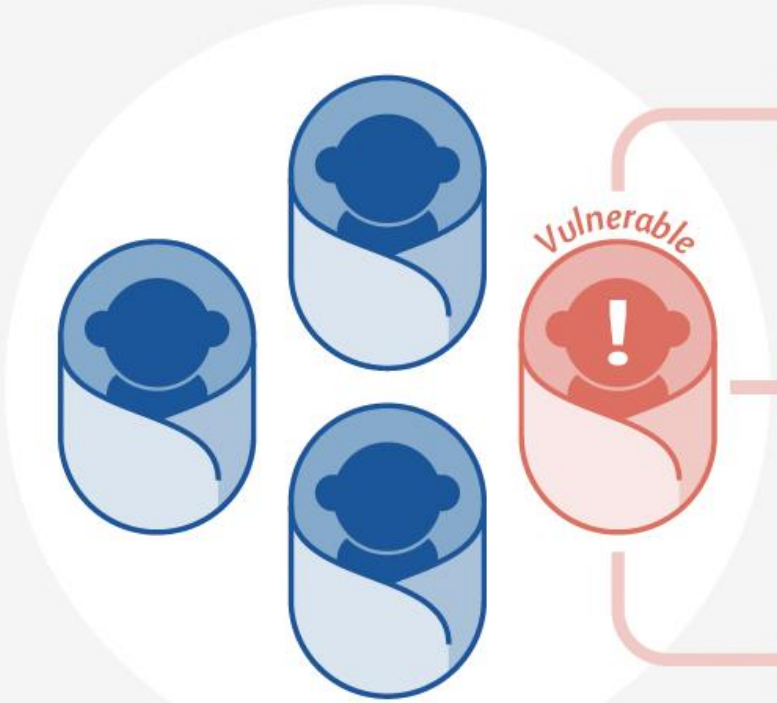
Source: UNICEF, Strategy for Improved Nutrition of Children and Women in Developing Countries, UNICEF, New York, 1990.

Intervening earlier to prevent stunting



Small Vulnerable Newborns—a new definition for improving global newborn and maternal health

In 2020, a quarter (an estimated 35·3 million) of babies born alive were born with one or more of three vulnerabilities:



Born too soon (preterm)
Born before 37 completed weeks of gestation

or

Born too small (SGA[1])
Birthweight below 10th centile

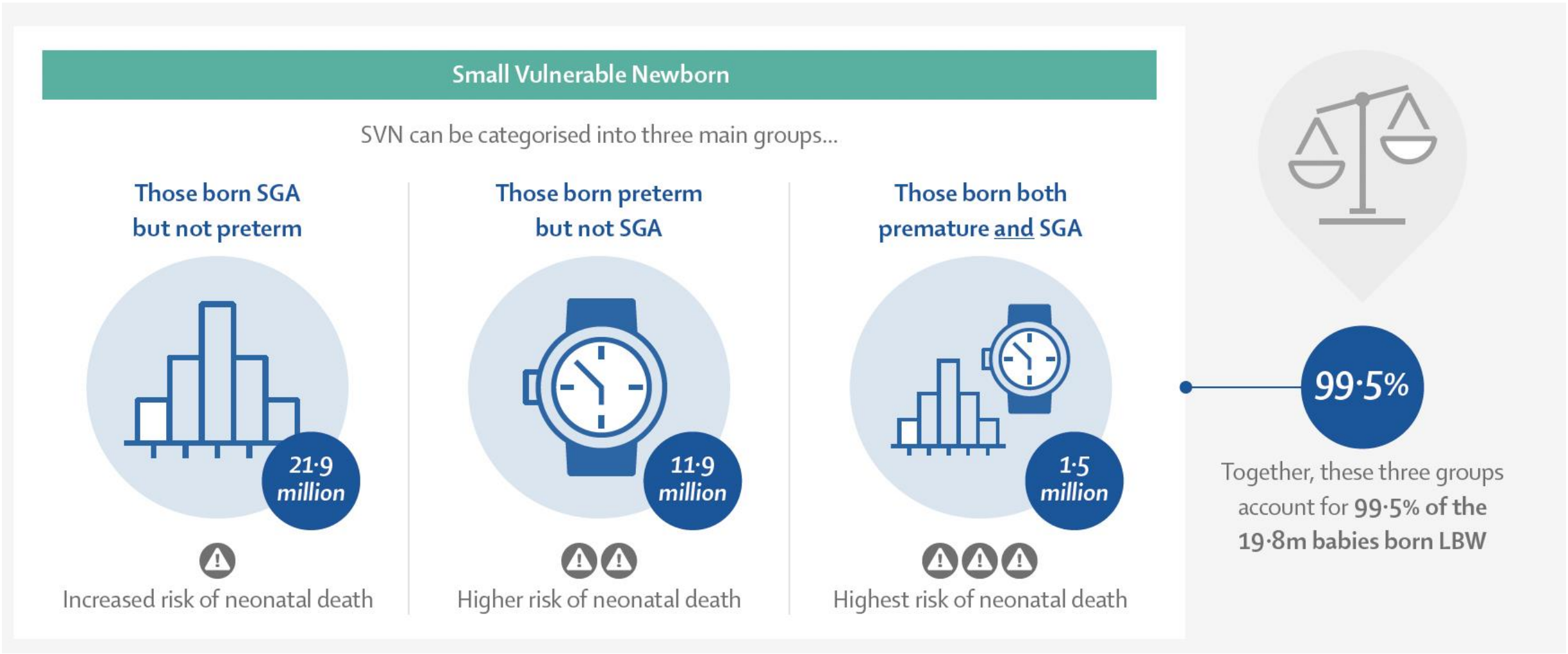
or

Low birthweight (LBW)
Less than 2500 g

These vulnerabilities account for **more than half of all neonatal deaths.**

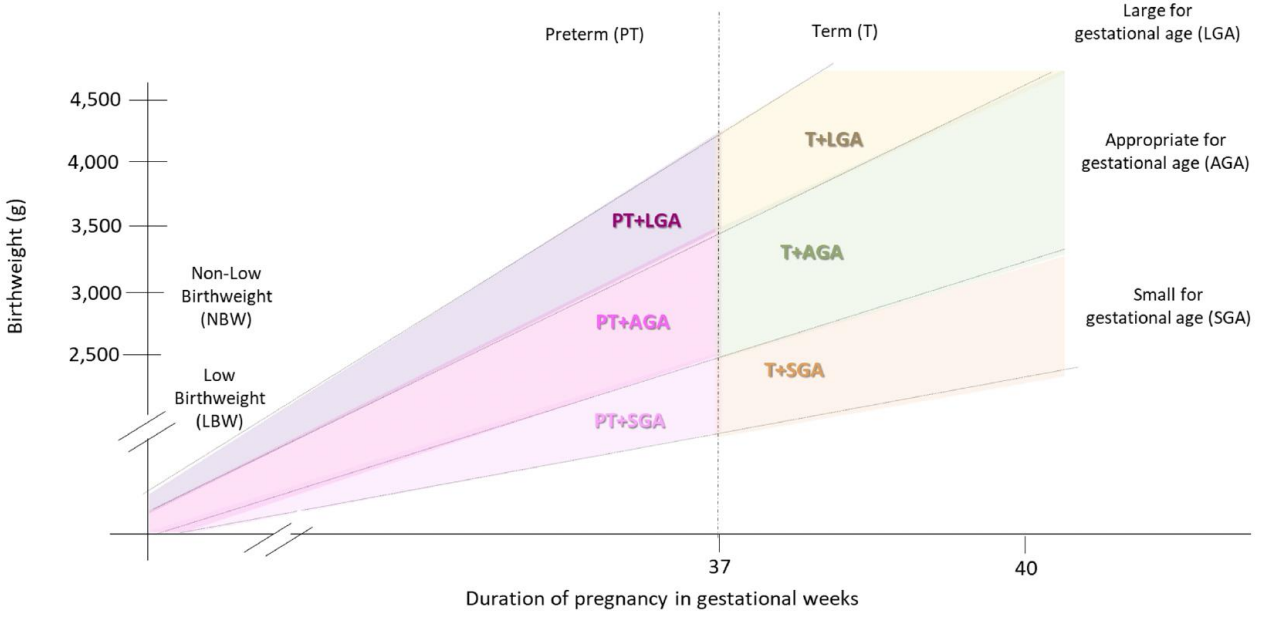
Babies born with these vulnerabilities are at **increased risk for a multitude of adverse health conditions throughout their lifespan.**

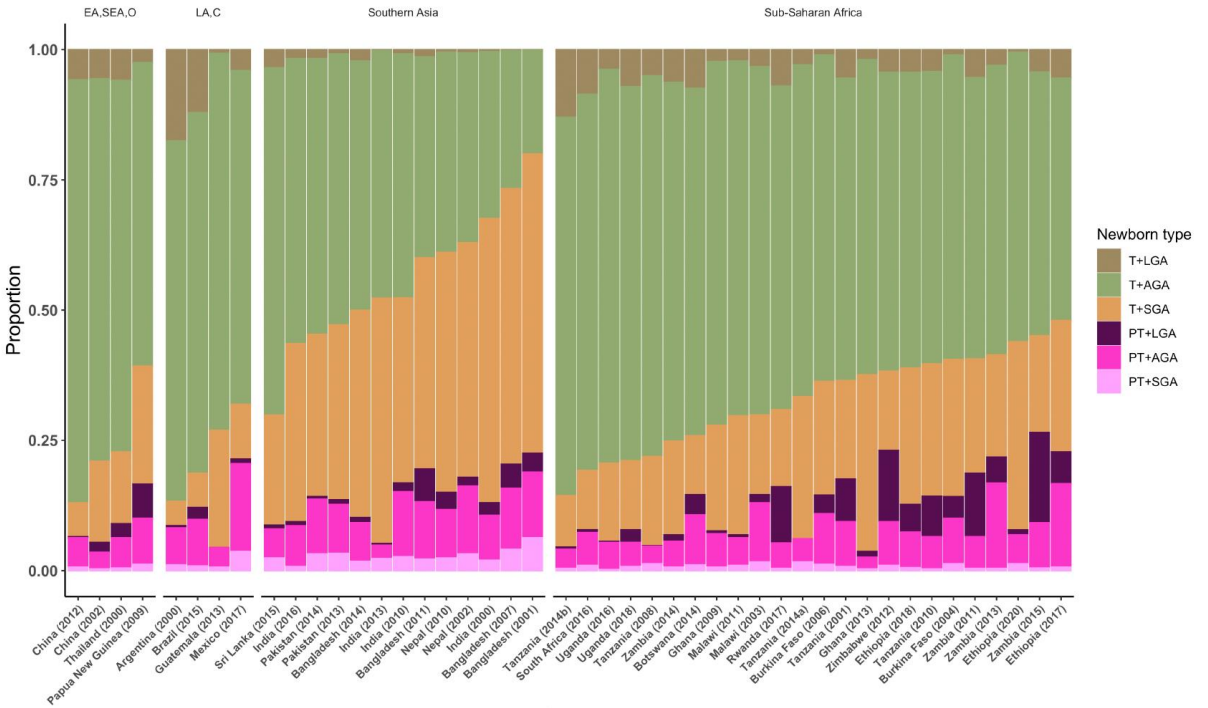
Lancet Small Vulnerable Newborns Series 2023



Lancet Small Vulnerable Newborns Series 2023

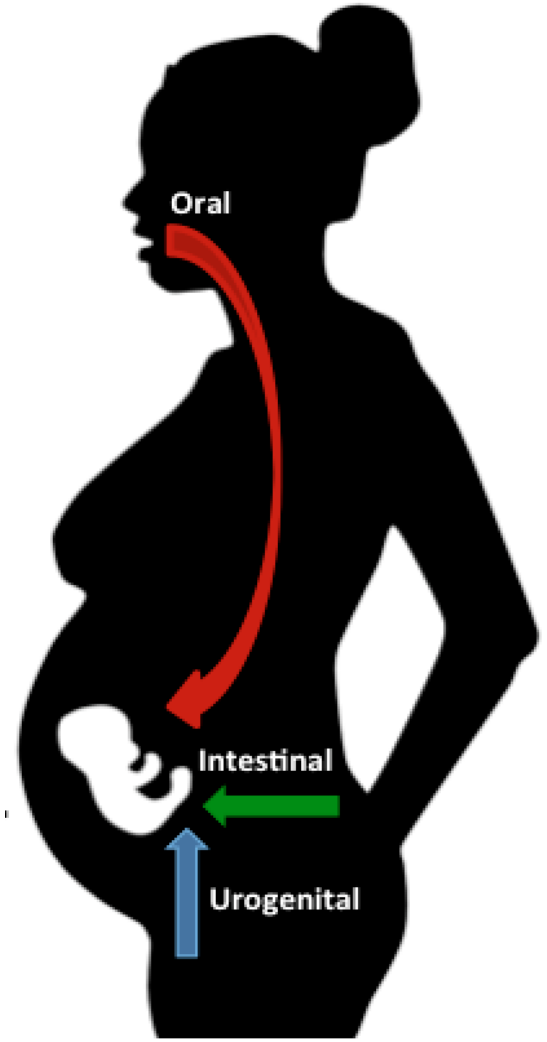
Newborn phenotypes in 541,285 live births in 23 countries

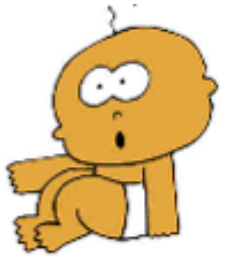


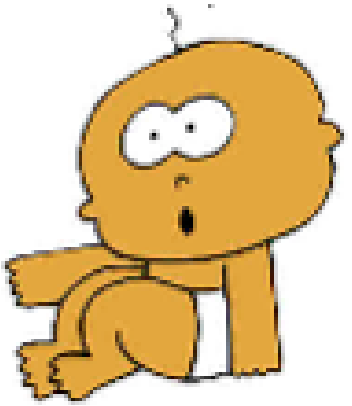


Erchick DJ et al., BJOG 2023

Infection and inflammation in pregnancy may drive adverse birth outcomes







Proinflammatory cytokines

Maternal plasma
Placenta
Amniotic fluid
Cord blood

Tjoa *et al*, J Reprod Immunol 2003
Bartha *et al*, Acta Obs Gynae 2003
Heyborne *et al*, AJOG 2003
Hahn-Zoric *et al*, Ped Res 2002
Neta *et al*, Am J Epidemiol
Trevisanuto *et al*, Neonatology 2007

Periapical infections associated with preterm birth and IUGR in Malawi

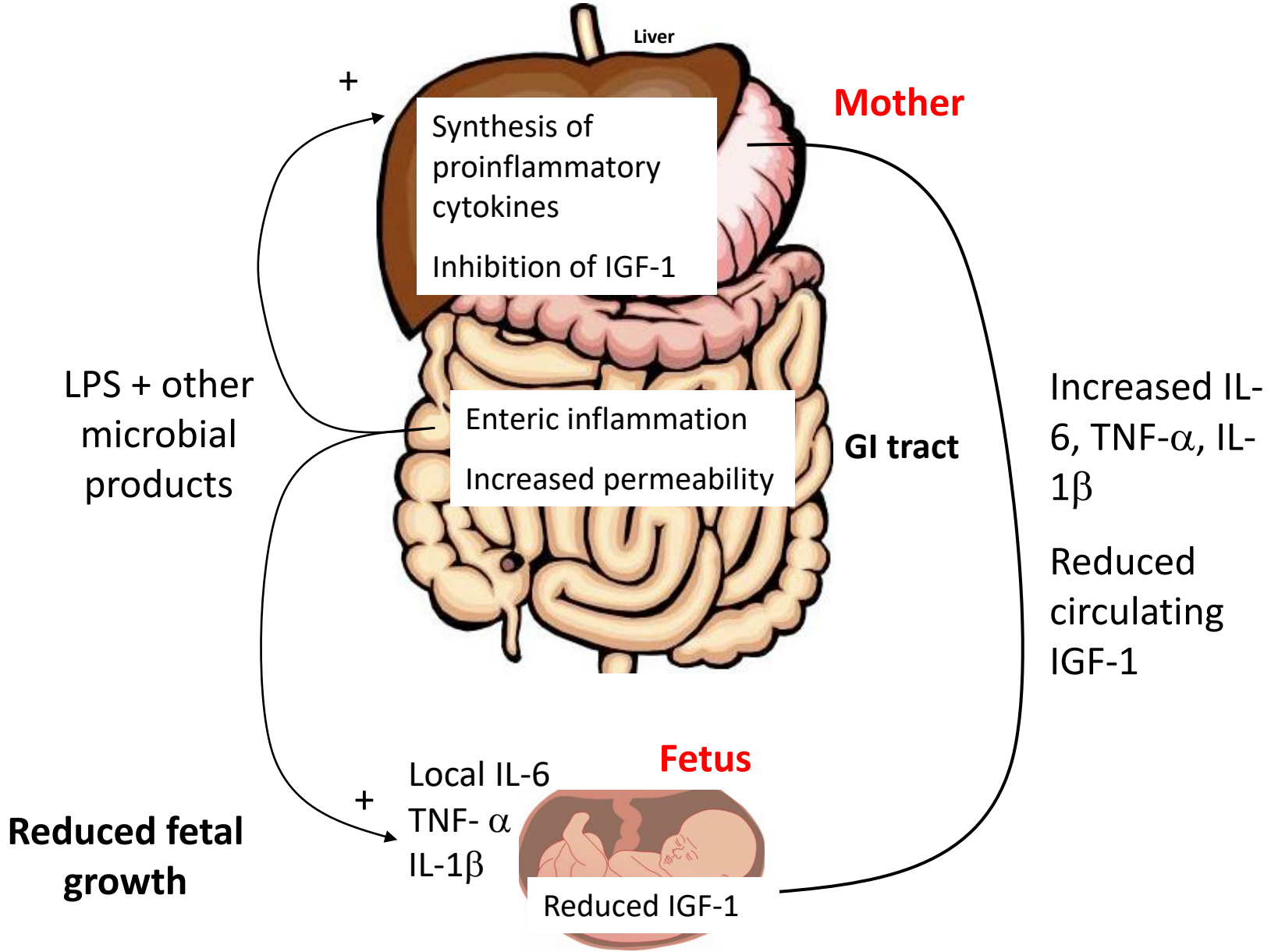
Periapical infections in 23.5% women
Preterm birth 10.0% versus 7.3% (adjusted diff 3.5%, 95%CI 1.1, 8.1)
Stunting 20.9% versus 14.2% (adjusted diff 9.0%, 95%CI 2.7, 15.2)
PAF due to periapical infection **9.7%** preterm birth, **12.8%** stunting)

Harjunmaa U, Trop Med Int Health 2015

Oral health assessments in rural Zimbabwe

- Basic Periodontal Examination
- Full mouth plaque score
- Gingival bleeding score

Could maternal EED reduce fetal growth?



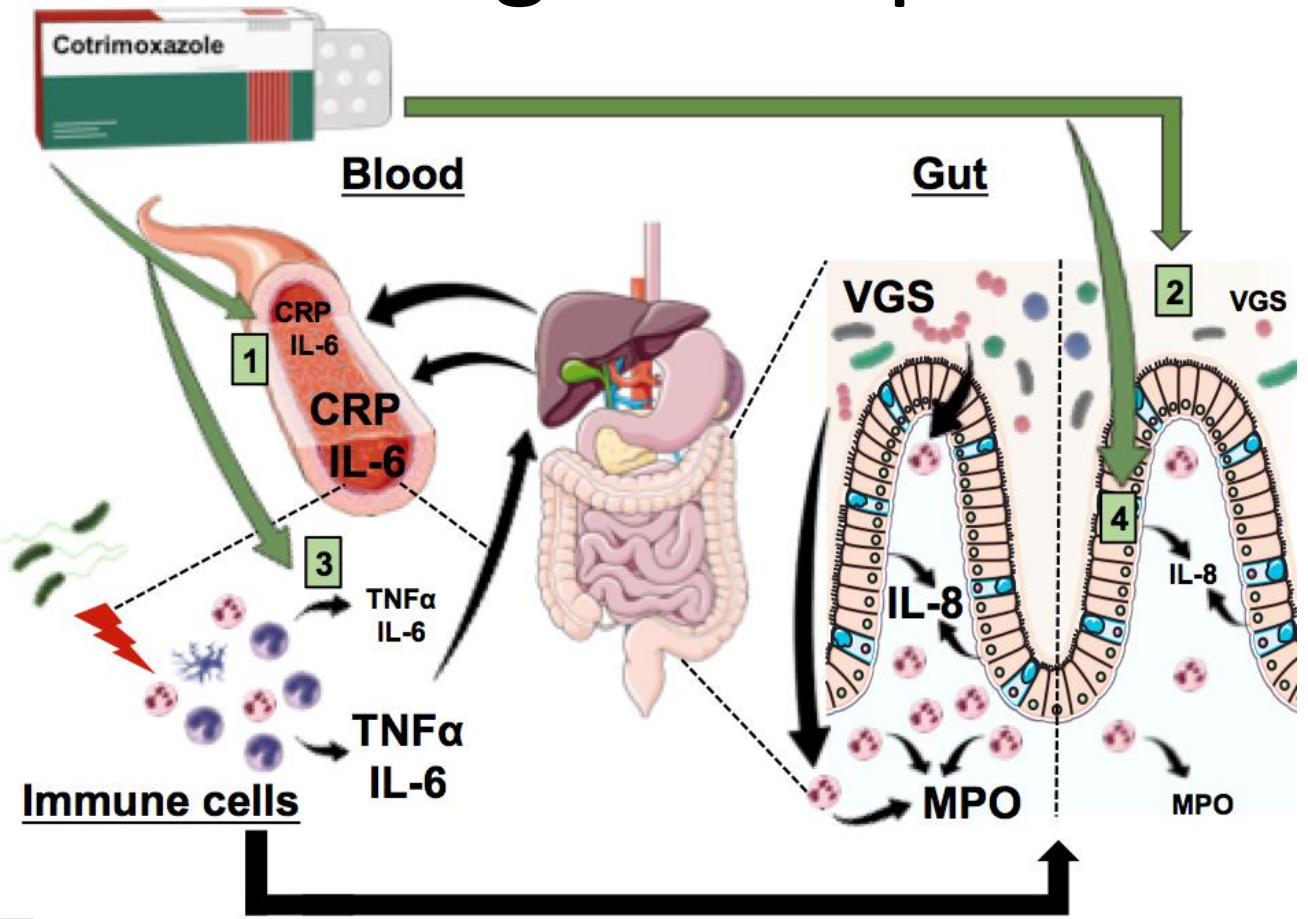
Antibiotics during pregnancy: COMBI trial

1000 pregnant women enrolled at ANC booking
Follow-up of infants to 31 December 2023

Primary outcome: Birth weight
Secondary outcomes: Preterm birth, SGA
Data in early 2024

PACTR registration: 202107707978619

Cotrimoxazole lowers systemic inflammation in HIV infection through multiple mechanisms

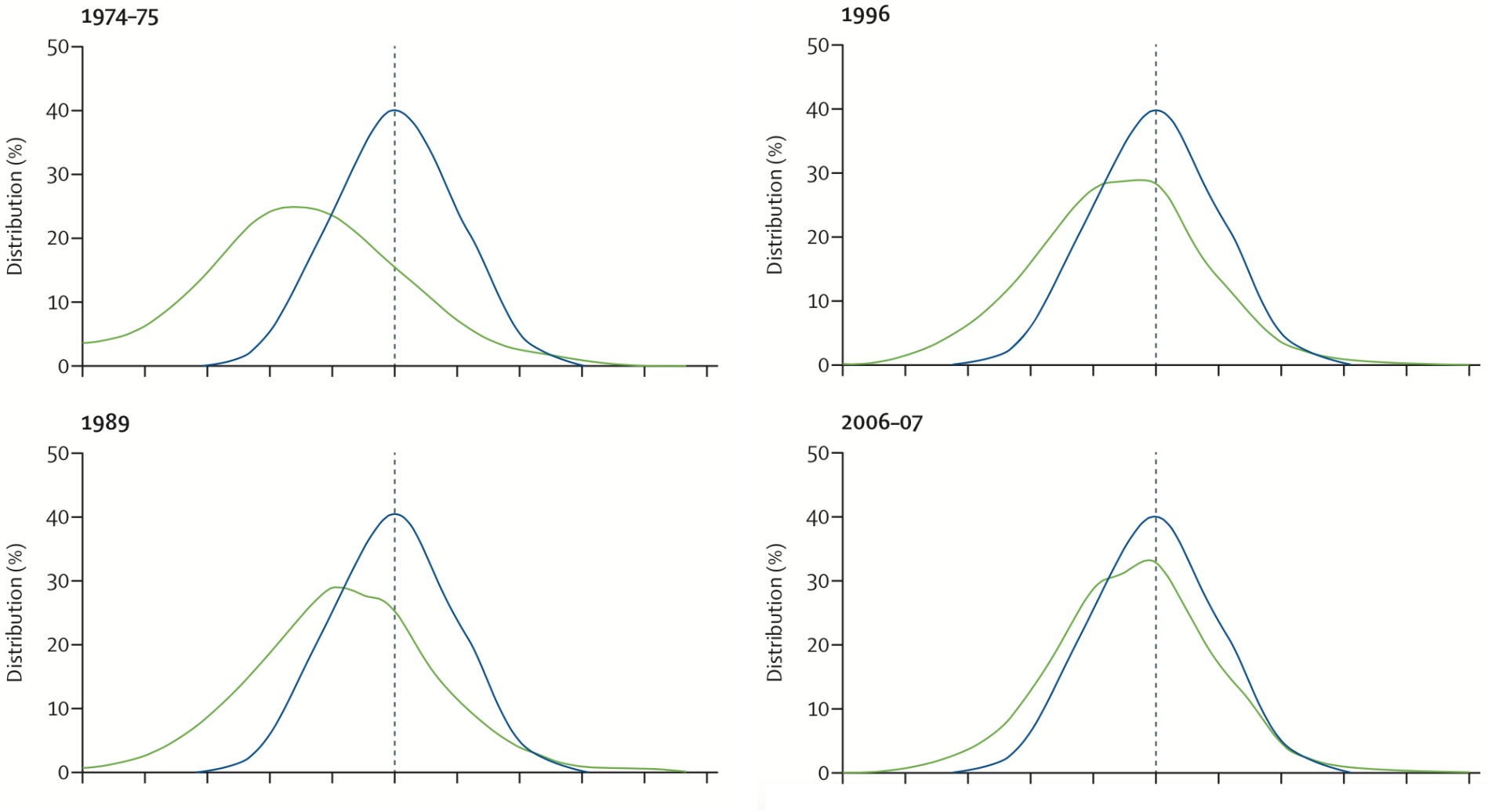


Bourke CD et al., Sci Transl Med 2019

Longer duration of intervention

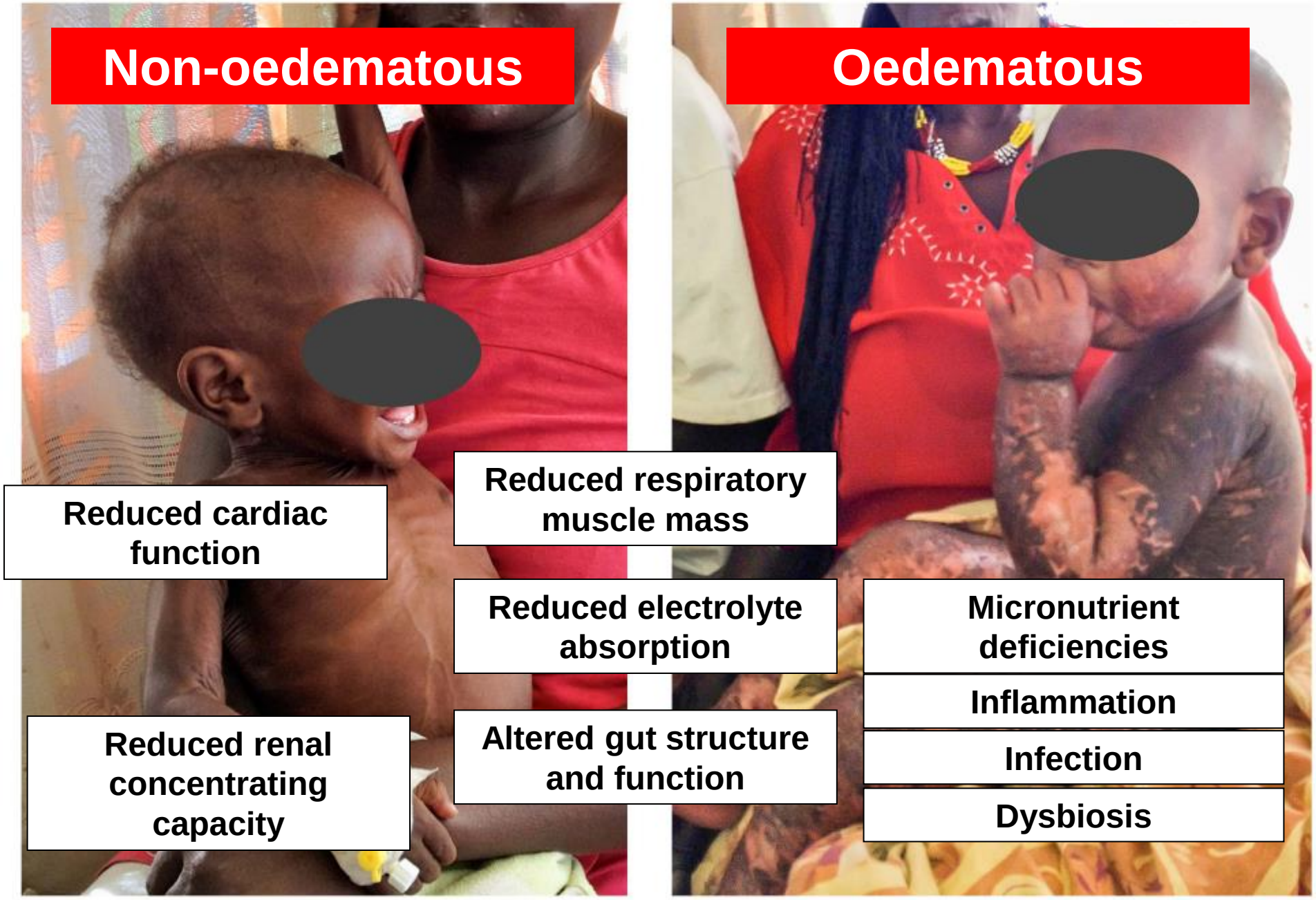
- The home environment continues to shape health, growth and development
- “Missing middle” of childhood (age 5 to adolescence)
- Ongoing nutrition, nurturing care, social protection, and education support may be critical
  - Few trials of interventions after the first 1000 days
  - Window of opportunity prior to the adolescence growth spurt

We know how to prevent stunting (slowly)

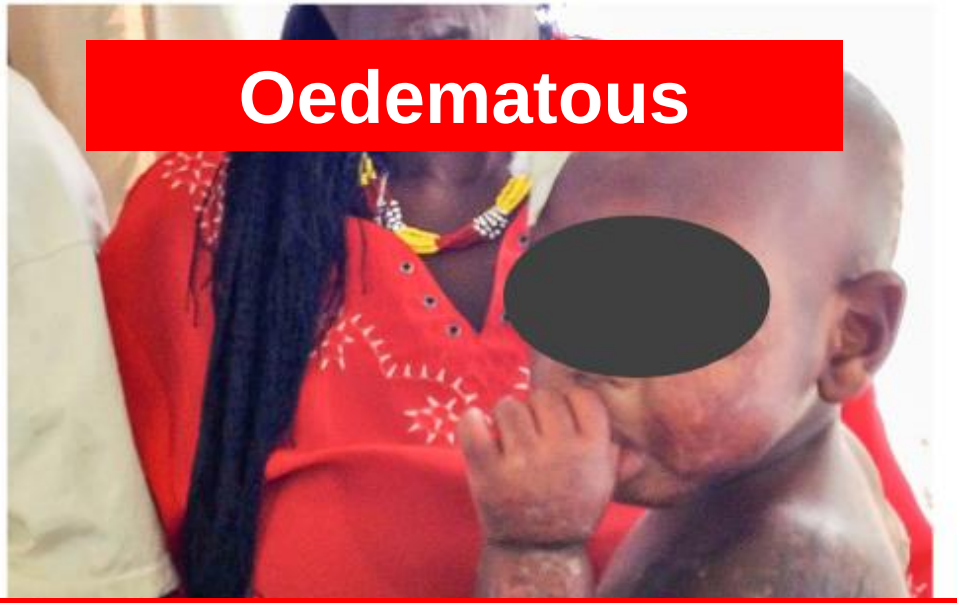


Part 2: Wasting

Rytter M *et al.*, PLOS One 2014

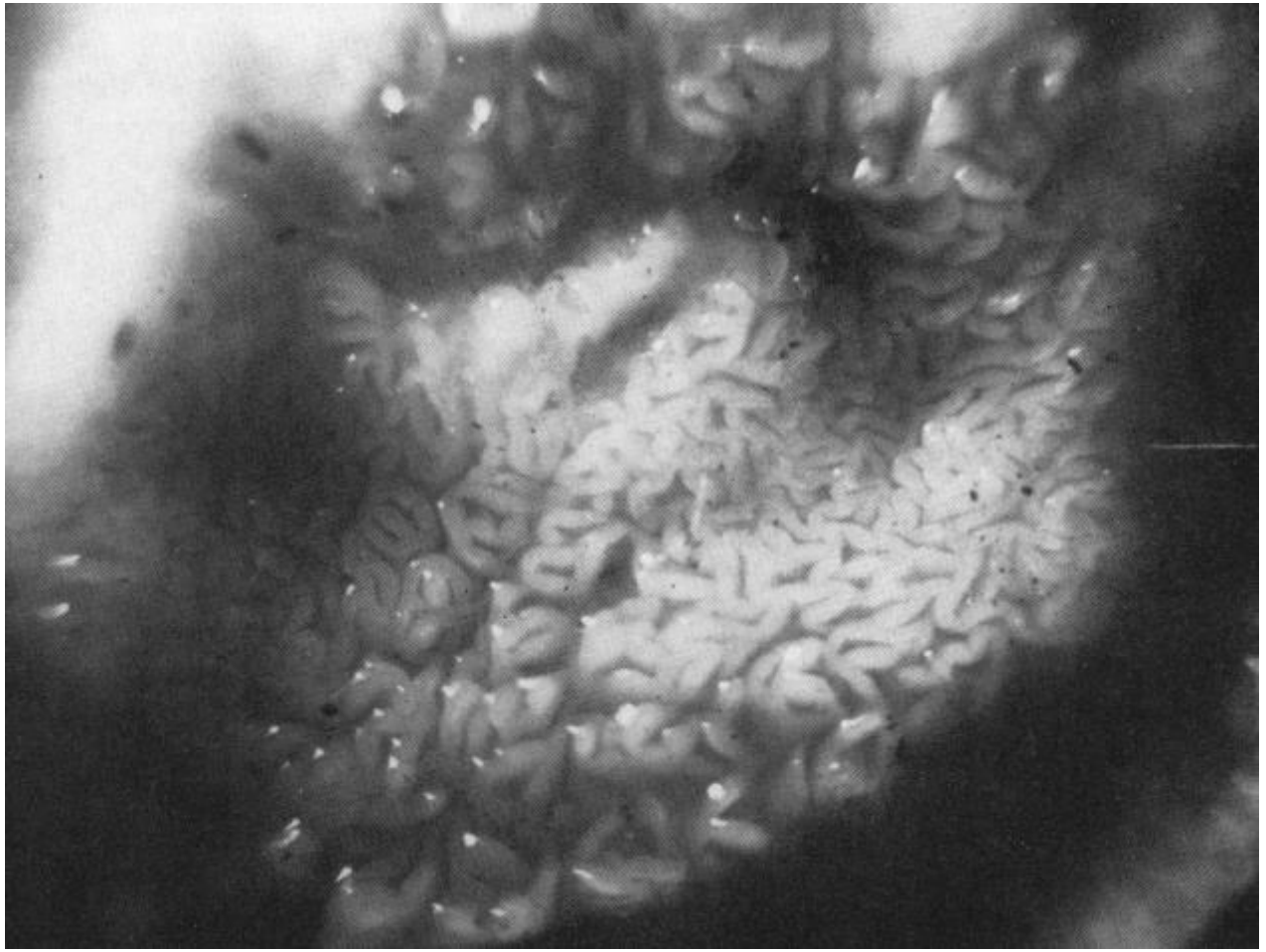


Rytter M *et al.*, PLOS One 2014



“…a multiple deficiency state” (Waterlow)

An extensive enteropathy occurs in malnutrition



"The 'tissue paper' intestine of patients with severe kwashiorkor is well known to tropical pathologists…"

Burman D, Arch Dis Child 1965

Therapeutic Approaches to Malnutrition Enteropathy (TAME)

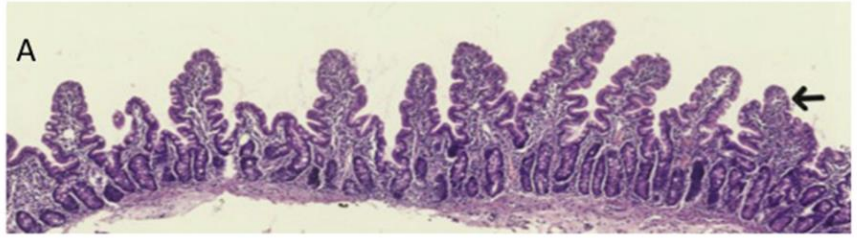
New interventions to target the gut in SAM

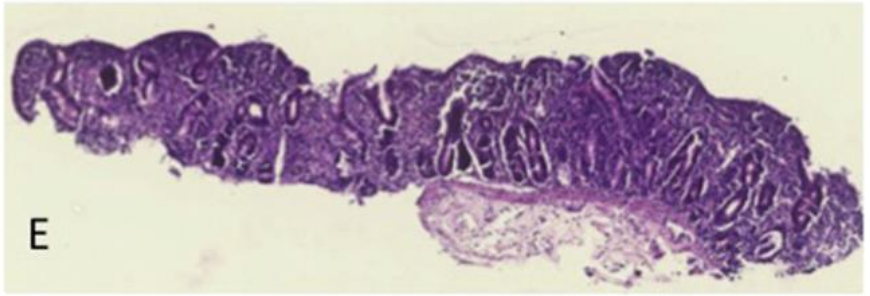
Budesonide

N-acetylglucosamine

Colostrum

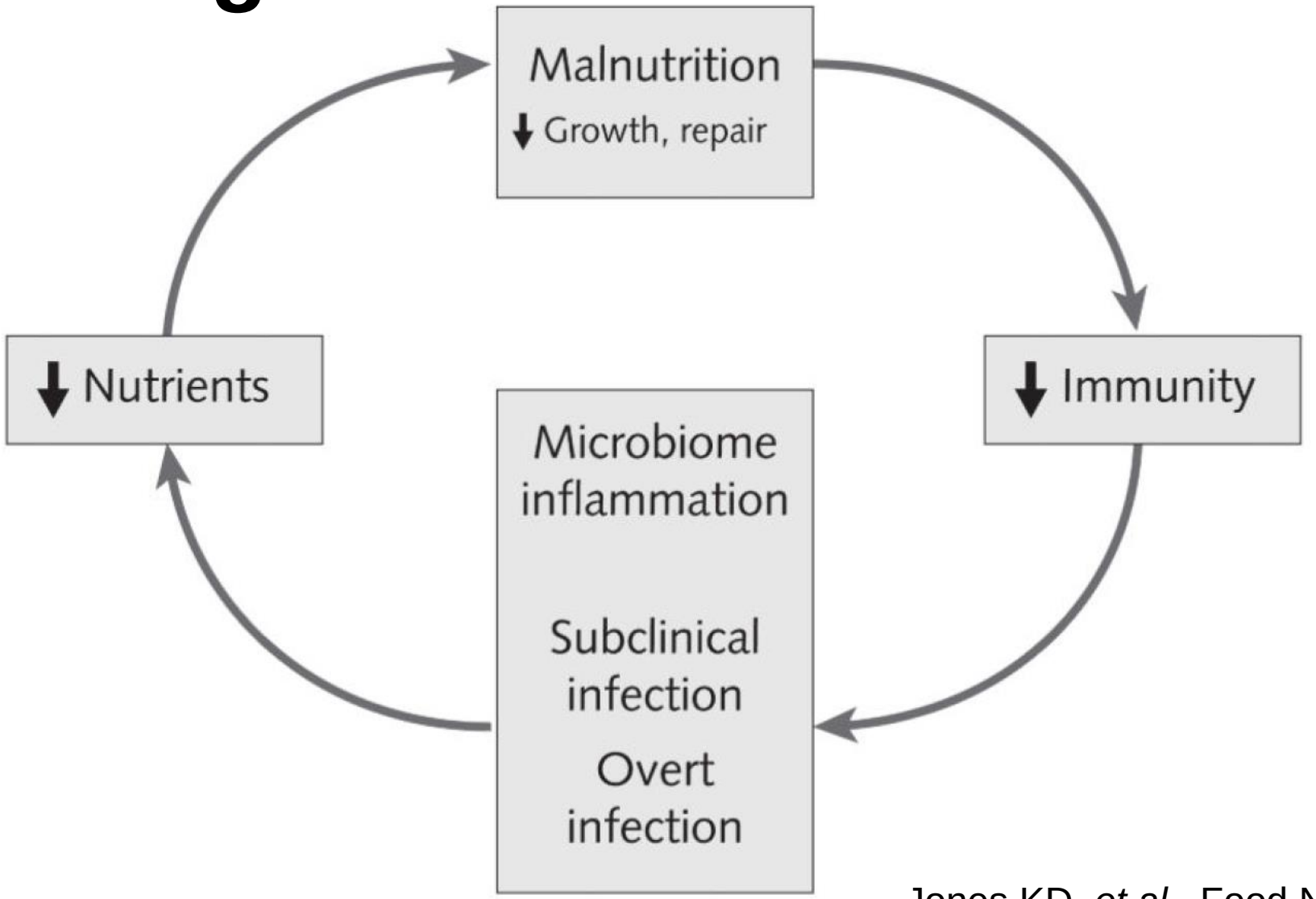
Teduglutide





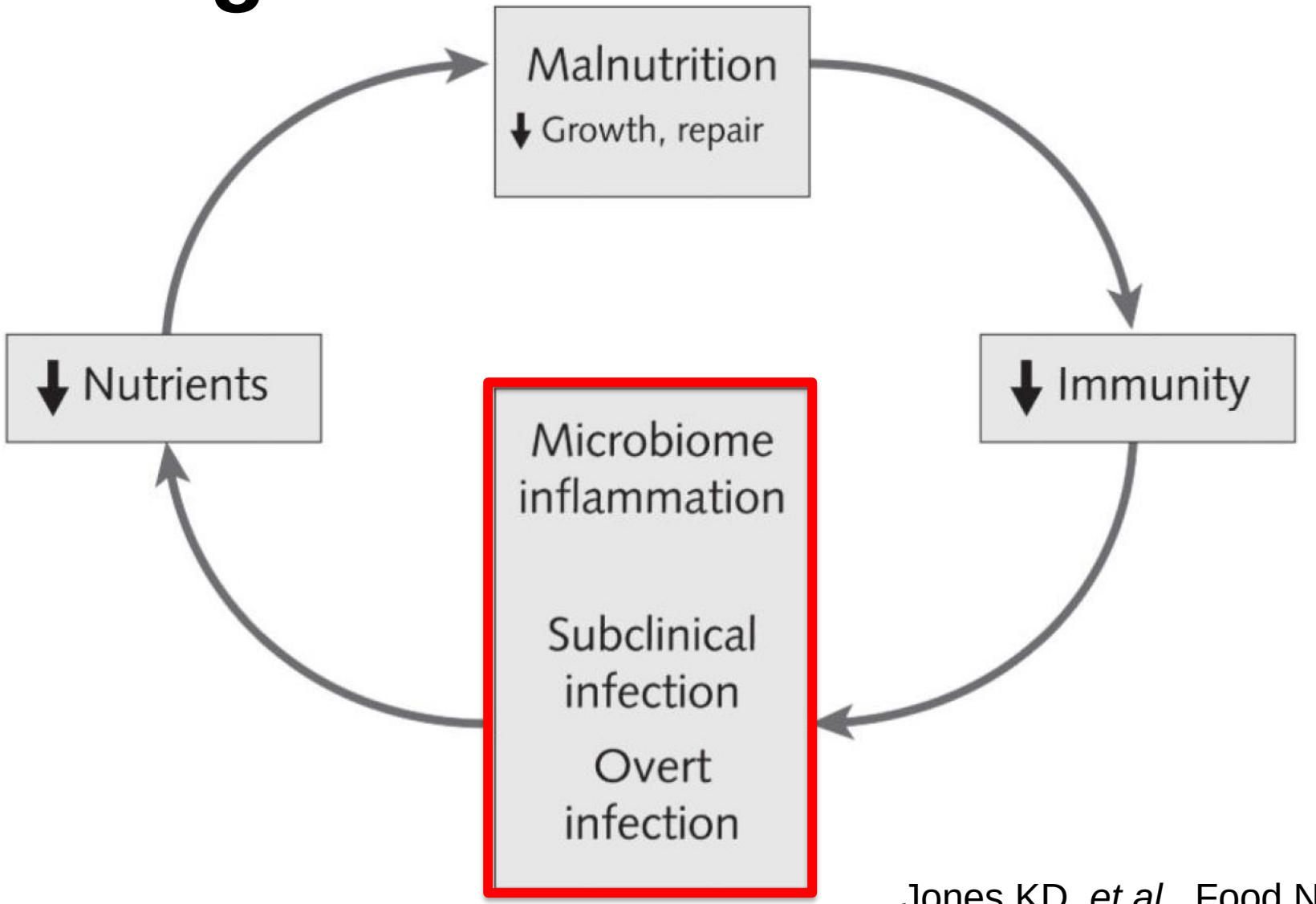
Amadi B et al., EBioMedicine 2017

Current concept of malnutrition pathogenesis



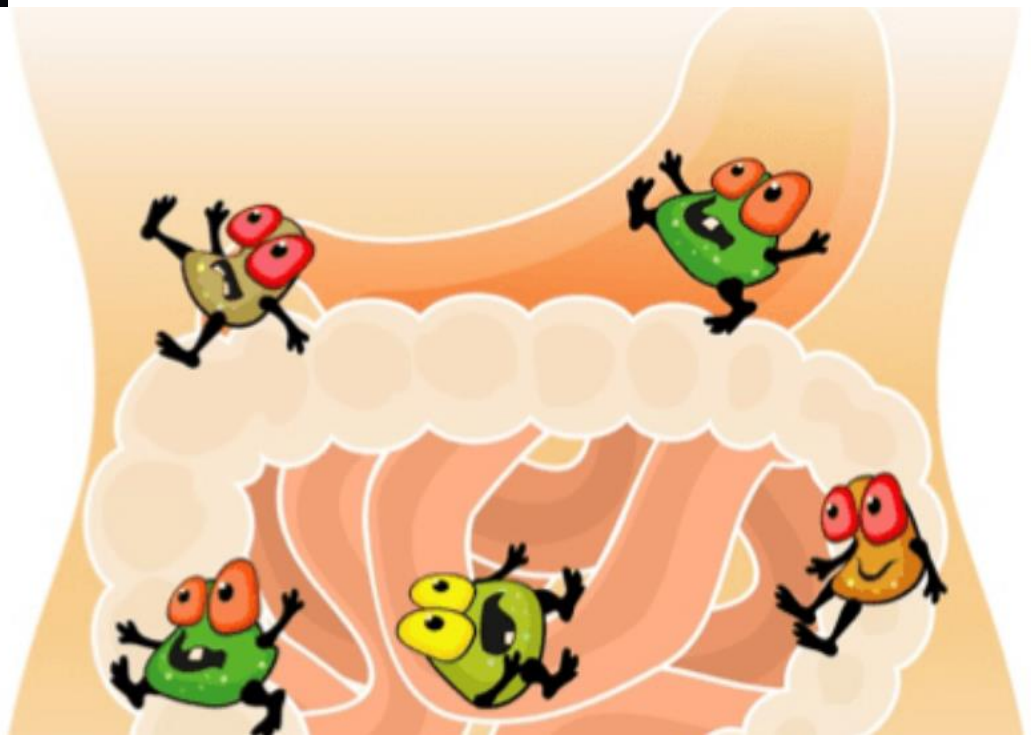
Jones KD, *et al.,* Food Nutr Bull 2014

Current concept of malnutrition pathogenesis



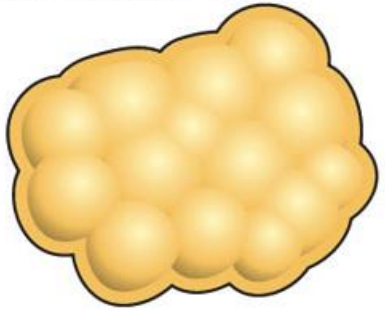
Jones KD, *et al.,* Food Nutr Bull 2014

Are Your Gut Bacteria Healthy?

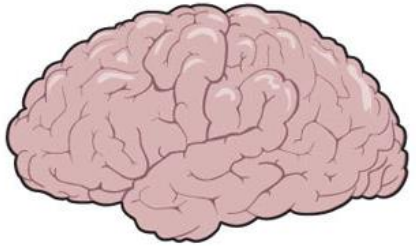


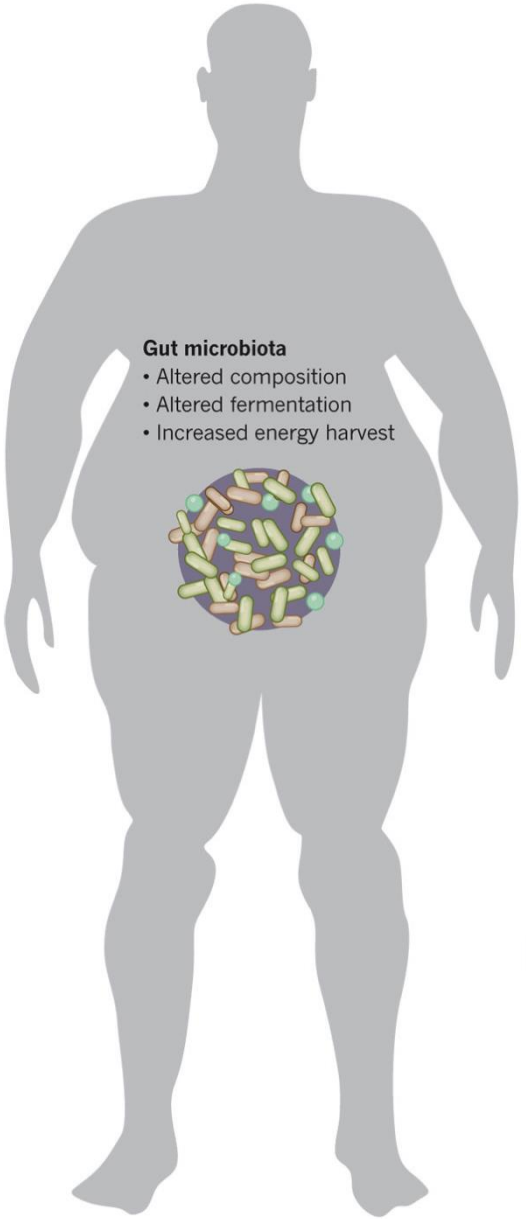
The Gut Microbiota – A Complex Ecosystem

Adipose tissue
↑ Triglyceride incorporation
↑ Inflammation

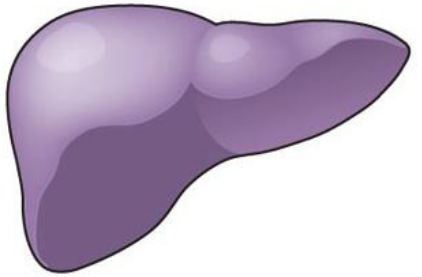


Brain
↓ Satiety



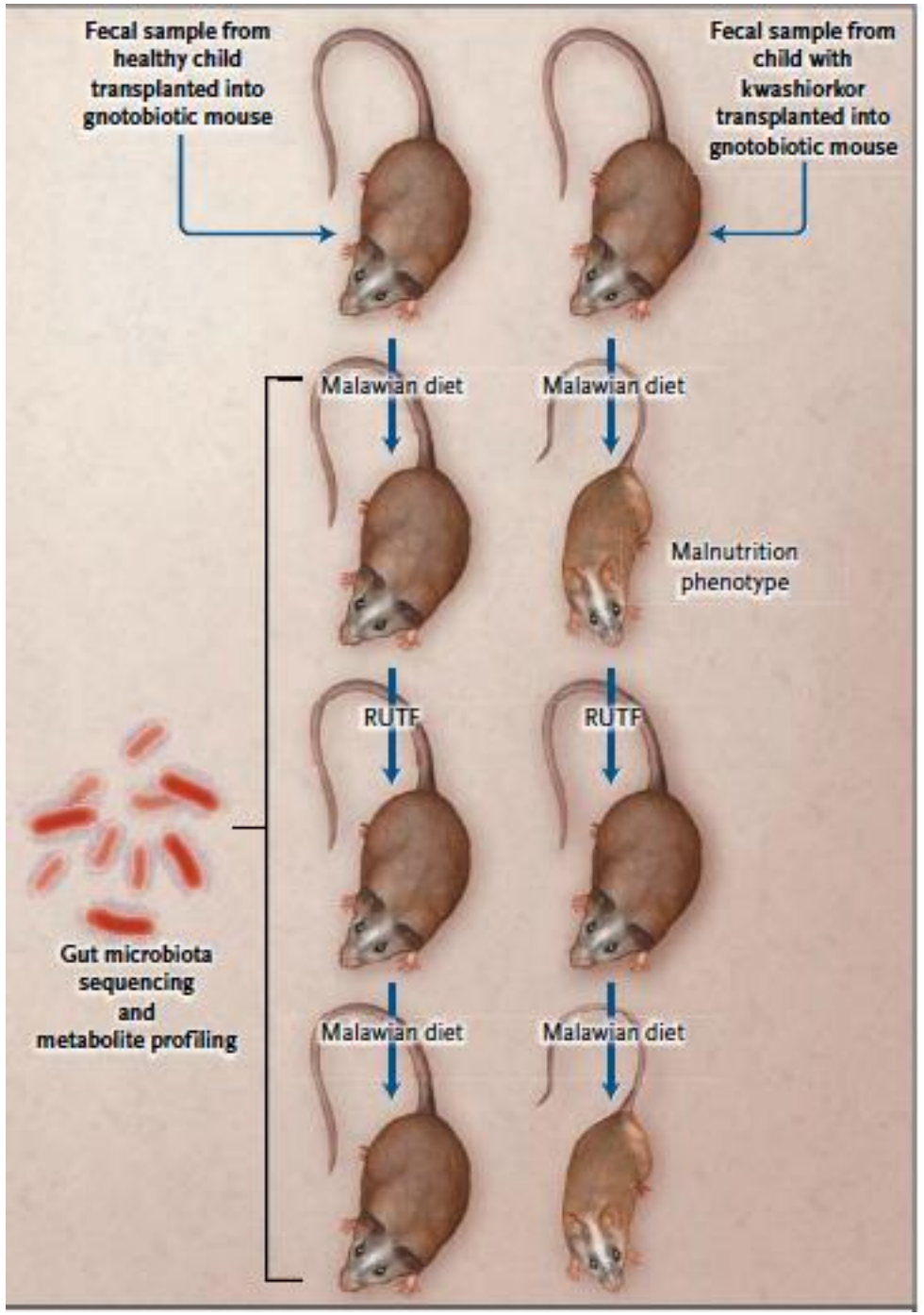


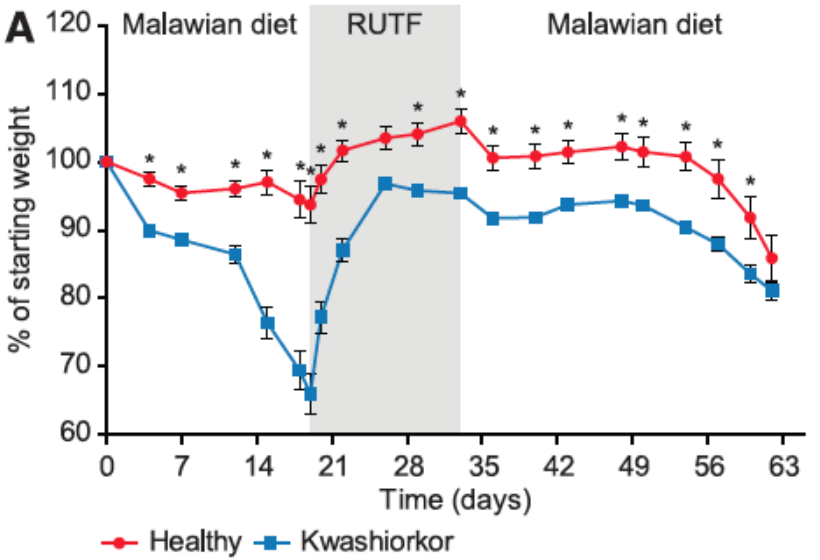
Liver
↑ Short-chain fatty acids
↑ Inflammation

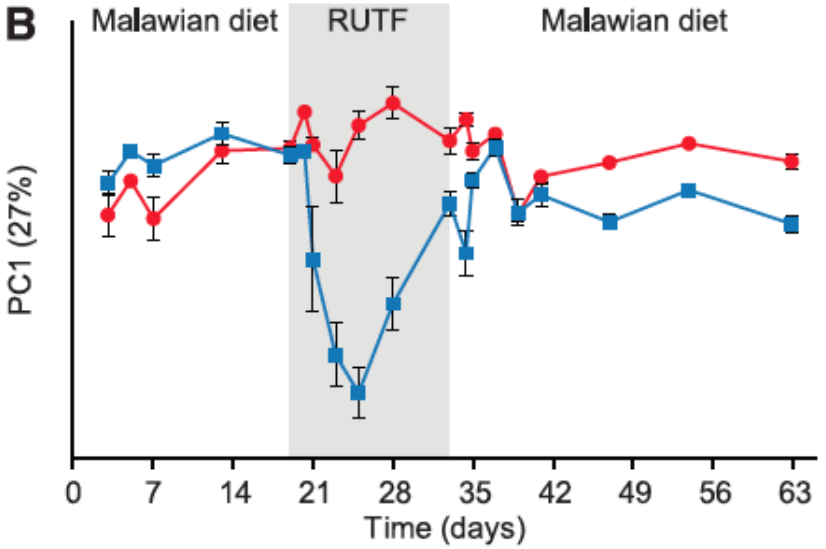


Epithelium
↑ Permeability of the epithelium
↓ PYY/GLP-1 from L-cells

Muscle
↓ Fatty-acid oxidation

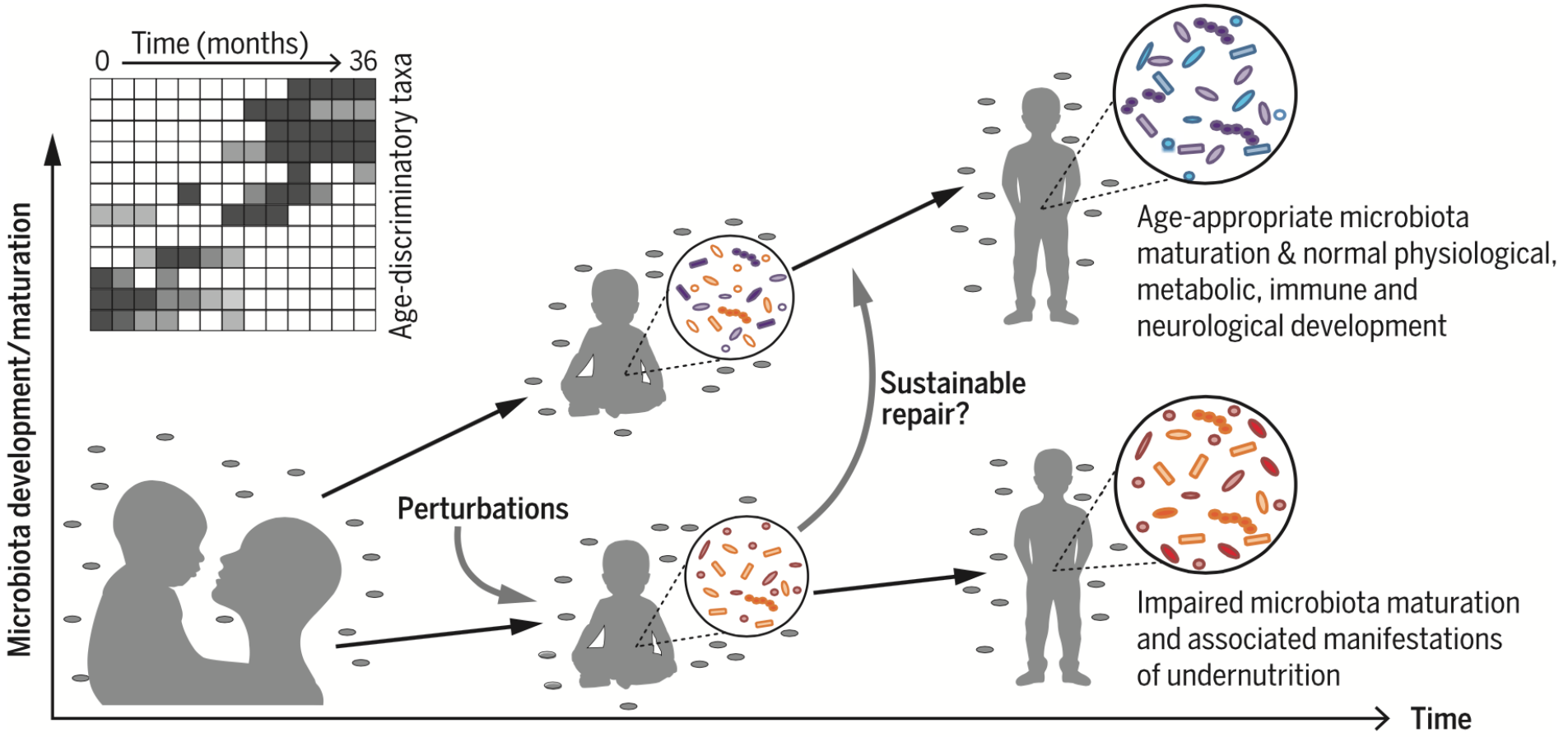






Smith MI, Science 2013

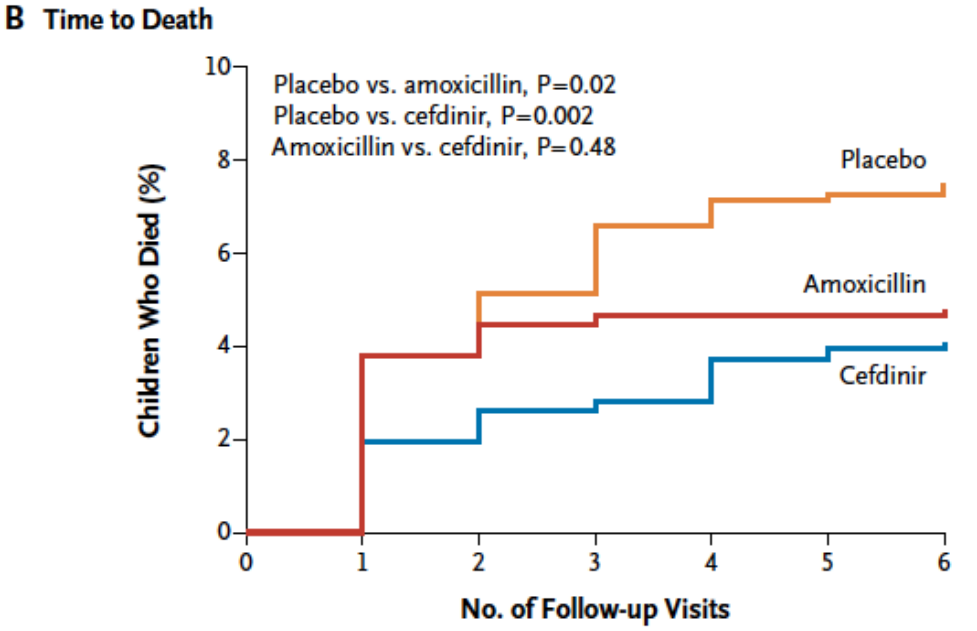
“Repair” of the microbiota



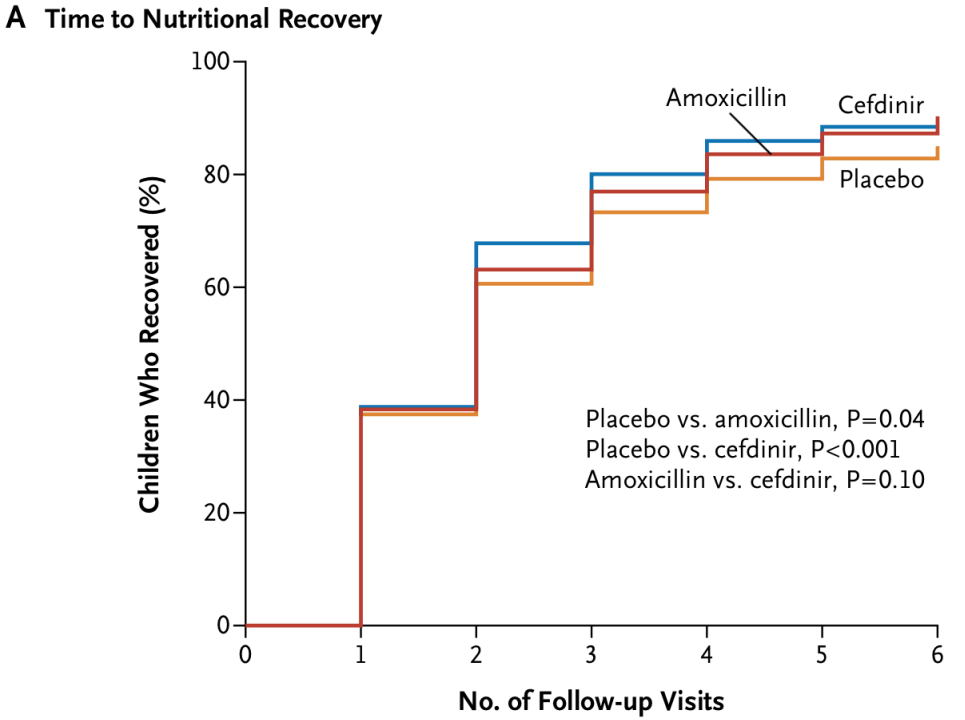
Blanton LV et al, Science 2016

Antibiotics for malnutrition

Malawian children 6-59mo old
7 days of amoxicillin vs cefdinir vs placebo
Mostly kwashiorkor, high HIV prevalence



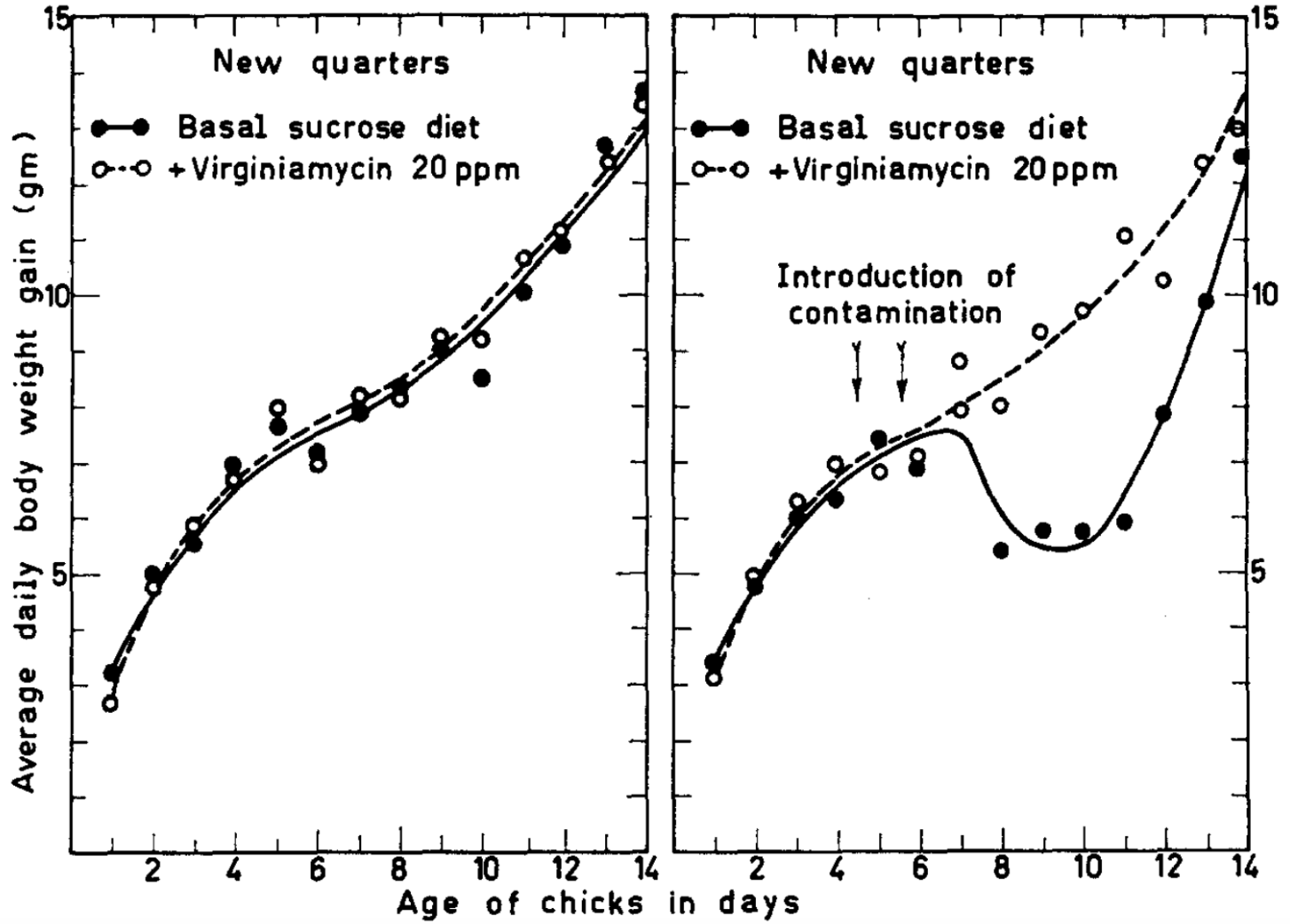
No. at Risk							
Amoxicillin	924	874	857	847	844	842	838
Cefdinir	923	895	882	873	863	860	857
Placebo	920	869	848	830	821	816	811



No. at Risk							
Amoxicillin	924	570	341	213	152	118	104
Cefdinir	923	565	296	184	130	107	84
Placebo	920	576	363	246	191	160	137

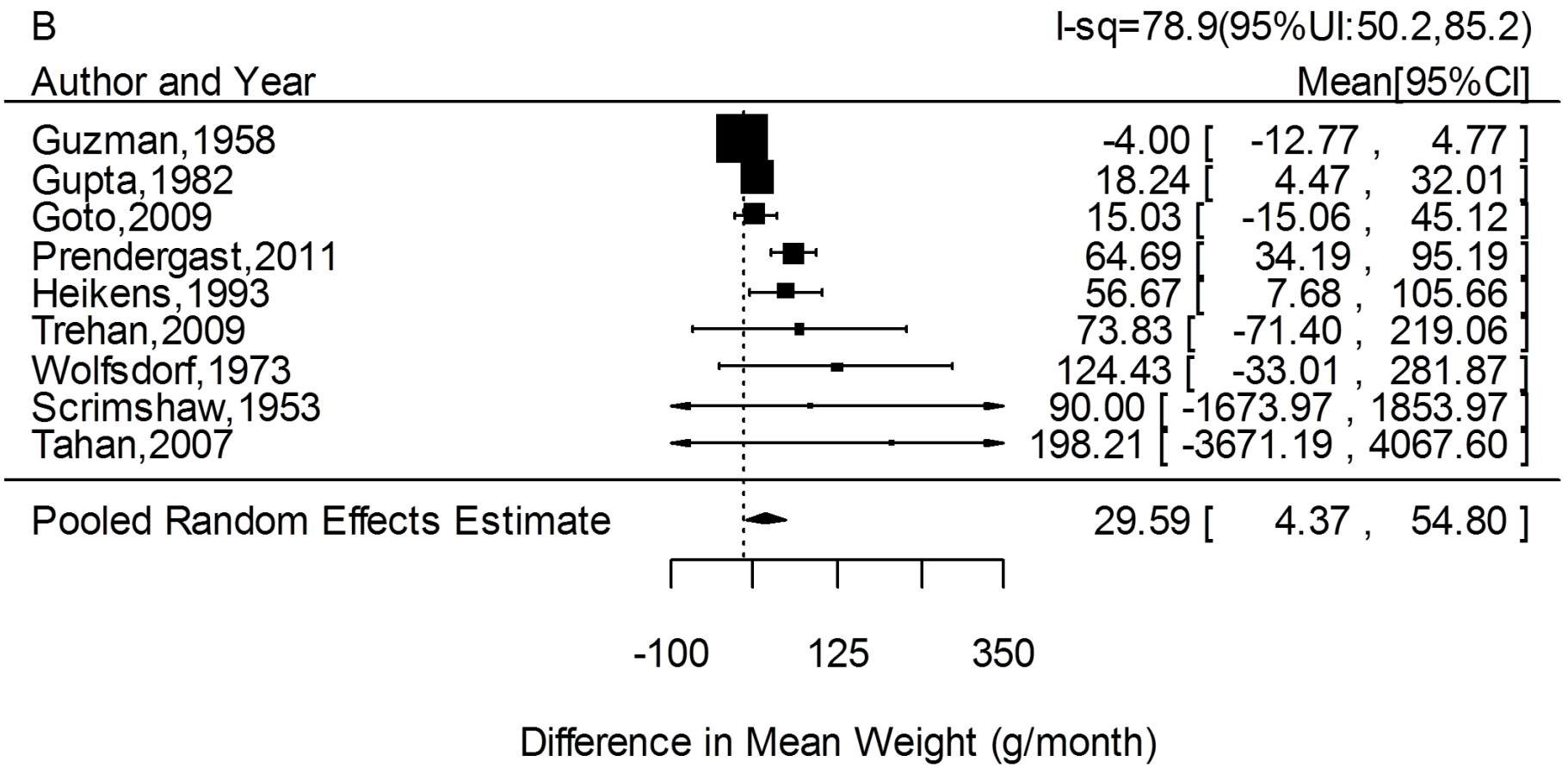
Trehan I *et al*., N Engl J Med 2013

Antibiotics improve growth in animals



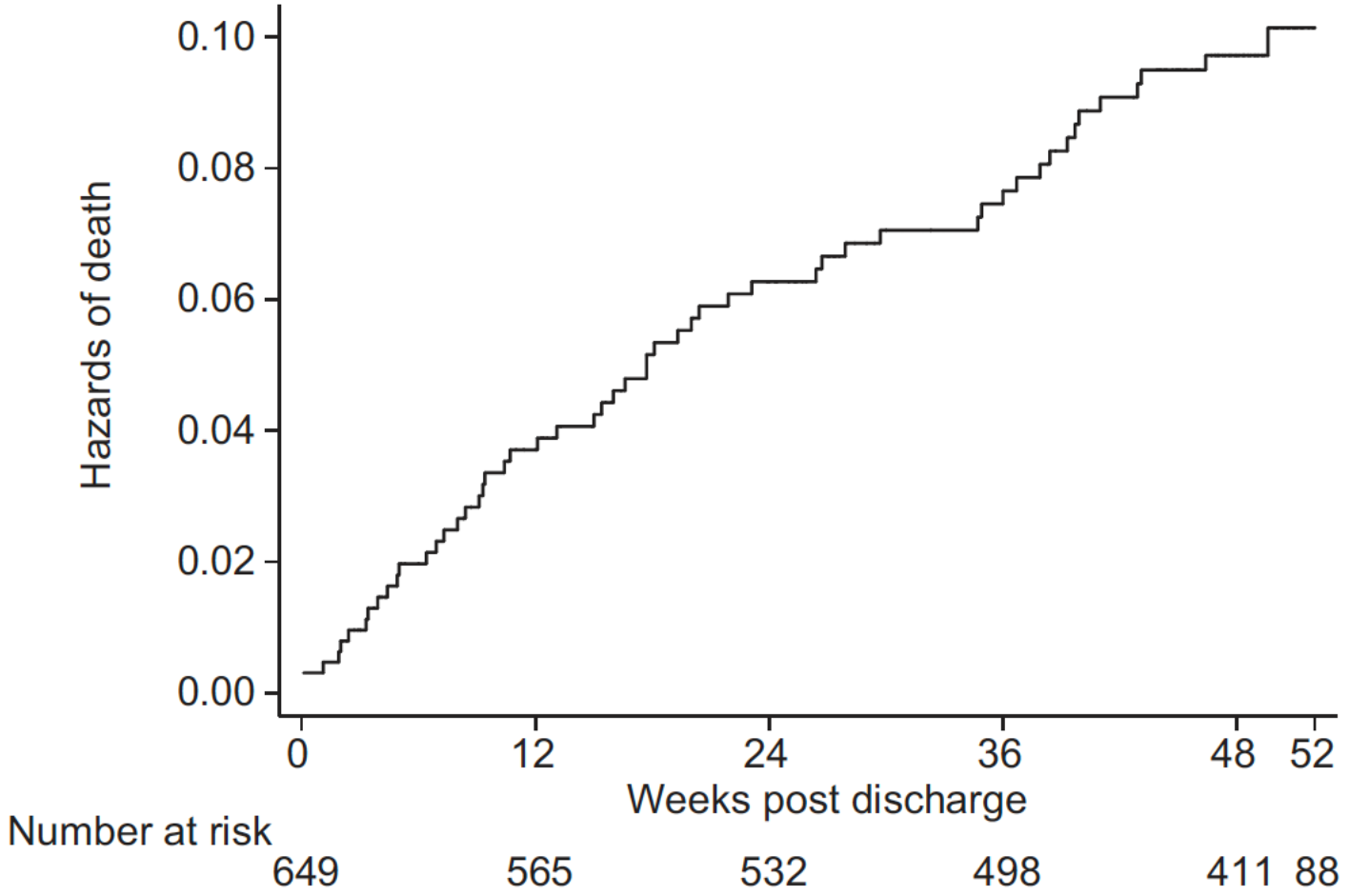
Eyssen and de Somer, J Exp Med 1962

Antibiotics improve growth in humans



Gough E *et al.,* BMJ 2014

Mortality remains high in children leaving hospital after treatment for severe malnutrition



- 745 children
- Zambia and Zimbabwe
- Admitted with complicated SAM
- Discharged from hospital and followed for 52 weeks

Bwakura-Dangarembizi et al., Am J Clin Nutr 2021

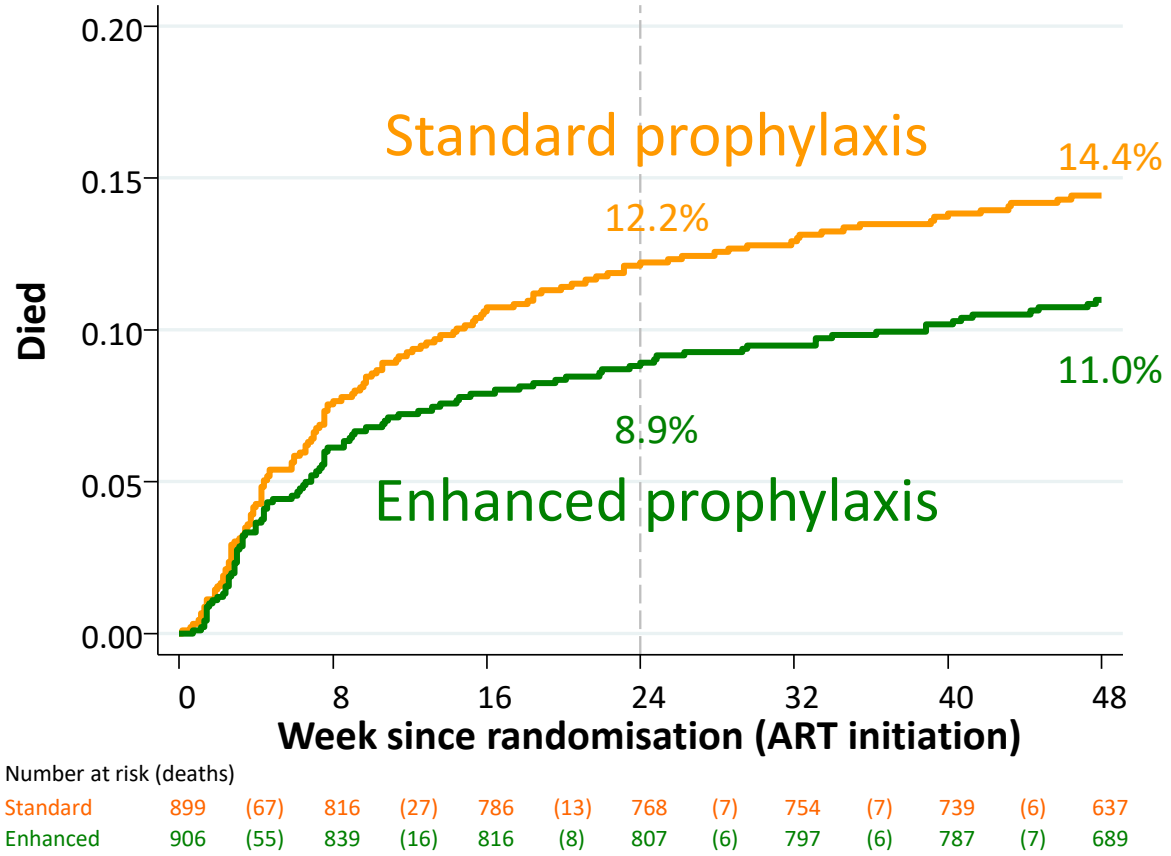
Broader packages of antimicrobials may be beneficial

ART-naïve HIV-infected adults & children >5 years with CD4<100 cells/mm^3

Standard prophylaxis: CTX
(most received additional INH/B6 from 12 weeks depending on national guidelines)*

Enhanced prophylaxis: CTX* +

-12 weeks INH/B6* 300/25mg/d	(anti-TB)
-12 weeks fluconazole 100mg/d	(anti-fungal)
-5 days azithromycin 500mg/d	(anti-bacterial & anti-protozoal)
-single-dose albendazole 400mg	(anti-helminth)

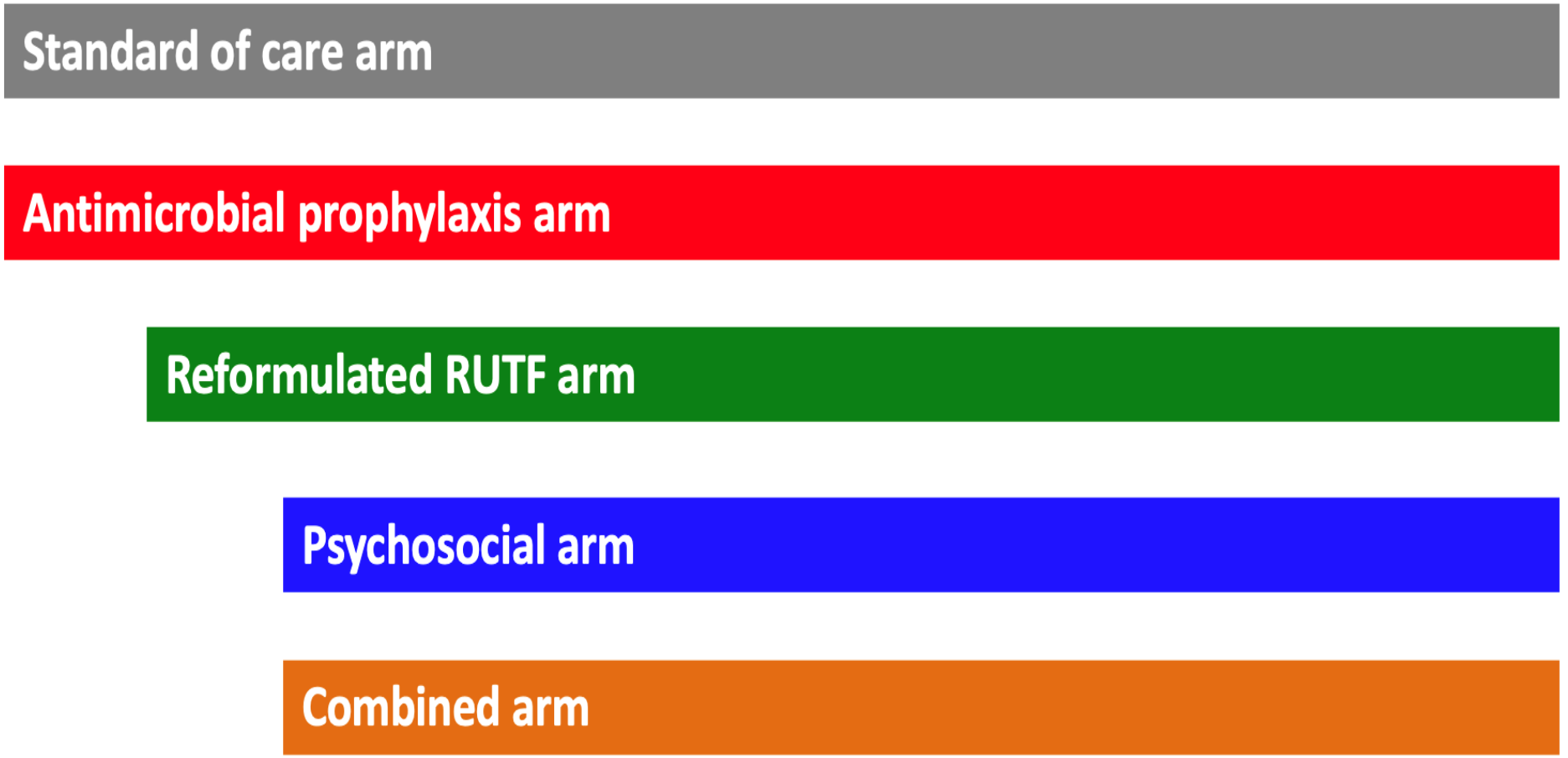


Number at risk (deaths)

Standard	899	(67)	816	(27)	786	(13)	768	(7)	754	(7)	739	(6)	637
Enhanced	906	(55)	839	(16)	816	(8)	807	(6)	797	(6)	787	(7)	689

Hakim J et al., N Engl J Med 2017

Co-SAM: An adaptive clinical trial to reduce mortality / readmission



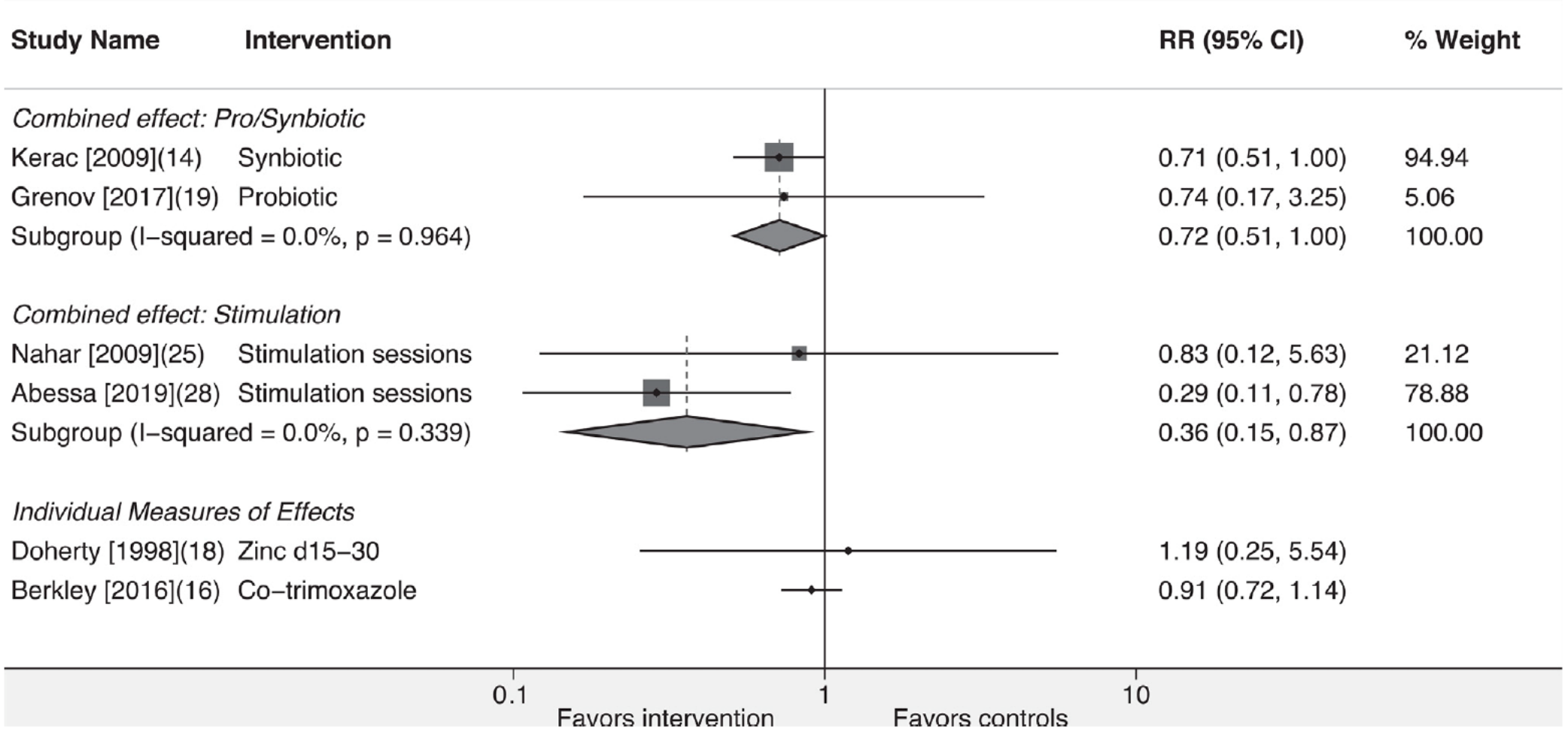
- Antibacterial
- Antifungal
- Anti-TB

- More digestible
- Anti-inflammatory
- Resolve metabolic disturbance

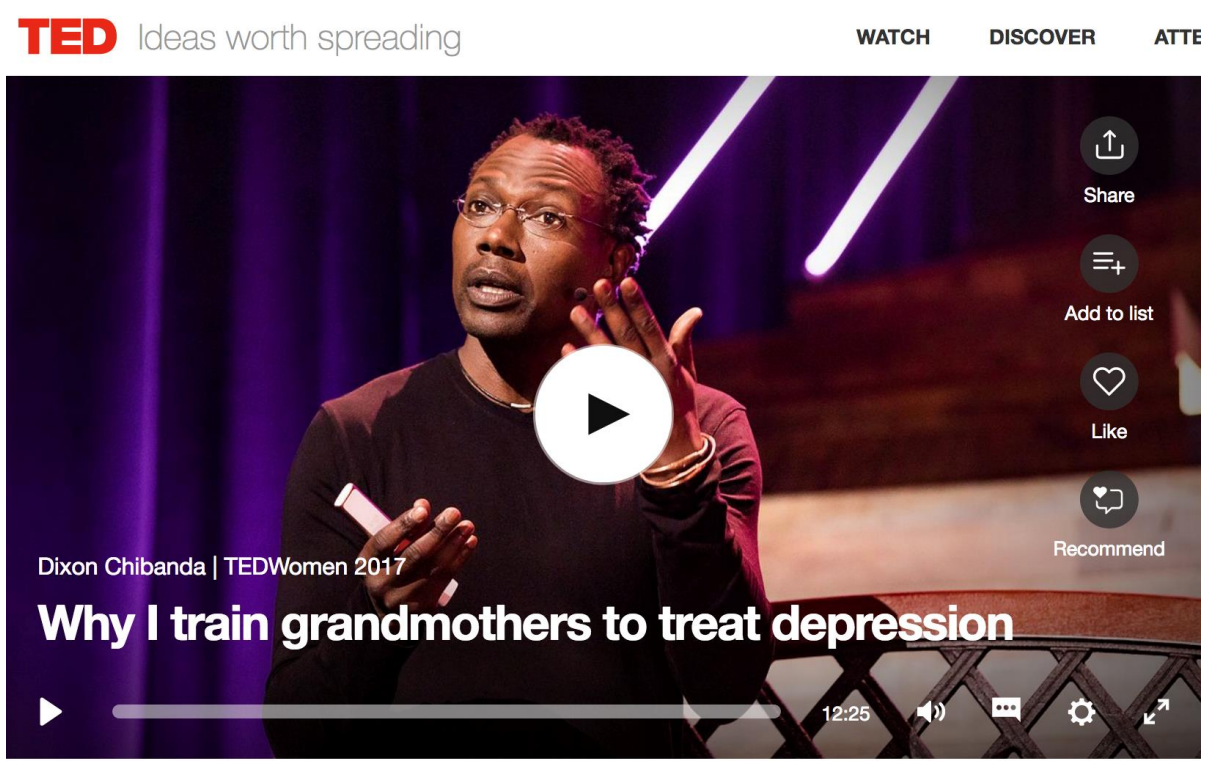
- Child play
- Friendship Bench

Nurturing Care Framework

Combined play and psychosocial support



Noble C et al., Am J Clin Nutr 2021


TED Ideas worth spreading
WATCH
DISCOVER
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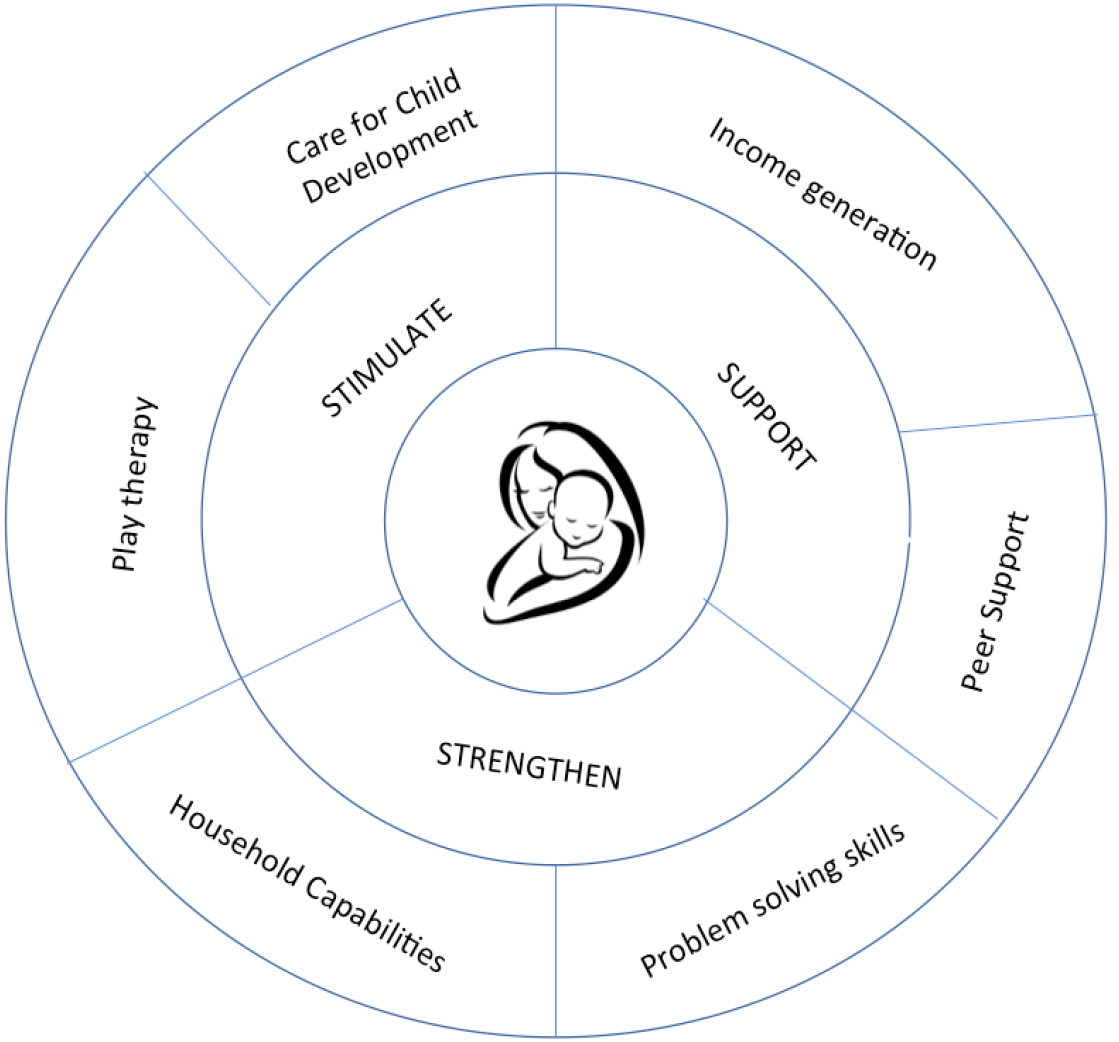
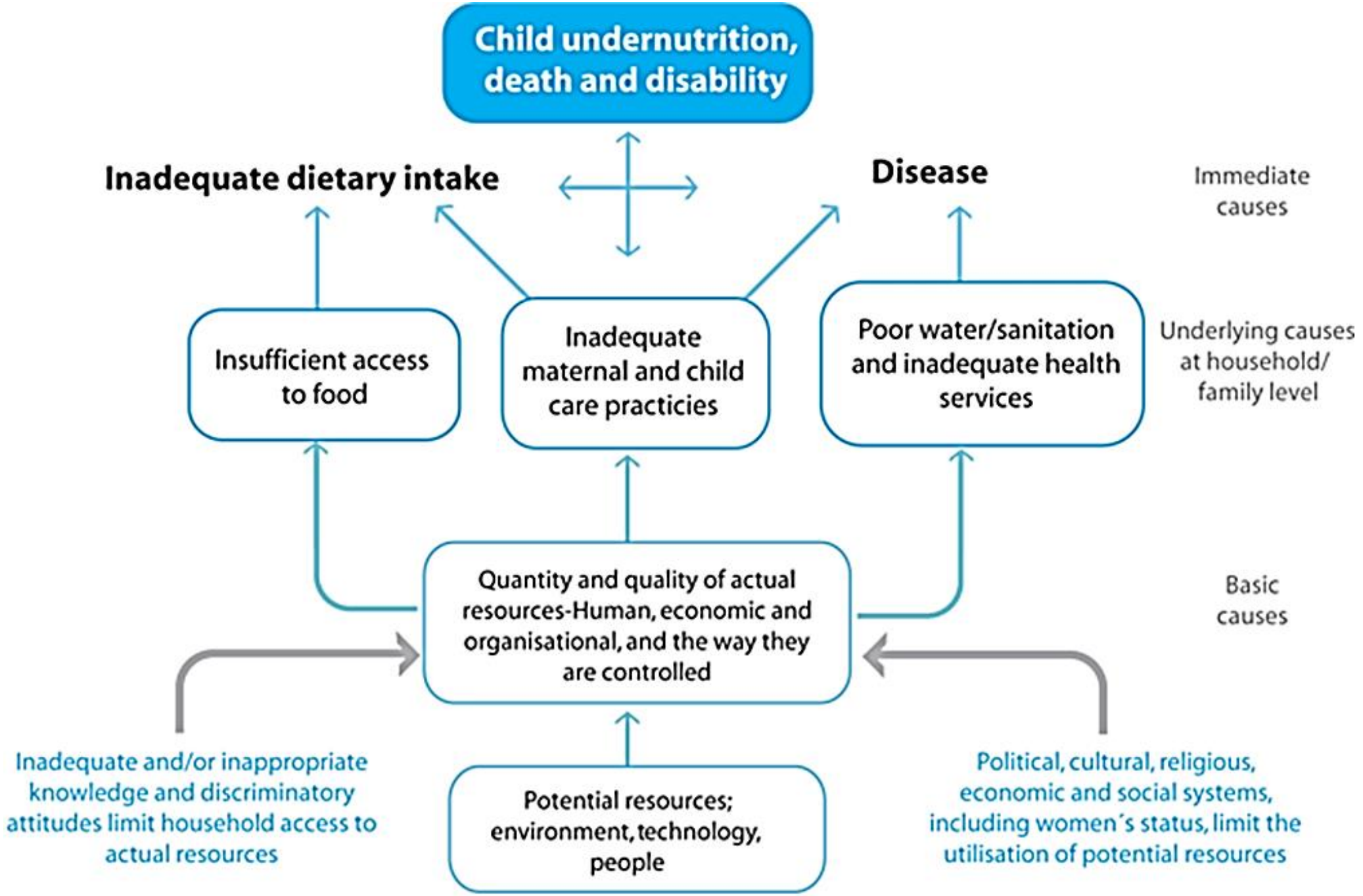
Like
Recommend
Dixon Chibanda | TEDWomen 2017
Why I train grandmothers to treat depression
12:25

Developing a convalescent package of care

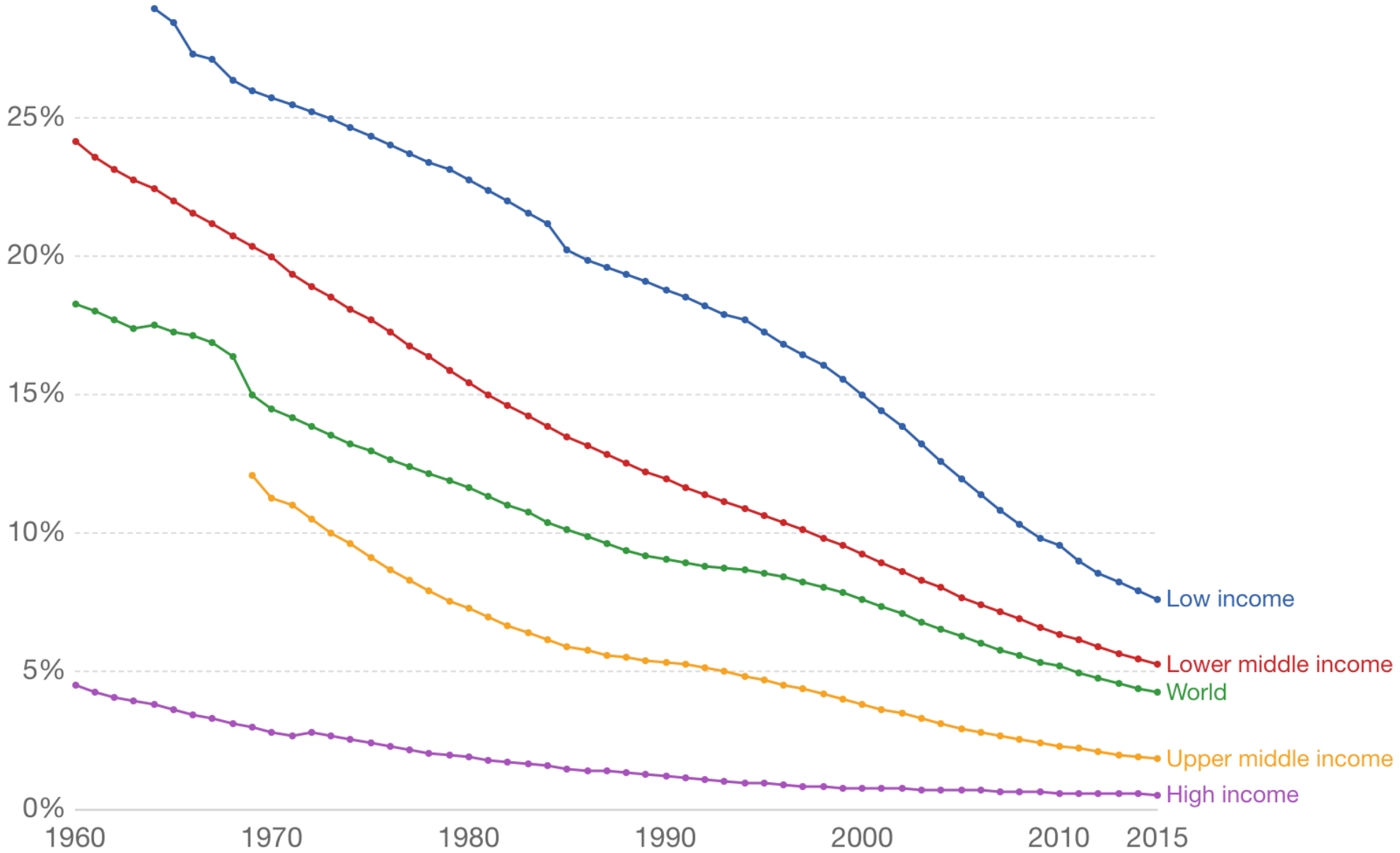



Child undernutrition, death and disability
Inadequate dietary intake
Disease
Immediate causes
Insufficient access to food
Inadequate maternal and child care practicies
Poor water/sanitation and inadequate health services
Underlying causes at household/ family level
Quantity and quality of actual resources-Human, economic and organisational, and the way they are controlled
Basic causes
Inadequate and/or inappropriate knowledge and discriminatory attitudes limit household access to actual resources
Potential resources; environment, technology, people
Political, cultural, religious, economic and social systems, including women´s status, limit the utilisation of potential resources

Child mortality by income level of country

The child mortality rate measures the share of children that die before reaching the age of 5.

Our World in Data



Source: World Bank – WDI

Tackling malnutrition at both ends

Prevention of stunting

Treatment of wasting

Convalescence following SAM