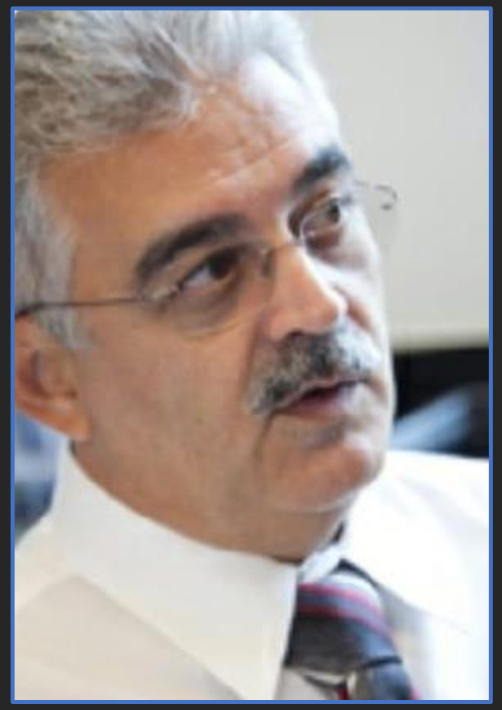
Pesquisa Translacional Aplicada a Medicina:



Impacto da disfunção entérica ambiental, infecções entéricas e desnutrição na infância e vida adulta

Aldo Ângelo Moreira Lima, MD, PhD
Professor Titular, Faculdade de Medicina
Universidade Federal do Ceará
21/03/2024

O que é pesquisa translacional?

Conceito:

Pesquisa translacional é a pesquisa que tem seu início na ciência básica e sua conclusão na aplicação prática do conhecimento apreendido.

Em especial tem-se sua aplicação na **MEDICINA / NUTRIÇÃO:**

Lima et al. Pharmacol. Toxicol. 1992; 70:163 / Chang et al. Gastroenterol 2023; 164:1086

A Rede de Desnutrição e Doenças entéricas (MAL-ED: www.mal-ed.fnih.org/):
Lancet Glob Health. 2018; 6:e1309
Lancet Glob Health. 2018; 6:e1319 / Badr et al., Lancet Global Health, 11:e373-e384, 2023
BMJ Glob Health 2018;3:e000752

Blanton et al. Science. 2016; 351(6275)
Raman et al. Science. 2019; 365(6449)
The Ki Child Growth Nature series papers 2023
Maciel et al. J Nutr 2020;151(1):170–8
Ribeiro et al. J Nutr. 2024 Feb 10:S0022-3166(24)00052-X.

Efeitos das toxinas do *Vibrio cholerae* e da *Escherichia coli* no rim perfundido

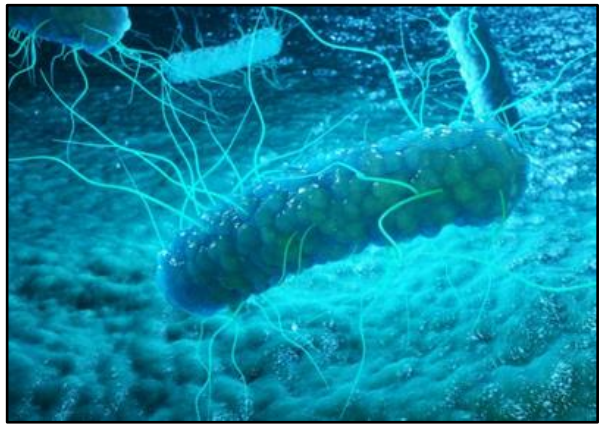
Lima, A. A. M. & M. C. Fonteles

Resumo no XVIII Congresso Brasileiro de Fisiologia. S-31, p. 46, abril *I* 1983. São Lourenço, MG, 1983

E. coli STa MW: 1,972 Da; Cholera toxin MW: 84 kDa

&

Suprimento de água no município de Pacatuba, CE - 1983



The Effects of *Escherichia coli* Heat-Stable Enterotoxin in Renal Sodium Tubular Transport

Aldo AM Lima, Helena SA Monteiro and Manassés C Fonteles

Esses efeitos sugerem a existência de um peptídeo endógeno semelhante à enterotoxina STa, que regula a função do transporte tubular de sódio renal.

decrease in potassium transport and increase in urinary potassium excretion. These effects suggest the existence of an endogenous peptide resembling STa enterotoxin, that regulates the function of renal sodium tubular transport.

Lima et al. Pharmacology & Toxicology 1992, 70,163-167

Efeitos das toxinas do *Vibrio cholerae* e da *Escherichia coli* no rim perfundido

Lima AAM and Fonteles MC, **Resumo** no XVIII Congresso Brasileiro de Fisiologia. S-31, p. 46, abril / 1983. São Lourenço, MG, 1983

Lima, Monteiro and Fonteles, Pharmacology & Toxicology 1992, 70,163-167 **(Received July 4, 1991; Accepted August 5, 1991)**

Currie MG et al. Guanylin: an endogenous activator of intestinal guanylate cyclase. Proc Natl Acad Sci U S A. 89:947, 1992.

Seminário *in Guanylins* – Mark Currie 24Out2014
INCT-Biomedicina, NUBIMED, FAMED, UFC

Celebração dos 70 anos da FAMED, UFC

Família de Guanilinas e Peptídeos de Enterotoxina de *Escherichia coli*: regulação hidrosalina e homeostase cripta-vilus intestinal

Aliment Pharmacol Ther 40:1302, 20014

The impact of abdominal pain on global measures in patients with chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis of two randomised, double-blind, placebo-controlled, phase 3 trials.

Chang L Lembo AJ Lavins BJ Shiff SJ Hao X Chickering JG Jia XD Currie MG Kurtz CB Johnston JM

Few clinical trials in chronic idiopathic constipation (CIC) patients have evaluated abdominal symptom severity and whether CIC patients with abdominal symptoms respond similarly to patients with limited abdominal symptoms.

CONCLUSIONS:

Linaclotide (145 µg and 290 µg; 14 aa) é um tratamento eficaz para sintomas abdominais e intestinais, mesmo em pacientes CIC com dor abdominal mais intensa no início do estudo. (Clinicaltrials.gov: NCT00765882, NCT00730015). **Linzess (*linaclotide;* Ironwood Pharmaceuticals, EUA) FDA approved 31Aug2012.**

Plecanatide 3 e 6 mg (Trulance™; 16 aa) Synergy Pharmaceuticals. *Am J Gastroenterol 2017; 12:613*. Chang et al. Gastroenterol 2023; 164:1086.

proximal renal de sódio e no transportador Na^+ -próton NHE3

Revisão da literatura

- ✓ **Embora a mortalidade por diarreia tenha diminuído substancialmente desde 1990, a incidência e morbilidade diarreicas continuam a ser um problema enorme.**

  Troeger C et al. Lancet Infect Dis 17:909, 2015; Guerrrant RL et al Nutr Rev 66:487, 2008; Lancet Glob Health. 2018; 6:e1309; Lancet Glob Health. 2018; 6:e1319.

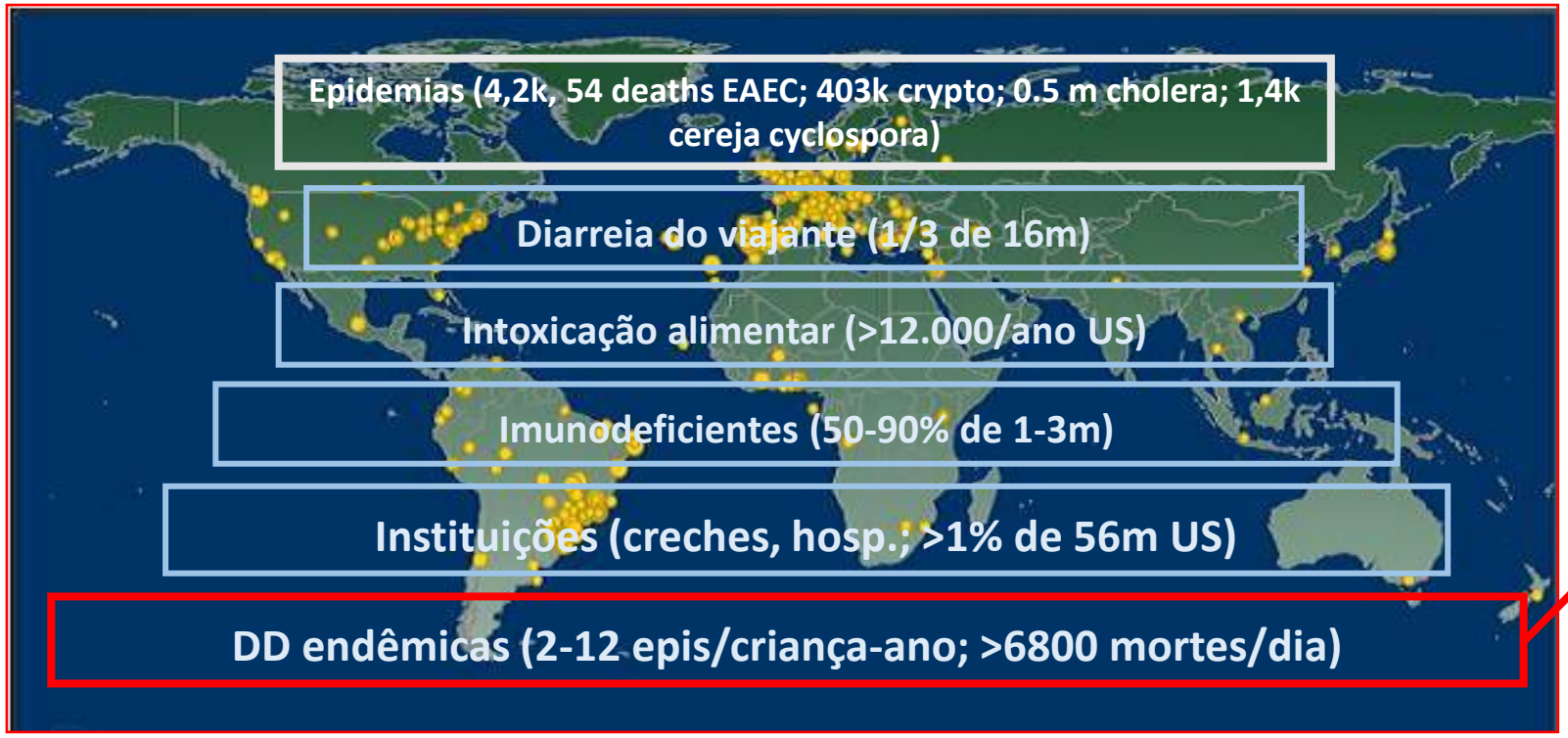
- ✓ **Os estudos etiológicos têm se concentrado em crianças que se apresentam aos cuidados terciários, mas isso representa a minoria dos episódios de diarreia.**

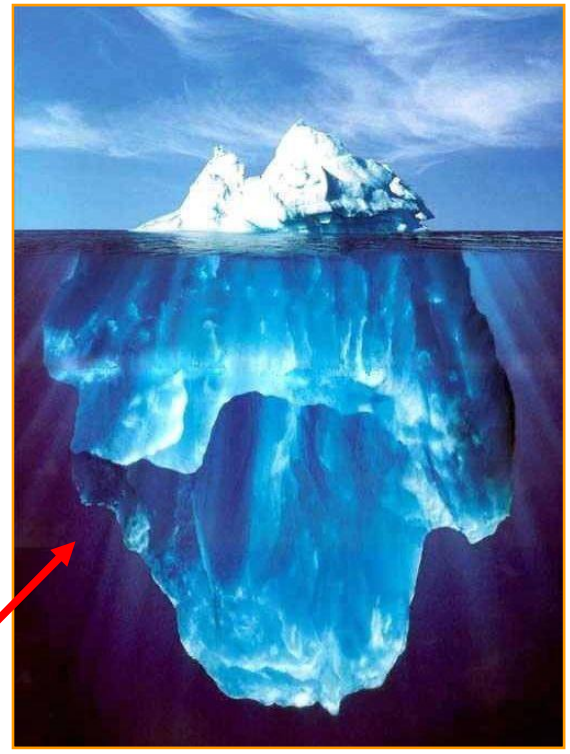
  Sreeramareddy CT et al BMC Ped 17:83, 2017; Lancet Glob Health. 2018; 6:e1309

- ✓ **A aplicação de diagnósticos moleculares para enteropatógenos tem oferecido aumento da sensibilidade e, por meio da quantificação, resolução para identificação da etiologia.**

  DJ et al. J Infect Dis 216:220, 2017; Liu J et al. Lancet 388:1291,2016; Lancet Glob Health. 2018; 6:e1309.

Diarrheal diseases morbidity and mortality





Vírus, Bactérias, Parasitos

36% dos casos: infecções virais (*Sapovirus, Rotavirus, Adenovirus, Norovirus, Astrovirus*)
25% dos casos: infecções bacterianas (*E. coli*, *Shigella spp*, *Campylobacter spp*)
4% dos casos: infecções por protozoários (*Cryptosporidium* spp)

Bernstein DI Pediatric Infect Dis 28:S50, 2009; Tam et al CID 54:1275, 2012; WHO, Global Burden of Diesases estimates, 2004; Lancet Glob Health. 2018 Dec;6(12):e1309-e1318.

Deaths due to diarrhoea in children less than 5 years old

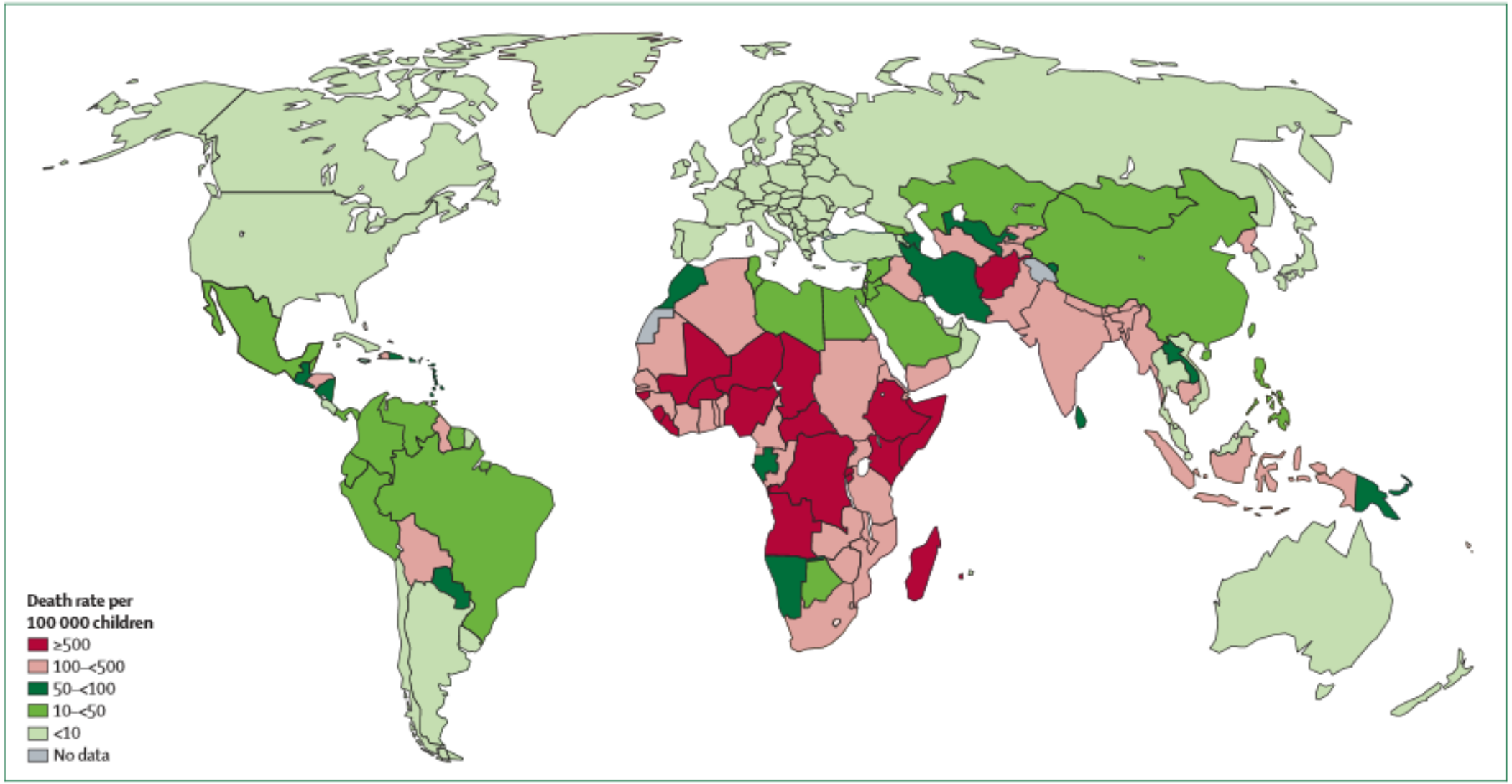


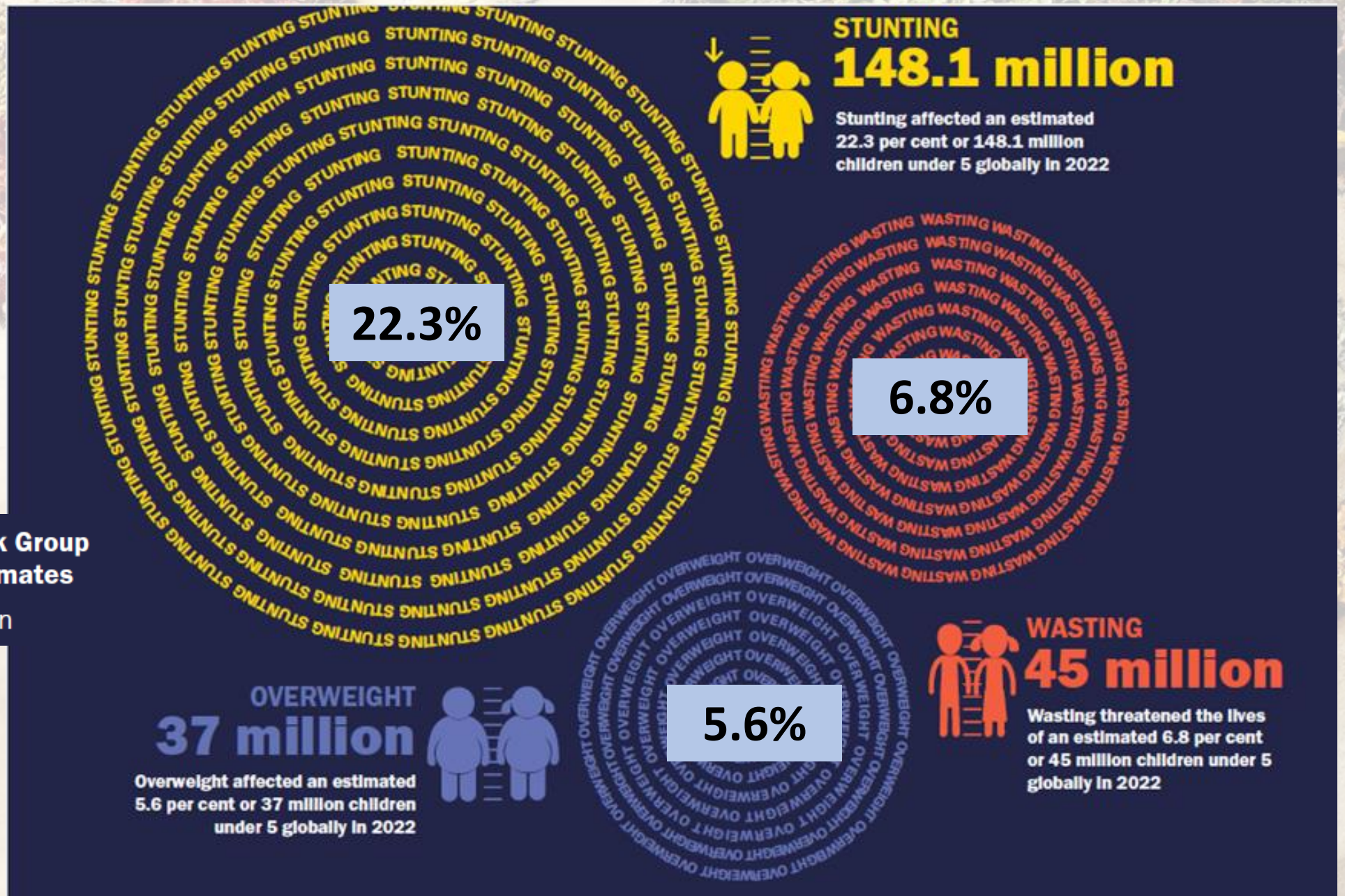
Figure 1: **Deaths due to diarrhoea per 100 000 children younger than 5 years**
Data from reference 1..

Santosham M et al Lancet 376:63, 2010

Background / Malnutrition: the double burden of overnutrition alongside undernutrition

UNICEF / WHO / World Bank Group Joint Child Malnutrition Estimates

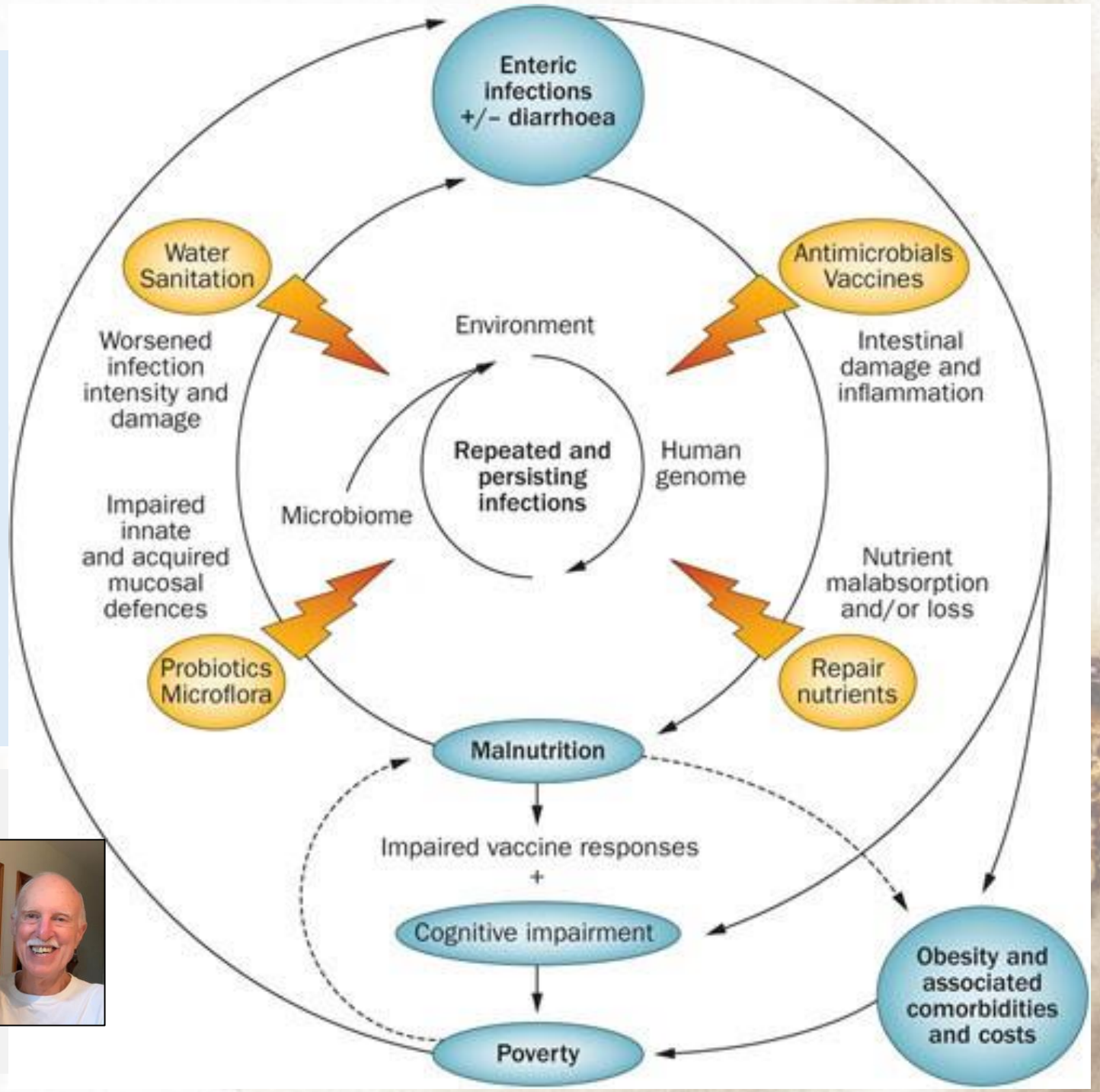
Key findings of the 2023 edition



Environmental enteropathy (EE)

Subclinical disorder that occurs among inhabitants of environments with poor sanitation and hygiene, such as those often found in developing countries. Chronic exposure to fecal pathogens, inflammation and structural changes in the small bowel, which ultimately result in functional changes. EE is marked by increased intestinal permeability, impaired gut immune function, malabsorption, growth faltering, and, potentially, oral vaccine failure, all in a seemingly asymptomatic individual without overt diarrhea.

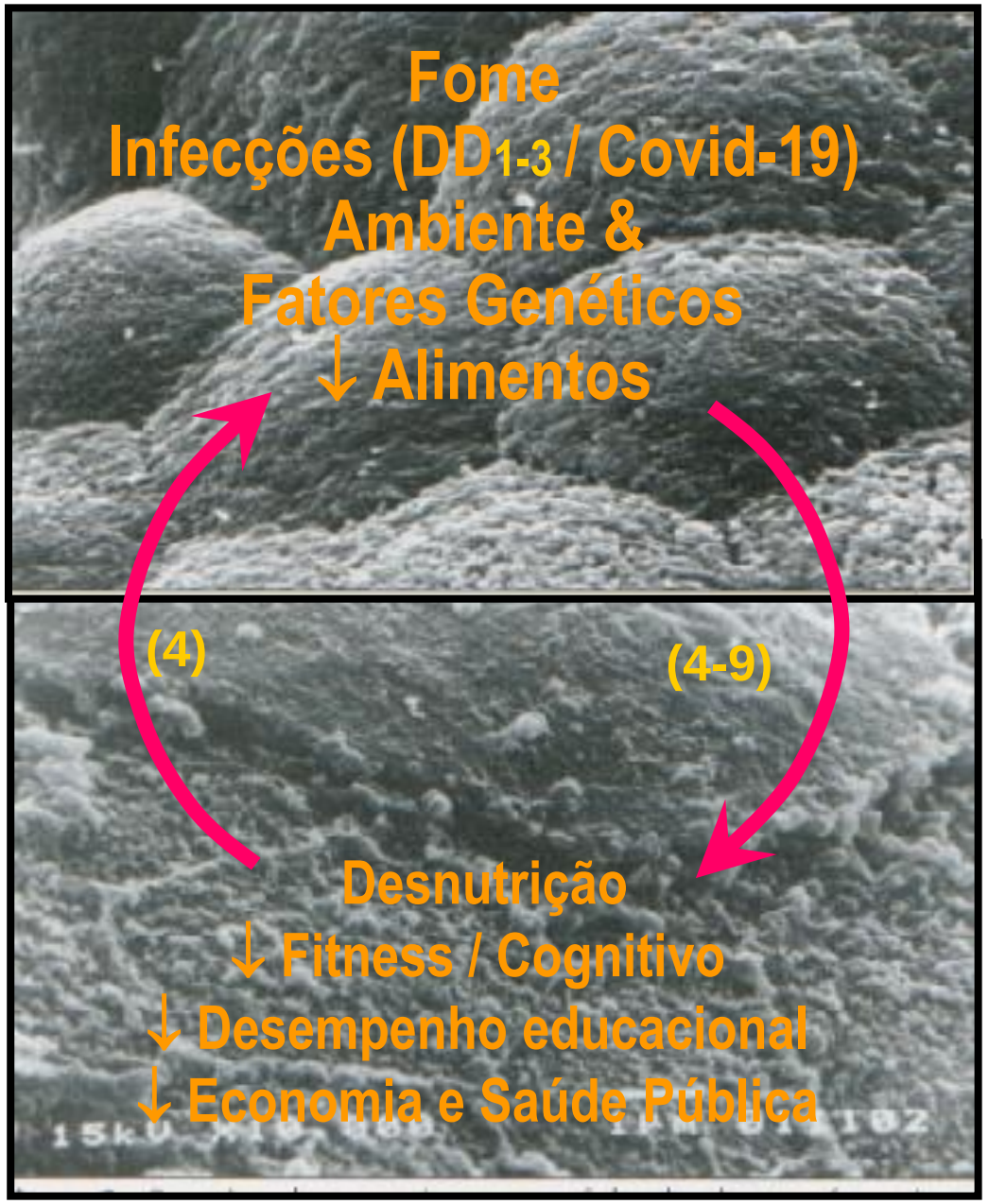
Korpe and Petri, 2012; Guerrant et al. 2013



Triple burden:
Diarrhoea, stunting and chronic disease

Ciclo vicioso de doenças diarreicas, desnutrição e enteropatia

- ✓ **Atrofia de vilosidades**
- ✓ **Alterações nas funções da barreira intestinal**
  - **Área de absorção, danos às células**
  - **Permeabilidade intestinal**



1. Lima et al., JPGN 40:28, 2005.
2. Lima et al. JID 181:1643 2000.
3. Steiner et al., JID 177:88, 1998.
4. Schorling et al., Lancet 335:599, 1990.
5. Guerrant DI et al., AJTMH 61: 707, 1999.
6. Niehaus et al., AJTMH 66:590, 2002.
7. Oria et al., PedRes 57:000, 2005.
8. Guerrant et al., Nut Rev 66:487, 2008.
9. Fagundes_Neto et al., BJMBR 33:1437, 2000.

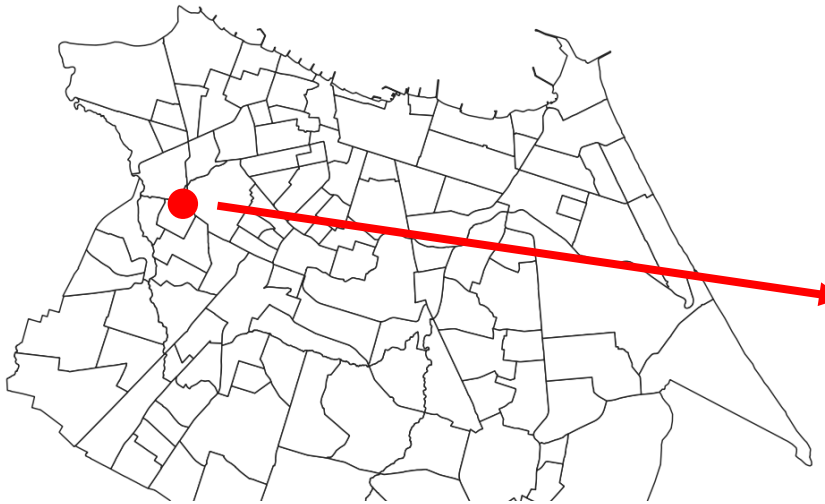
Use of quantitative molecular diagnostic methods to assess the aetiology, burden, and clinical characteristics of diarrhoea in children in low-resource settings: a reanalysis of the MAL-ED cohort study

James A Platts-Mills, Jie Liu*, Elizabeth T Rogawski, Furqan Kabir, Paphavee Lertsethtakarn, Mery Siguas, Shaila S Khan, Ira Praharaj, Arinao Murei, Rosemary Nshama, Buliga Mujaga, Alexandre Havt, Irene A Maciel, Timothy L McMurry, Darwin J Operario, Mami Taniuchi, Jean Gratz, Suzanne E Stroup, James H Roberts, Adil Kalam, Fatima Aziz, Shahida Qureshi, M Ohedul Islam, Pimmada Sakpaisal, Sasikorn Silapong, Pablo P Yori, Revathi Rajendiran, Blossom Benny, Monica McGrath, Benjamin J J McCormick, Jessica C Seidman, Dennis Lang, Michael Gottlieb, Richard L Guerrant, Aldo A M Lima, Jose Paulo Leite, Amidou Samie, Pascal O Bessong, Nicola Page, Ladaporn Bodhidatta, Carl Mason, Sanjaya Shrestha, Ireen Kiwelu, Estomih R Mduma, Najeeha T Iqbal, Zulfiqar A Bhutta, Tahmeed Ahmed, Rashidul Haque, Gagandeep Kang, Margaret N Kosek, Eric R Houpt, and The MAL-ED Network Investigators†*

Lancet Glob Health. 2018; 6:e1309.

November 2014

The Brazilian MAL-ED site



Crowed, unsanitary living at NE of Brazil

Field surveillance team at the urban community.

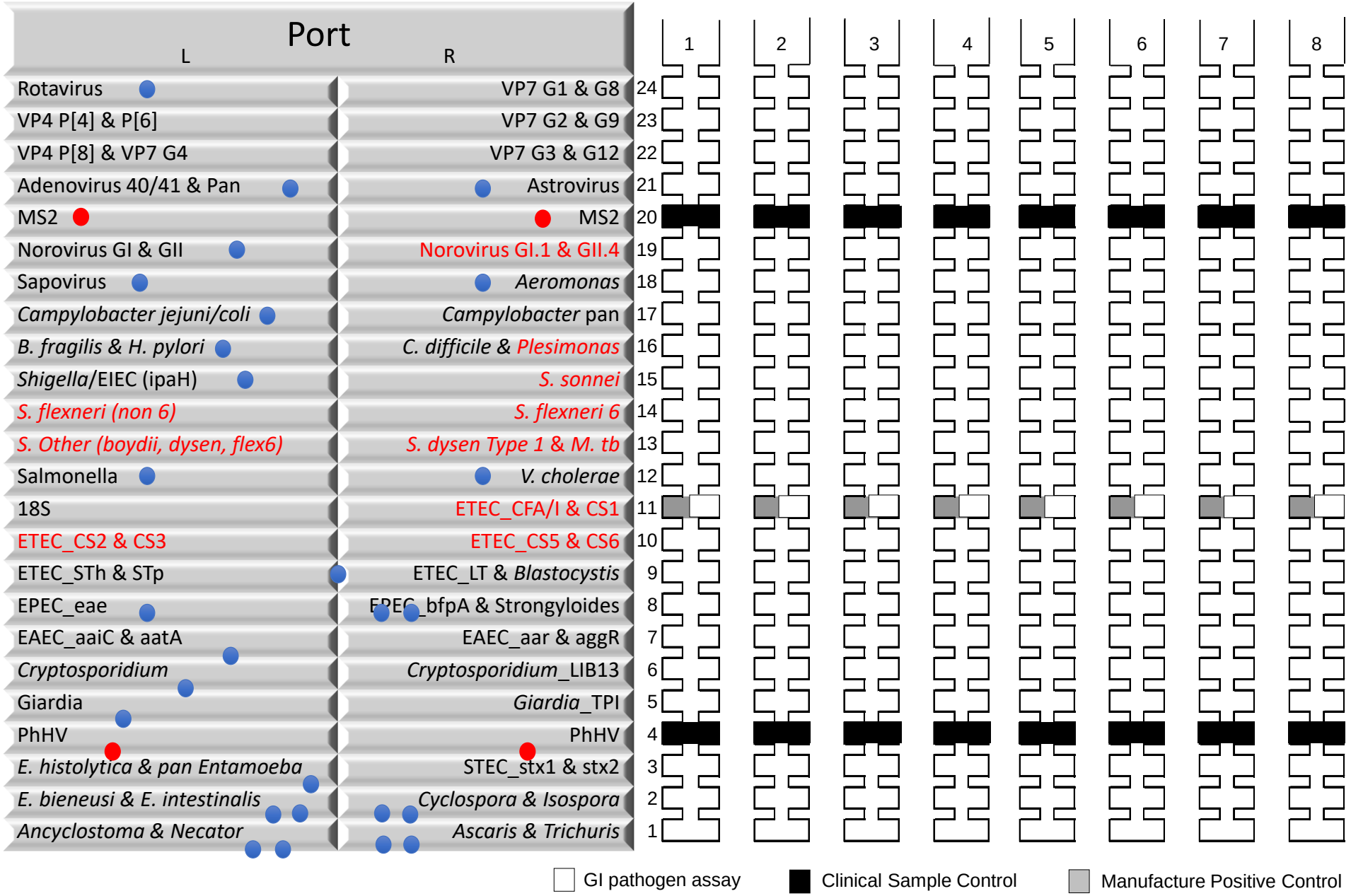
Cronograma do teste, amostra ou coleta de pesquisa, 0-24 meses

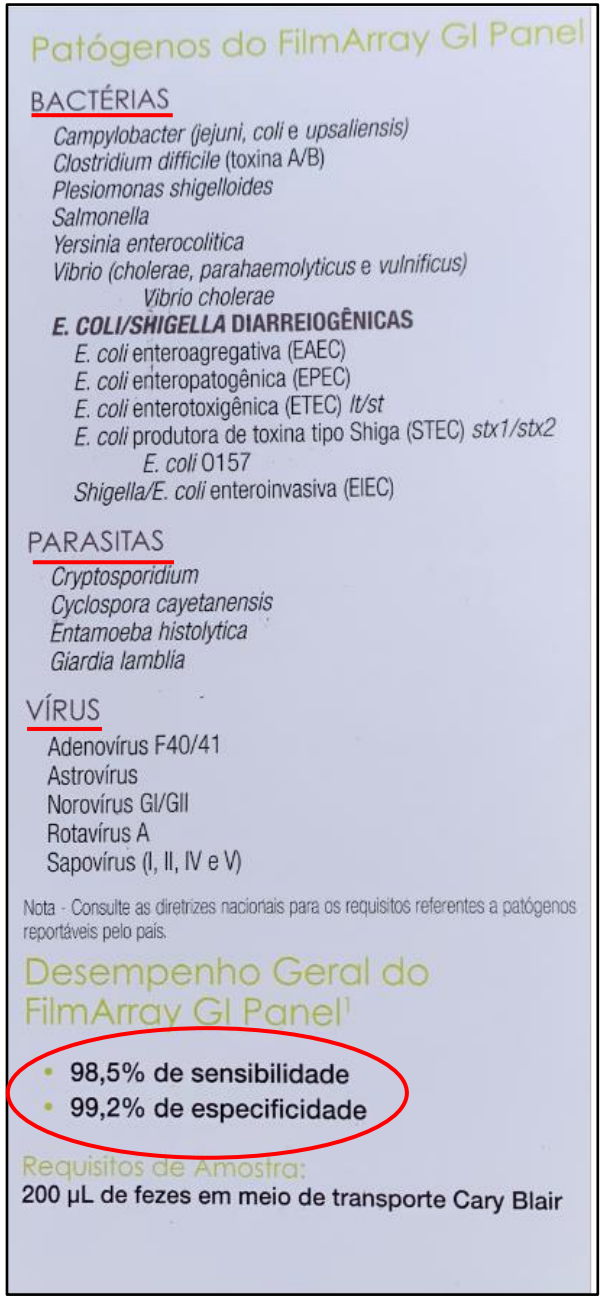
	Months																
	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24
Integridade intestinal				X			X			X				X			
Inflamação intestinal	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Incidência e prevalência de patógenos entéricos	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Incidência de diarreia	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antropometria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nutrição	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Micronutrientes								X						X			
Função cognitiva							X							X			
Avaliação doméstica / materna	X						X							X			
Resposta vacinal								X						X			
Vigilância de outras doenças	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Tipos de amostra
Urina
Fezes
Sangue
Entrevista

MAL-ED

CARTÃO *MALED TAC ARRAY*





FilmArray Gastrointestinal Panel – Biomérieux Co. (Marcy-l'Étoile, France).

LACEN – SESA, CE

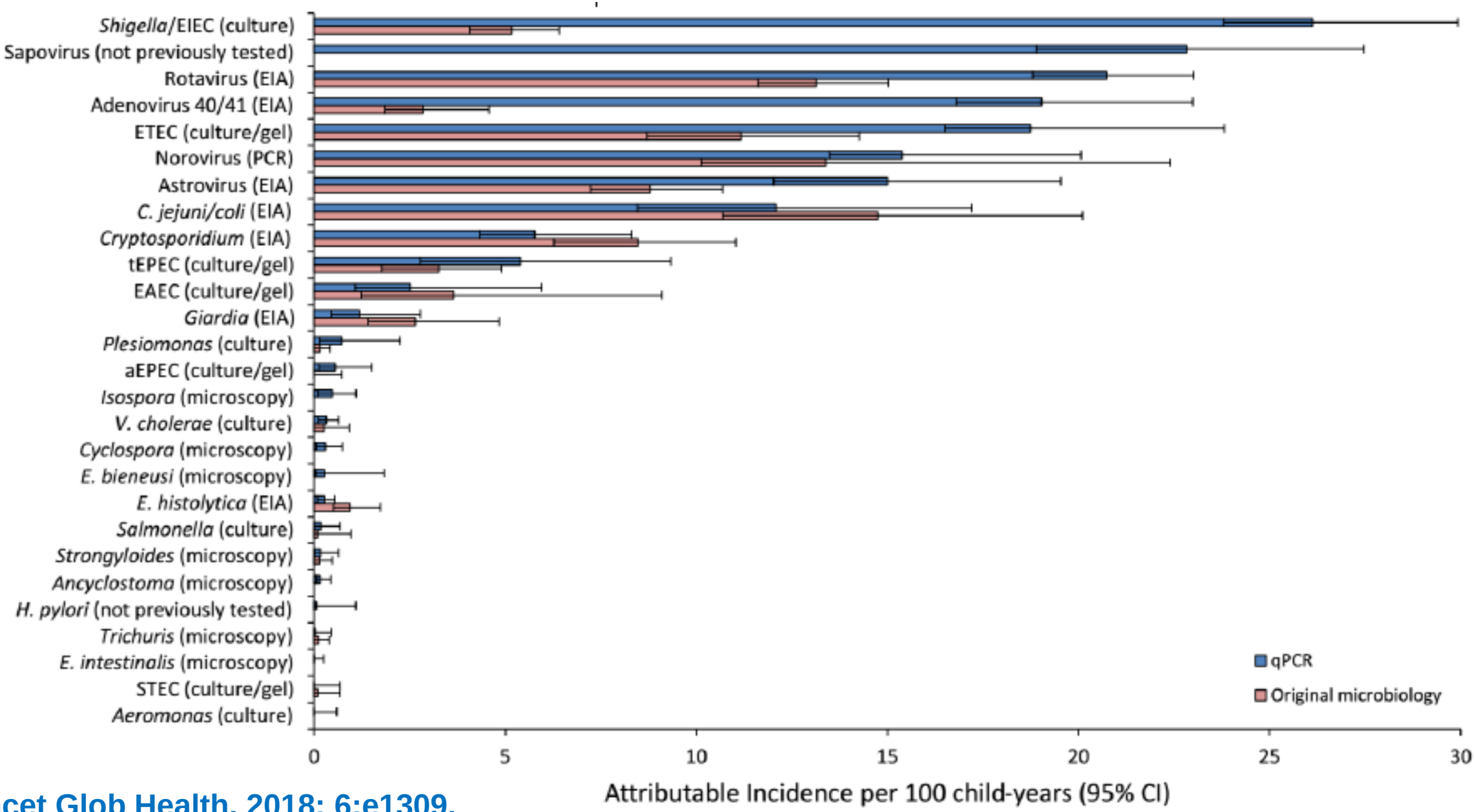
Resultados

Vigilância da diarreia, coleta de amostra e teste de fezes por qPCR na coorte MAL-ED

	Crianças matriculadas	Crianças com acompanhamento até 24 meses	Episódios de diarreia relatados	Fezes diarreicas coletadas de episódios únicos	Fezes diarreicas disponíveis para teste	Fezes diarreicas com resultados válidos*	Fezes de vigilância coletadas	Bancos de vigilância disponíveis para teste	Bancos de vigilância com resultados válidos*	Vigilância de fezes incluídas na análise de etiologia**
Dhaka, Bangladesh	265	210	1520	1438 (94·6%)	1392 (96·8%)	1374 (98·7%)	4528	4353 (96·1%)	4267 (98·0%)	3787
Vellore, India	251	227	960	722 (75·2%)	675 (93·5%)	623 (92·3%)	5058	4924 (97·4%)	4689 (95·2%)	2767
Bhaktapur, Nepal	240	227	1060	955 (90·1%)	911 (95·4%)	899 (98·7%)	5160	5065 (98·2%)	5011 (98·9%)	4457
Naushero Feroze, Pakistan	277	246	3110	2123 (68·3%)	1871 (88·1%)	1789 (95·6%)	4871	4676 (96·0%)	4499 (96·2%)	4518
Venda, South Africa	314	237	295	179 (60·7%)	147 (82·1%)	113 (76·9%)	5399	5160 (95·6%)	4428 (85·8%)	3458
Haydom, Tanzania	262	209	537	178 (33·1%)	164 (92·1%)	155 (94·5%)	4657	4345 (93·3%)	4033 (92·8%)	3833
Fortaleza, Brasil	233	165	168	117 (69·6%)	100 (85·5%)	88 (88·0%)	3242	2994 (92·4%)	2795 (93·4%)	4291
Loreto, Peru	303	194	1742	1642 (94·3%)	1617 (98·5%)	1584 (98·0%)	4301	4236 (98·5%)	4059 (95·8%)	3857
Total	2.145	1.715	9.392	7.354 (78%)	6.877 (94%)	6.625 (96%)	37.216	35.753 (96%)	33.781 (95%)	30.968

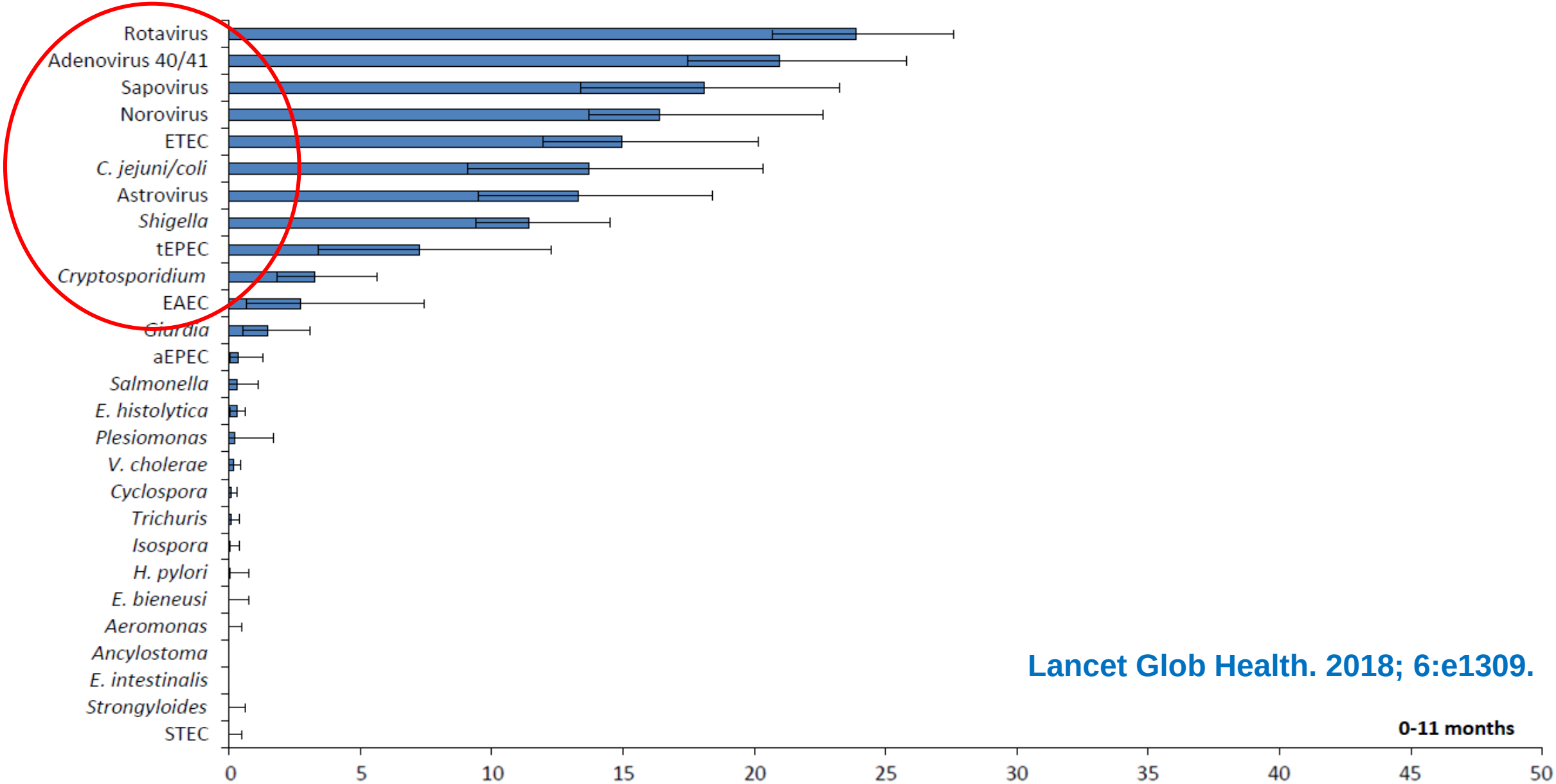
* Resultados válidos necessários para todos os 27 enteropatógenos incluídos na análise de etiologia (Plesiomonas foi incluído em um subconjunto de cartões (5.015/6.877 fezes diarreicas testadas e 32.276/35.753 fezes de vigilância testadas). ** Para a análise etiológica, apenas fezes de vigilância que foram coletadas pelo menos 7 dias antes e depois de qualquer episódio relatado de diarreia foram incluídos.

Comparação entre as estimativas da incidência atribuível global por PCR quantitativo vs. a microbiologia do estudo original



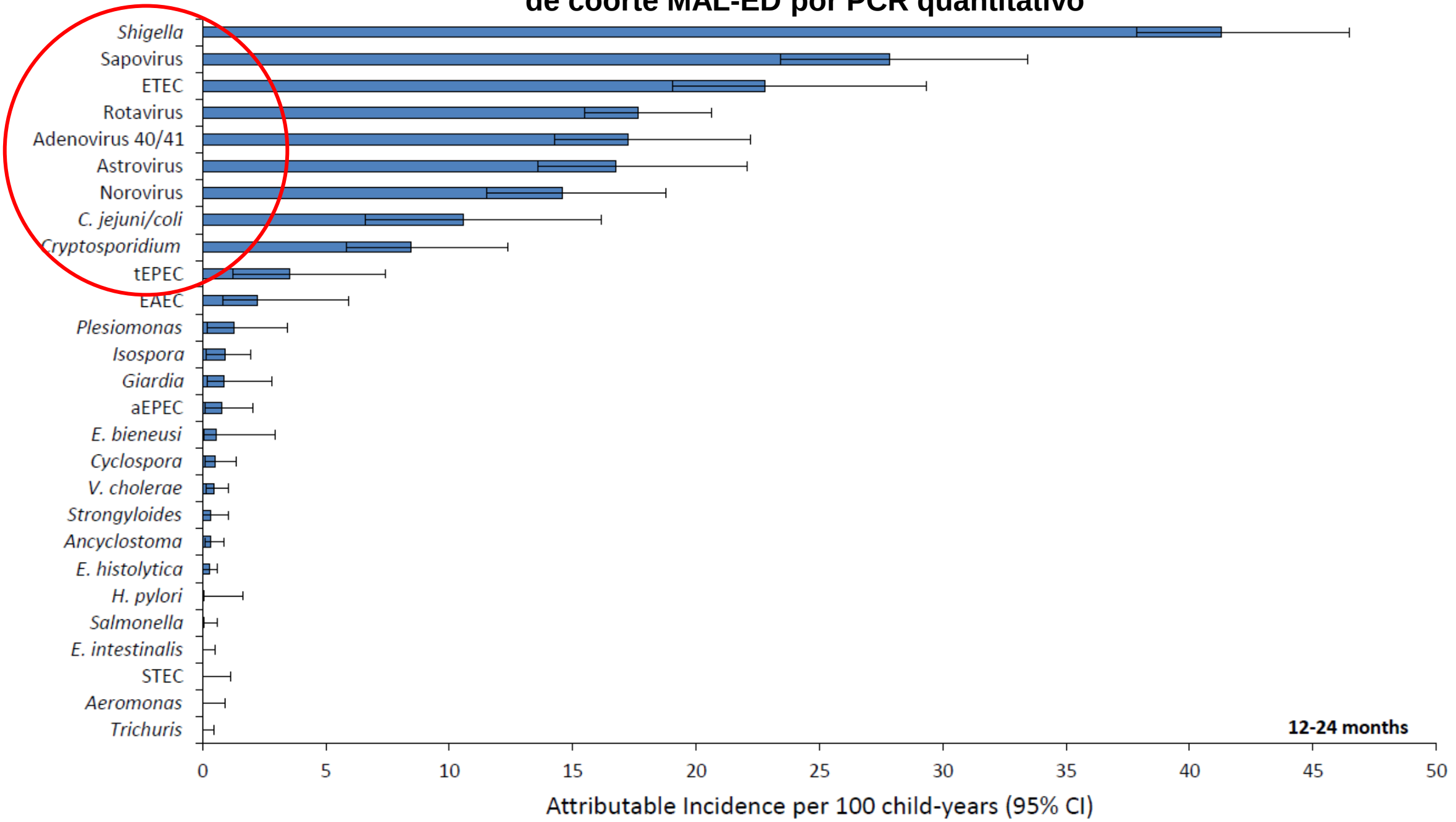
Lancet Glob Health. 2018; 6:e1309.

Incidência atribuível de diarreia específica do patógeno na idade de 0-11 meses no estudo de coorte MAL-ED por PCR quantitativo

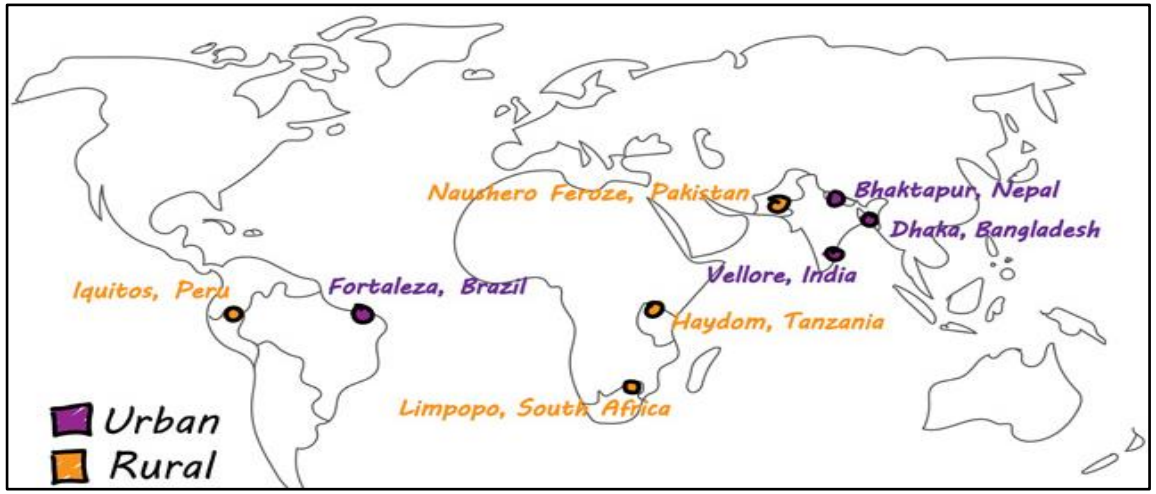


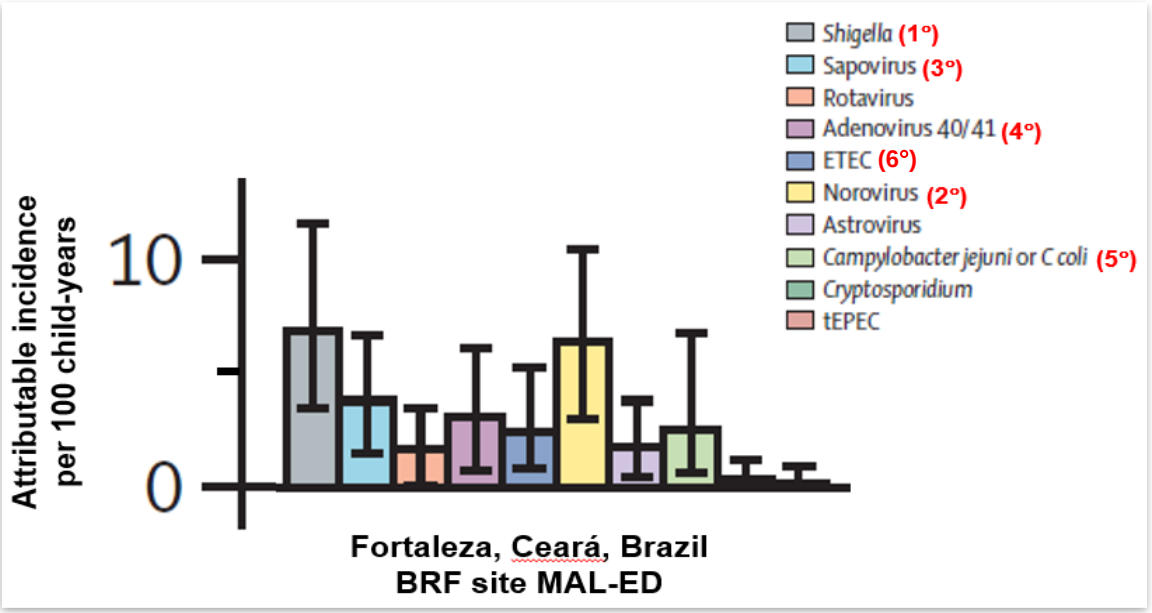
Lancet Glob Health. 2018; 6:e1309.

Incidência atribuível de diarreia específica do patógeno nas idades de 12-24 meses no estudo de coorte MAL-ED por PCR quantitativo



Etiologias de doenças diarreicas no semiárido brasileiro



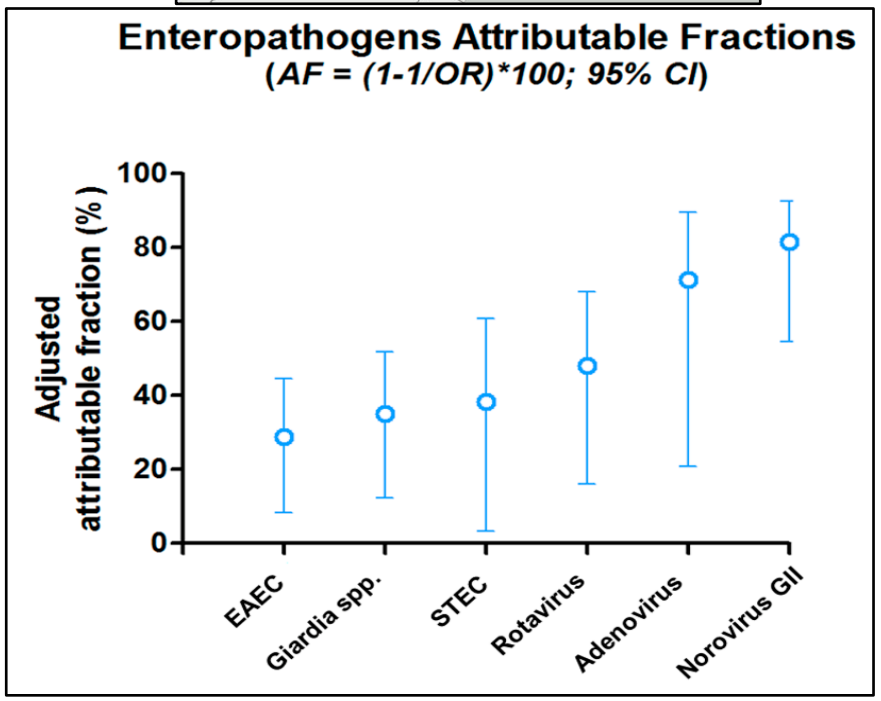


The MAL-ED network Lancet GH 2018; 6:e1309

MAL-ED

MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E INOVAÇÕES

UNIFOR
Ensinando e Aprendendo



Lima et al. PLoS Negl Trop Dis. 2019;13(2):e0007154

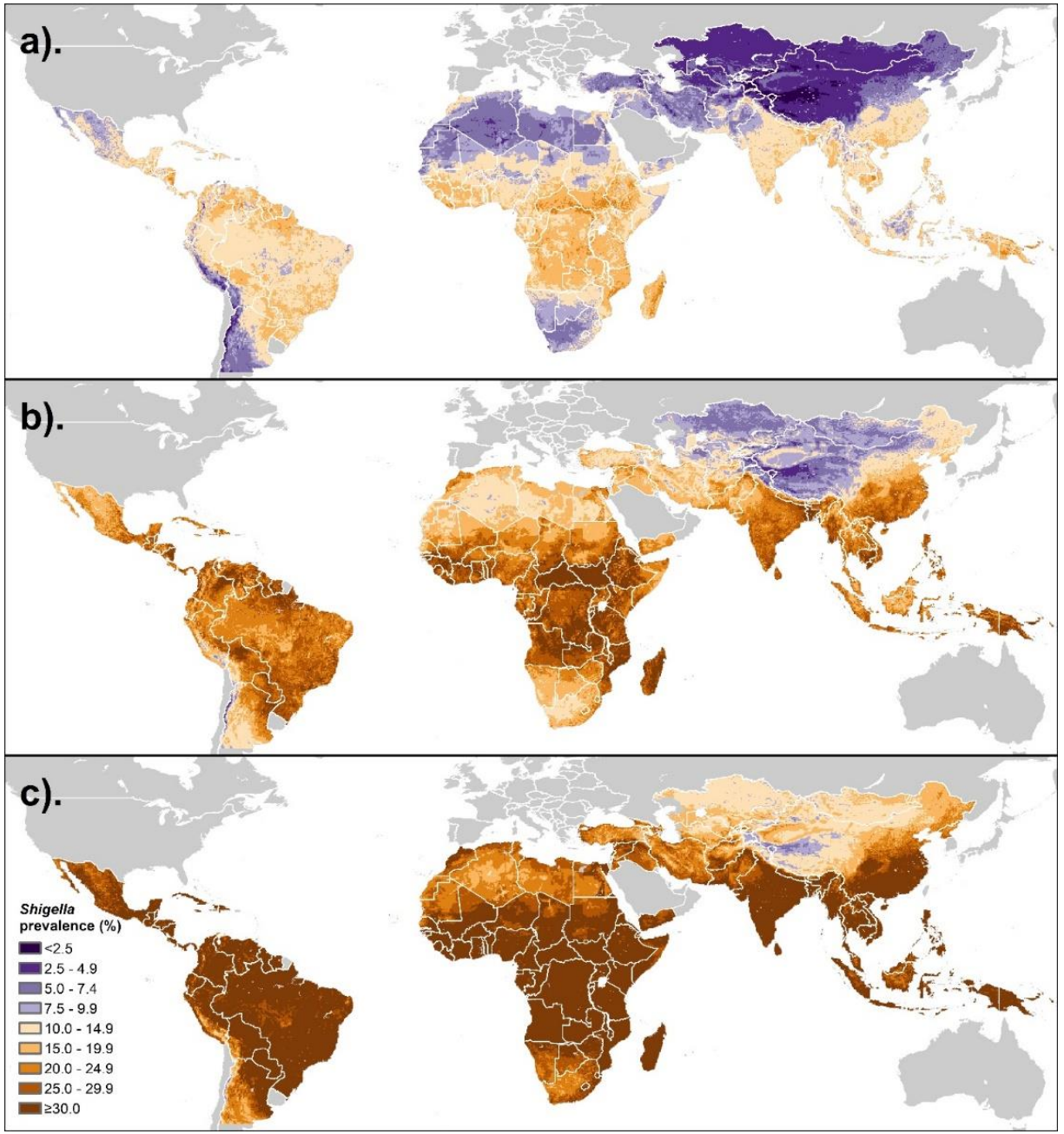
Prevalência anual de infection por *Shigella* spp. e por região geográfica no mundo

Distribuição geográfica da prevalência média anual da infecção por *Shigella* spp. em crianças de 12 a 23 meses:

a) Indivíduos assintomáticos;

b) Casos de diarreia detectados na comunidade;

c) Casos de diarreia com acompanhamento medico.



Badr et al., Lancet Global Health, 11:e373-e384, 2023

Origem do povo nordestino

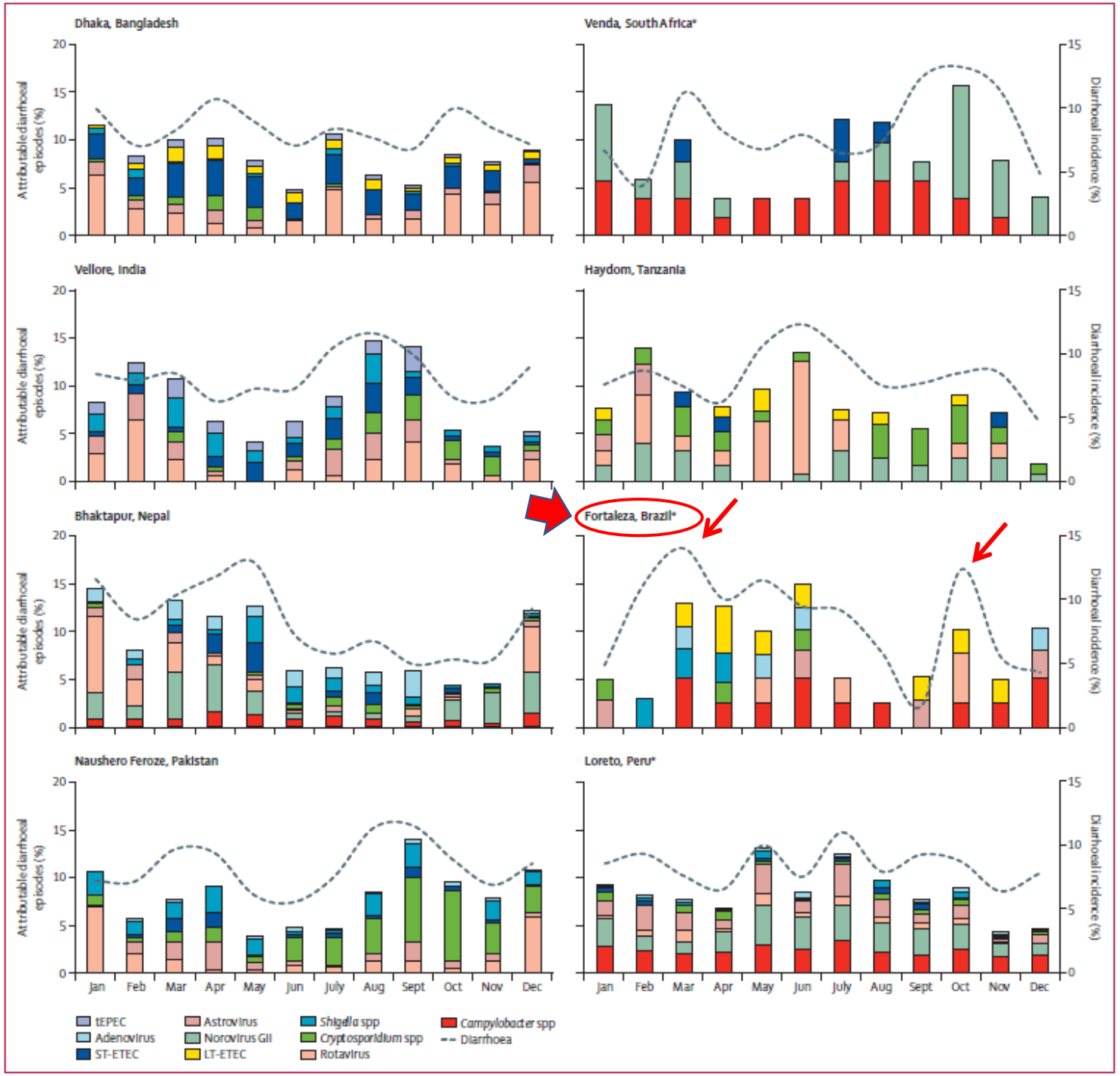
Mychaleckyj et al. Molecular Biol Evol 2017;msw249

Lima et al. PLoS Negl Trop Dis. 2019;13(2):e0007154

Associação entre patógenos individuais e incidência de diarreia sazonal

- ✓ **tEPEC** = *Escherichia coli* enteropatogênica típica;
- ✓ **LT-ETEC** = *E. coli* enterotoxigênica produtora de LT;
- ✓ **ST-ETEC** = *E. coli* enterotoxigênica produtora de ST.
- ✓ O eixo y primário mostra a porcentagem da incidência atribuível total de diarreia para patógenos individuais;
- ✓ O eixo y secundário (e linha pontilhada) mostra a incidência anual de diarreia por mês de calendário.

***** A vacina monovalente do rotavírus foi introduzida no mercado nacional.



Lancet Glob Health 2015; 3: e564–75.

Características clínicas associadas à diarreia específica da etiologia

	Sangue nas fezes(n=315)	Febre (n=2.170)	Duração prolongada (≥ 7 days) (n=1.381)	Desidratação (n=692)	Vômito (n=1.778)	Alta frequência (> 6 fezes moles em 24 horas) (n=1.697)	Severa (score > 6) (n=1.120)
	Prevalence ratio (95% CI)						
Bacteria							
Campylobacter jejuni / coli	4·53 (2·71–7·57)	1·30 (0·98–1·72)	1·19 (0·82–1·73)	0·59 (0·33–1·09)	0·68 (0·48–0·97)	1·08 (0·76–1·54)	0·69 (0·42–1·11)
tEPEC	0·24 (0·07–0·87)	1·19 (0·84–1·70)	1·09 (0·69–1·70)	0·94 (0·48–1·84)	0·99 (0·64–1·52)	0·82 (0·53–1·27)	1·36 (0·84–2·19)
ETEC	0·54 (0·29–1·02)	0·98 (0·77–1·25)	0·96 (0·69–1·34)	1·23 (0·78–1·93)	1·11 (0·87–1·41)	1·21 (0·94–1·57)	1·37 (0·98–1·92)
Shigella	7·39 (5·20–10·49)	1·32 (1·10–1·58)	1·66 (1·31–2·10)	1·55 (1·11–2·16)	0·81 (0·65–1·02)	1·73 (1·40–2·14)	1·28 (0·96–1·70)
Viruses							
Adenovirus 40/41	1·06 (0·55–2·06)	1·22 (0·92–1·62)	0·87 (0·58–1·29)	2·14 (1·24–3·69)	1·29 (0·99–1·68)	0·95 (0·70–1·29)	1·36 (0·91–2·01)
Astrovirus	0·24 (0·09–0·62)	0·92 (0·71–1·20)	0·78 (0·55–1·11)	1·38 (0·90–2·12)	1·10 (0·83–1·46)	1·23 (0·92–1·65)	1·09 (0·75–1·58)
Norovirus	0·45 (0·20–0·99)	0·79 (0·58–1·07)	0·66 (0·44–1·00)	1·59 (0·95–2·67)	1·81 (1·36–2·42)	0·86 (0·61–1·23)	1·38 (0·91–2·09)
Rotavirus	0·46 (0·24–0·89)	1·47 (1·24–1·74)	0·79 (0·60–1·04)	3·23 (2·44–4·28)	2·31 (1·97–2·72)	1·66 (1·38–1·99)	2·46 (1·99–3·06)
Sapovirus	0·39 (0·21–0·74)	0·84 (0·68–1·05)	0·83 (0·62–1·11)	1·21 (0·84–1·74)	1·51 (1·22–1·88)	1·01 (0·79–1·29)	1·12 (0·83–1·53)
Protozoa							
Cryptosporidium	0·25 (0·06–1·00)	1·26 (0·87–1·84)	1·50 (0·93–2·43)	1·57 (0·83–2·95)	1·27 (0·82–1·96)	1·06 (0·64–1·75)	1·29 (0·71–2·33)
No aetiology identified	0·69 (0·50–0·96)	0·84 (0·75–0·96)	1·03 (0·88–1·21)	0·48 (0·38–0·60)	0·61 (0·53–0·70)	0·72 (0·62–0·83)	0·59 (0·49–0·70)

A análise inclui todos os episódios de diarreia com resultados completos e válidos de qPCR e características clínicas para esses dez patógenos (n = 6.676). tEPEC = *E. coli* enteropatogênica típica. ETEC = *E. coli* enterotoxigênica.

The MAL-ED network Lancet GH 2018; 6:e1309

Resumo I

1. O diagnóstico molecular quantitativo melhorou as estimativas de cargas específicas de patógenos de diarreia infantil no ambiente comunitário;
2. As causas virais predominaram, incluindo uma carga substancial de sapovírus; no entanto, *Shigella* spp. teve a carga geral mais alta, com alta incidência no segundo ano de vida;
3. Esses dados podem melhorar o controle da diarreia nesses locais de poucos recursos.

Lancet Glob Health. 2018; 6:e1309

Resumo II

4. **Menos de um em cada cinco episódios de shigelose foi acompanhado por sangue nas fezes. Se a *Shigella* não disentérica justificar a terapia com antibióticos, pode ser possível alavancar as características clínicas para melhorar as diretrizes para o manejo sindrômico da diarreia infantil nesses locais.**

5. **Alguns enteropatógenos estão associados principalmente a déficits de crescimento (por exemplo, EAEC e Giardia), enquanto outros estão associados a diarréia e déficits de crescimento (por exemplo, *Shigella*, *Campylobacter* e Norovirus GII);**

6. **Outros estão associados principalmente à diarreia (por exemplo, Rotavírus, Sapovírus, Adenovírus e *Escherichia coli* enterotoxigênica).**

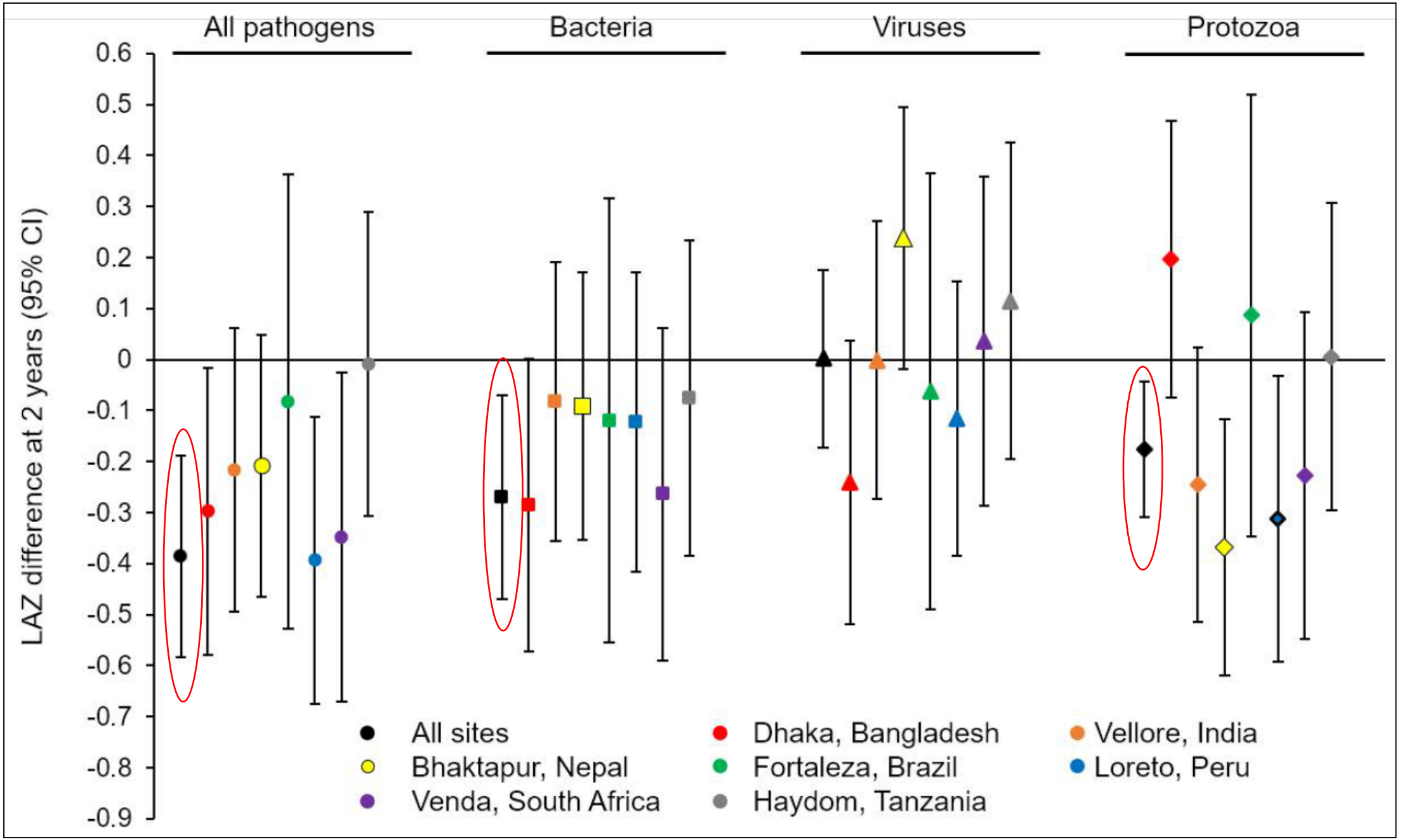
Lancet Glob Health. 2018; 6:e1309

Use of quantitative molecular diagnostic methods to investigate the effect of enteropathogen infections on linear growth in children in low-resource settings: longitudinal analysis of results from the MAL-ED cohort study

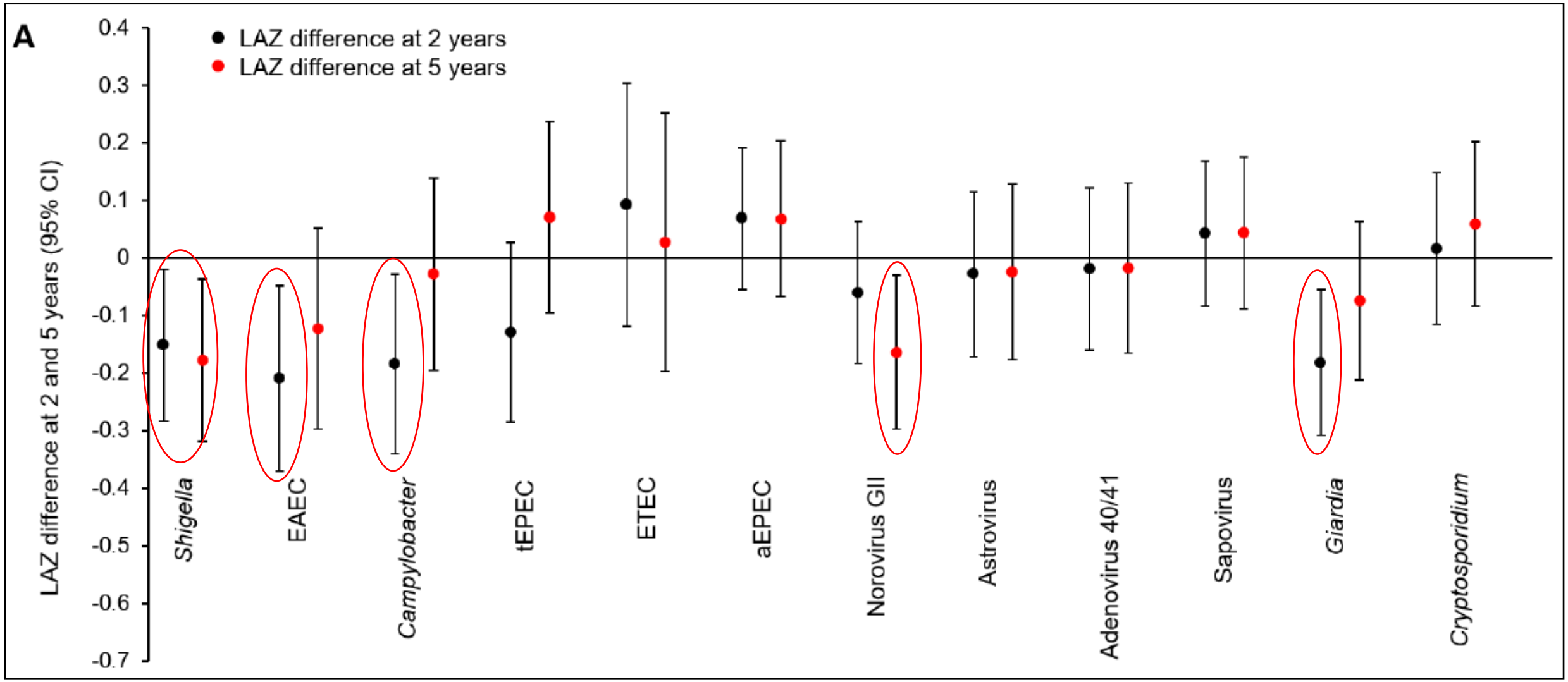
Elizabeth T Rogawski, Jie Liu*, James A Platts-Mills, Furqan Kabir, Paphavee Lertsethtakarn, Mery Siguas, Shaila S Khan, Ira Praharaj, Arinao Murei, Rosemary Nshama, Buliga Mujaga, Alexandre Havt, Irene A Maciel, Darwin J Operario, Mami Taniuchi, Jean Gratz, Suzanne E Stroup, James H Roberts, Adil Kalam, Fatima Aziz, Shahida Qureshi, M Ohedul Islam, Pimmada Sakpaisal, Sasikorn Silapong, Pablo P Yori, Revathi Rajendiran, Blossom Benny, Monica McGrath, Jessica C Seidman, Dennis Lang, Michael Gottlieb, Richard L Guerrant, Aldo A M Lima, Jose Paulo Leite, Amidou Samie, Pascal O Bessong, Nicola Page, Ladaporn Bodhidatta, Carl Mason, Sanjaya Shrestha, Ireen Kiwelu, Estomih R Mduma, Najeeha T Iqbal, Zulfiqar A Bhutta, Tahmeed Ahmed, Rashidul Haque, Gagandeep Kang, Margaret N Kosek, Eric R Houpt, and The MAL-ED Network Investigators†*

Lancet Glob Health. 2018; 6:e1319.

Efeitos específicos do local de infecções combinadas de enteropatógeno aos 2 anos de idade



Efeito de infecções específicas por enteropatógenos na altura aos 2 e 5 anos de vida



Difference and 95% CI in length-for-age z-score (LAZ) at 2 (back circles) and 5 (red circles) years of age between high (90th percentile) and low (10th percentile) pathogen prevalence.

Resumo III

7. **A infecção subclínica e a quantidade de patógenos, particularmente *Shigella*, *Escherichia coli* enteroagregativa, *Campylobacter* e *Giardia*, tiveram uma associação negativa substancial com o crescimento linear, que foi sustentado durante os primeiros 2 anos de vida e, em alguns casos, até 5 anos;**

8. **Reduzir com sucesso a exposição a certos patógenos pode reduzir o nanismo global.**

Lancet Glob Health. 2018; 6:e1319

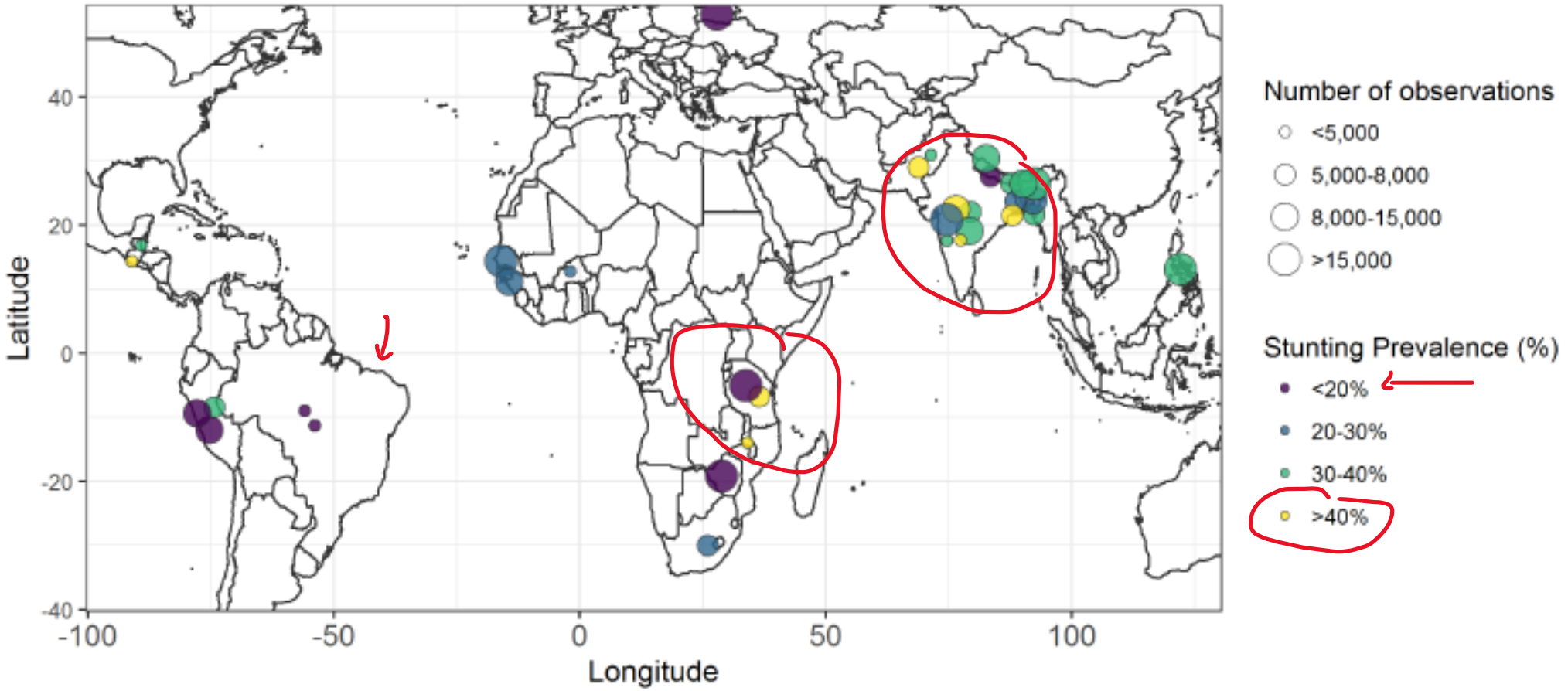
Article

Nature Sep. 2023 - https://doi.org/10.1038/s41586-023-06418-5.

Early-childhood linear growth faltering in low- and middle-income countries

Stunting prevalence by geographic location of ki cohorts

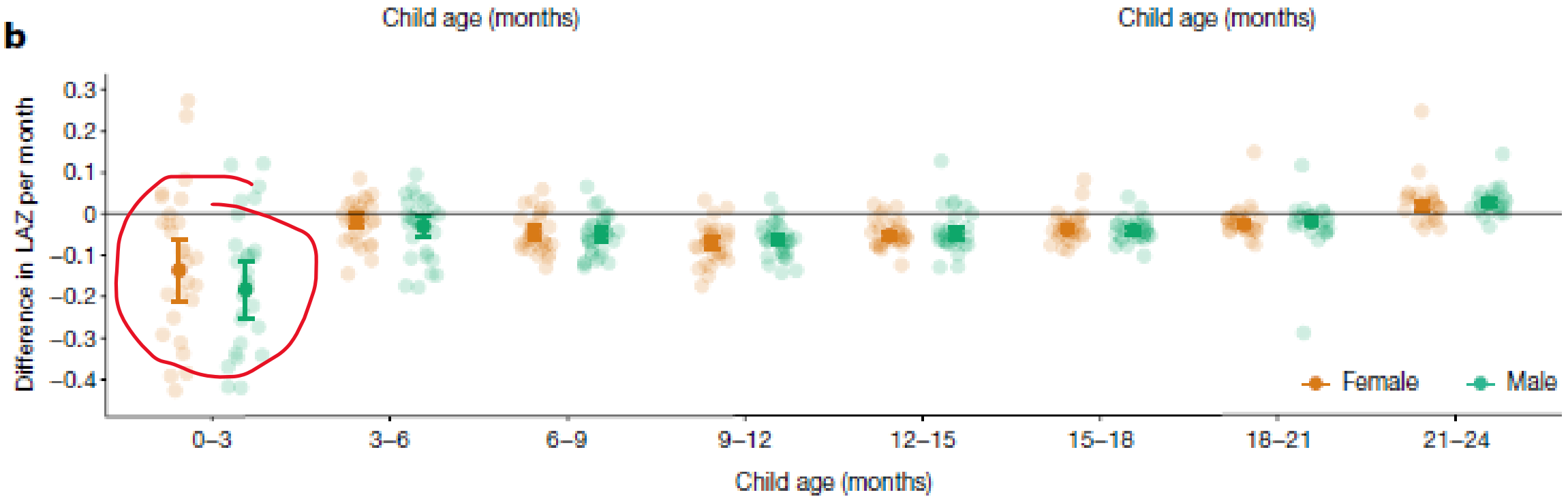
N = 32 cohorts, N = 52,640 children (0-24 months) in LMICs



Article

Nature Sep. 2023 - https://doi.org/10.1038/s41586-023-06418-5.

Early-childhood linear growth faltering in low- and middle-income countries

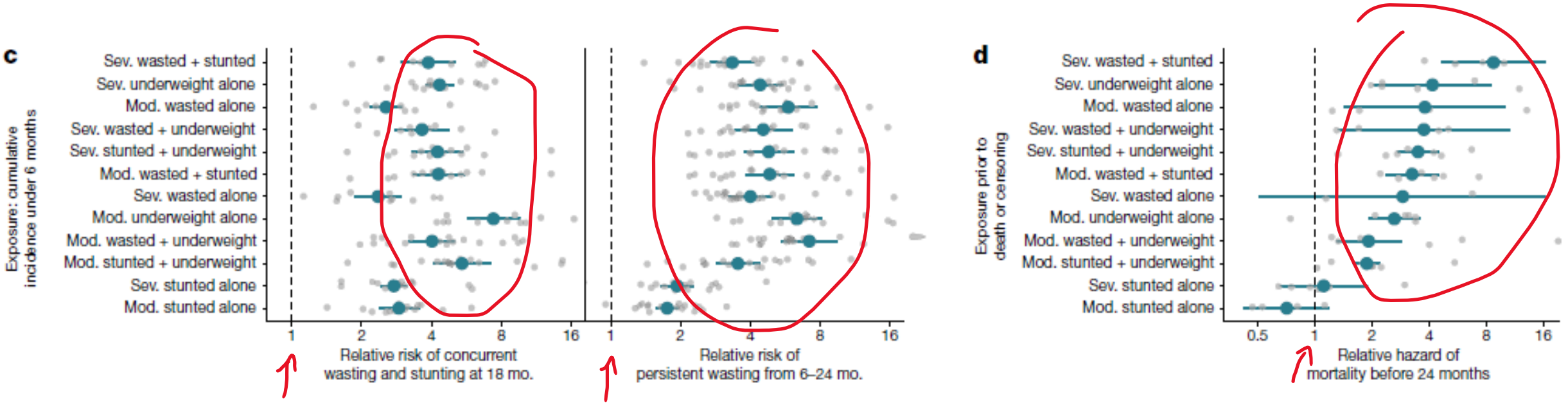


Key messages: Improving children's linear growth will require life course interventions for women of childbearing age and a greater emphasis on interventions for children under 6 months of age.

Article

Nature Sep. 2023 - https://doi.org/10.1038/s41586-023-06501-x.

Causes and consequences of child growth faltering in low-resource settings

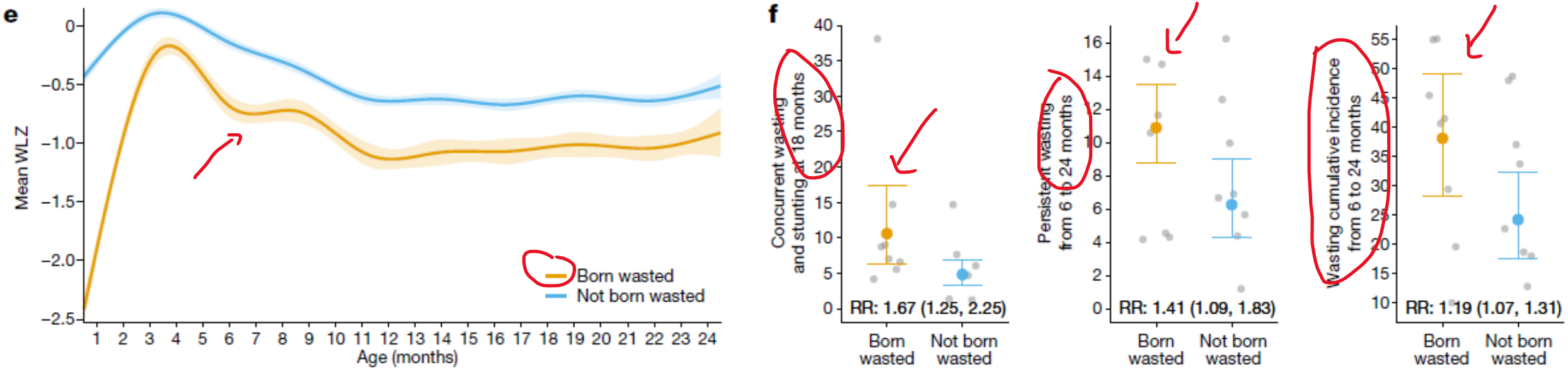


Key messages: Focus on pre-conception and pregnancy as a key opportunity for new preventive interventions.

Article

Nature Sep. 2023 - https://doi.org/10.1038/s41586-023-06480-z.

Child wasting and concurrent stunting in low- and middle-income countries



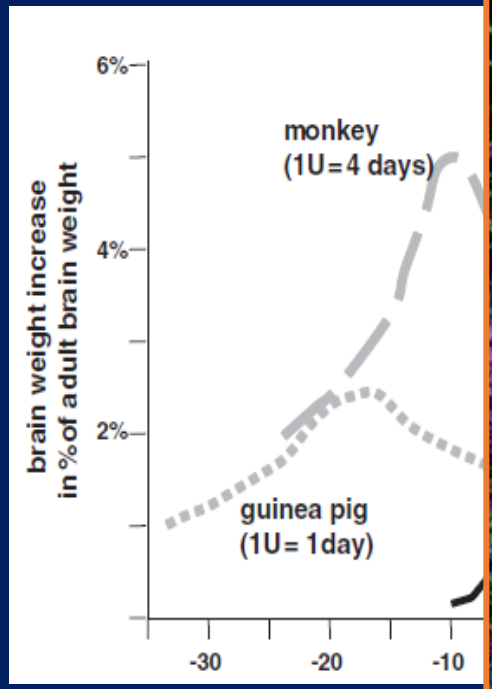
Key messages: Results show the importance of establishing interventions to prevent wasting from birth to the age of 6 months. Improved maternal nutrition, to complement current programmes that focus on children aged 6–59 months.

Early childhood cognitive development is affected by interactions among illness, diet, enteropathogens and the home environment: findings from the MAL-ED birth cohort study

MAL-ED Network Investigators

BMJ Glob Health 2018;3:e000752

O crescimento e desenvolvimento do cérebro humano ocorre nos primeiros 2 anos de vida



Mapa do cérebro na plataforma Neroglancer mostra neurônios e sinapses (Pac. 45 anos) – 1 mm^3

Cérebro do *Homo sapiens* 60 Kg: 1200 – 1400 cm^3

Corel, JL.
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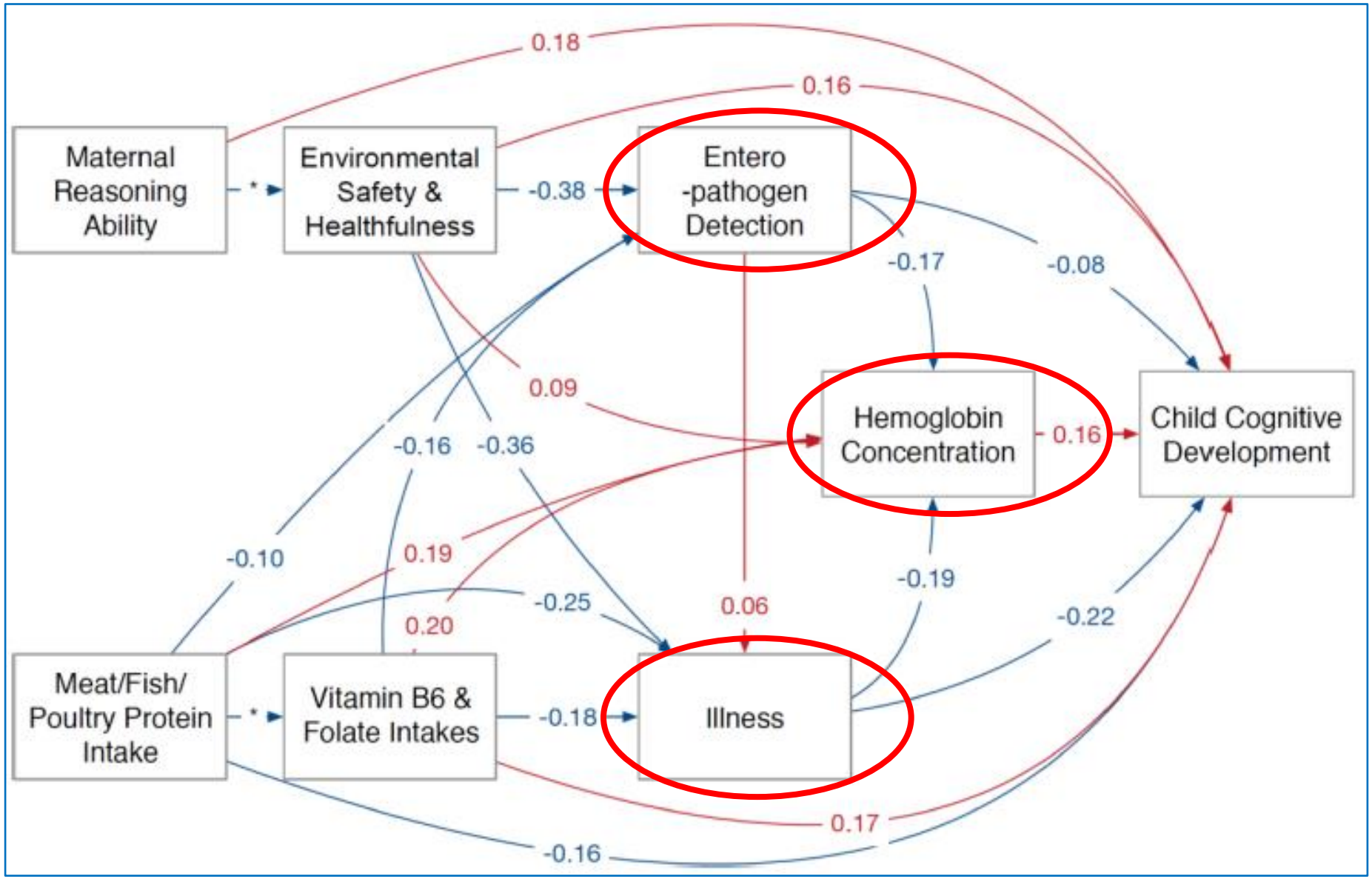
neuronais ou "perd

Escalas Bayley de Desenvolvimento Infantil

- ✓ **A Escala Bayley de Desenvolvimento Infantil (Bayley-III)** é uma série padrão de medições originalmente desenvolvida pela psicóloga **Nancy Bayley** usada principalmente para avaliar **o desenvolvimento de bebês e crianças pequenas, com idades de 1 a 42 meses** (**MAL-ED: 15 e 24 meses**);
- ✓ O **Bayley-III** tem três subtestes principais;
  - **Escala cognitiva,** que inclui itens como atenção a objetos familiares e desconhecidos, procura de um objeto caído e brincadeira de faz de conta;
  - **Escala de linguagem,** que explora a linguagem de compreensão e expressão, por exemplo, reconhecimento de objetos e pessoas, seguindo orientações e nomeando objetos e imagens; e
  - **Escala motora,** que avalia as habilidades motoras grossas e finas, como agarrar, sentar, empilhar blocos e subir escadas.

A detecção de enteropatógenos em fezes diarreicas e não diarreicas está negativamente relacionada ao desenvolvimento cognitivo da criança. Os efeitos dos enteropatógenos no desenvolvimento cognitivo são mediados pelas doenças e pelas concentrações de hemoglobina.



BMJ Glob Health 2018;3:e000752

Resumo IV

9. A detecção de enteropatógenos em fezes diarreicas e não diarreicas está negativamente relacionada ao desenvolvimento cognitivo da criança;
10. Os efeitos dos enteropatógenos no desenvolvimento cognitivo são mediados pelas doenças e pelas concentrações de hemoglobina;
11. O direcionamento de intervenções para melhorar o desenvolvimento cognitivo deve incluir um foco na redução de doenças e na melhoria da área de recreação e ingestão alimentar da criança.

BMJ Glob Health 2018;3:e000752

Microbiota agents for malnourished children

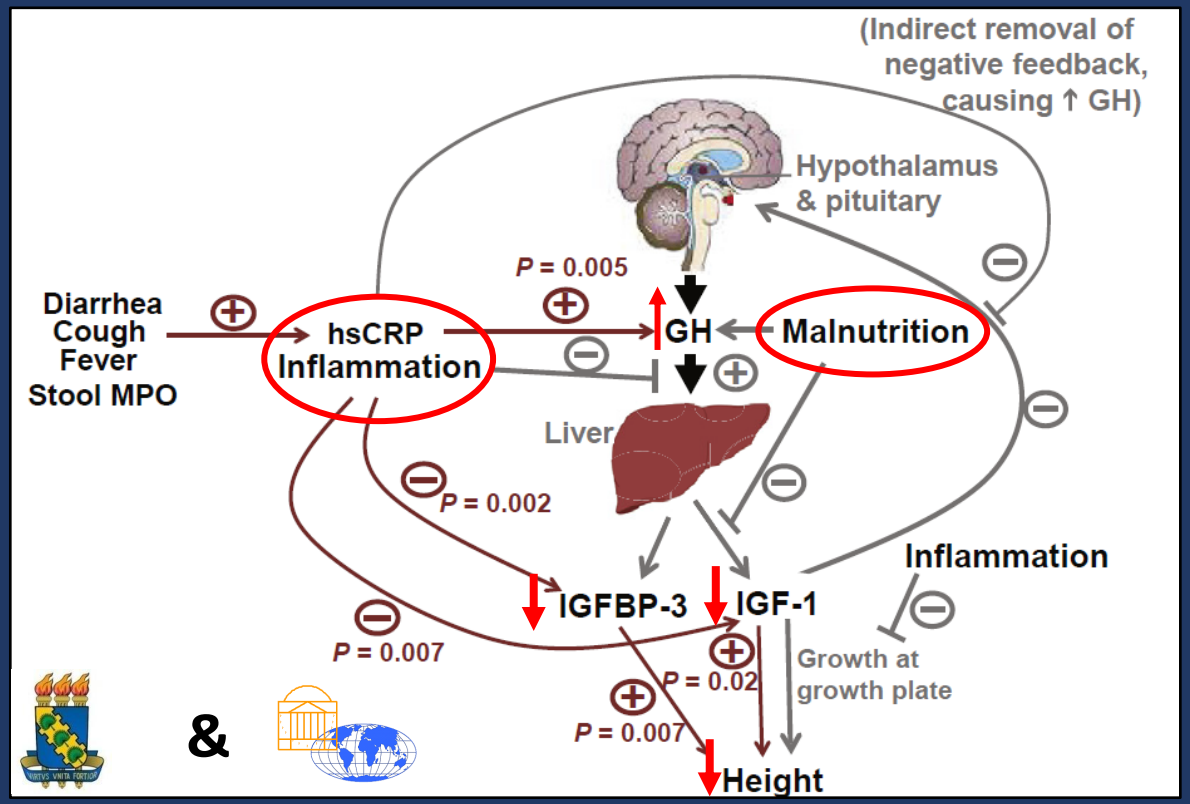
Disease	Relevant microbiota agents	Study type and design	Outcome and efficacy rate	Reference
Gut microbiota that prevent growth in malnourished children	*Faecalibacterium prausnitzii*, *Ruminococcus gnavus*, *Clostridium nexile*, *Clostridium symbiosum*, and *Dorea formicigenerans*	Malawian birth cohort (0-28 months) and gnotobiotic mice experiments.	Unlike microbiota from healthy children, immature microbiota transmit impaired growth, altered bone morphology, and metabolic abnormalities in the muscle, liver, and brain to recipient gnotobiotic mice.	**Blanton et al., 2016**
Dysbiosis in malnourished children	*Bifidobacterium longum*, *Bifidobacterium*, *Streptococcus gallolyticus*, *Lactobacillus ruminis*, and *Escherichia coli* (5/15 microorganisms)	Bangladesh birth cohort (1-60 months)	The results revealed an "ecogroup" of 15 covarying bacterial taxa that provide a concise description of microbiota development in healthy children.	**Raman et al., 2019**

Human microbiome project: >1.000 species different distributed in 50 different *Filos*.
Filos predominant on health intestinal microbiome: (1) *Firmicutes* (genero: *Lactobacillus* and *Clostridium*); (2) *Bacteroidetes* (*Bacteroides* and *Provetella*); (3) *Actinobacteria* (family *Bifidobacteriaceae*); and (4) *Proteobacterias* (family *Enterobacteriaceae*).

Lloy-Price et al., Nature 2017, 61-66

Growth hormone, inflammation and linear growth in malnourished children attended at IPREDE in Fortaleza, CE, Brazil

- DeBoer et al Nutrition 33:248-253, 2017
- Lima et al Pediatr Infect Dis J 36:1177, 2017
- Guerrant et al PLoS ONE 11:e0158772, 2016



Crianças e equipe do IPREDE em Fortaleza, CE.

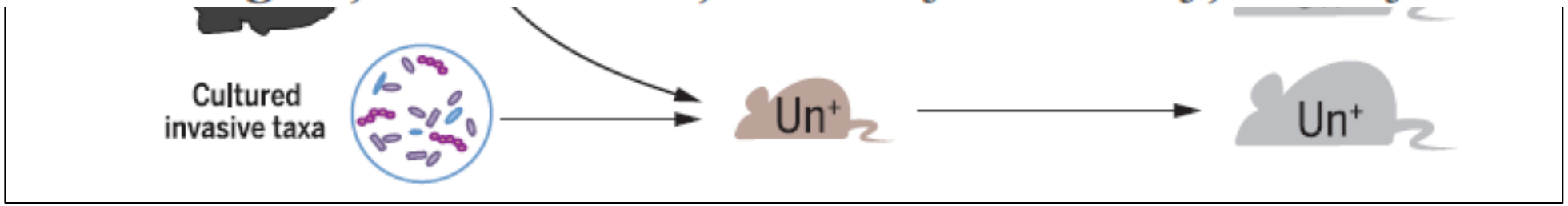
RESEARCH ARTICLE

Science. 2016 Feb 19;351(6275).

MICROBIOME

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children

Laura V. Blanton,[1] Mark R. Charbonneau,[1] Tarek Salih,[1] Michael J. Barratt,[1] Siddarth Venkatesh,[1] Olga Ilkaveya,[2] Sathish Subramanian,[1] Mark J. Manary,[3,4] Indi Trehan,[3,5] Josh M. Jorgensen,[6] Yue-mei Fan,[7] Bernard Henrissat,[8,9] Semen A. Leyn,[10] Dmitry A. Rodionov,[10,11] Andrei L. Osterman,[11] Kenneth M. Maleta,[4] Christopher B. Newgard,[2,12] Per Ashorn,[7,13] Kathryn G. Dewey,[6] Jeffrey I. Gordon[1]*



A Spars RESEARCH ARTICLE SUMMARY hy and

MICROBIOME

A Sparse Co-Varying Unit of the Human Gut Microbiota that Describes Healthy and Impaired Community Development

Arjun S. Raman, Jeanette L. Gehrig, Sathish Subramanian, Siddarth Venkatesh, Gagandeep Kang, Pascal O. Bessong, Aldo A.M. Lima, Margaret Kosek, William A. Petri Jr., Sayeeda Huq, Ishita Mostafa, Munirul Islam, Mustafa Mahfuz, Rashidul Haque, Tahmeed Ahmed, Michael J. Barratt, and Jeffrey I. Gordon*

Science. 2019; 365(6449):eaau4735

Profa. Bruna L. L. Maciel
UFRN-Natal, RGN

The Journal of Nutrition
Community and International Nutrition

J Nutr 2021;151:170–178.

See corresponding commentary on pa

Higher Energy and Zinc Intakes from Complementary Feeding Are Associated with Decreased Risk of Undernutrition in Children from South America, Africa, and Asia

Bruna LL Maciel,[1] Priscila N Costa,[1] José Q Filho,[2] Samilly A Ribeiro,[2] Francisco AP Rodrigues,[2] Alberto M Soares,[2] Francisco S Júnior,[2] Ramya Ambikapathi,[3] Elizabeth TR McQuade,[4] Margaret Kosek,[5] Tahmeed Ahmed,[6] Pascal Bessong,[7] Gangadeep Kang,[8] Sanjaya Shresthra,[9] Estomih Mduma,[10] Eliwaza Bayo,[10] Richard L Guerrant,[11] Laura E Caulfield,[12] and Aldo AM Lima[2] for the MAL-ED Network Investigators

Maciel et al. J Nutr 2020;151(1):170–8.

The Journal of Nutrition
Community and International Nutrition
J Nutr 2021;151:170–178.

See corresponding commentary on p

Higher Energy and Zinc Intakes from Complementary Feeding Are Associated with Decreased Risk of Undernutrition in Children from South America, Africa, and Asia

Bruna LL Maciel,[1] Priscila N Costa,[1] José Q Filho,[2] Samilly A Ribeiro,[2] Francisco AP Rodrigues,[2] Alberto M Soares,[2] Francisco S Júnior,[2] Ramya Ambikapathi,[3] Elizabeth TR McQuade,[4] Margaret Kosek,[5] Tahmeed Ahmed,[6] Pascal Bessong,[7] Gangadeep Kang,[8] Sanjaya Shresthra,[9] Estomih Mduma,[10] Eliwaza Bayo,[10] Richard L Guerrant,[11] Laura E Caulfield,[12] and Aldo AM Lima[2] for the MAL-ED Network Investigators

Dietary data analysis

24h recalls: Beginning at 9 months and monthly. From 24h recalls:

- ✓ Energy, macronutrients and fiber intakes
- ✓ 6 vitamins: niacin, riboflavin, thiamin, folate, vitamins A and C
- ✓ 6 minerals: calcium, iron, magnesium, potassium, phosphorus and zinc

Usual dietary intake from complementary feeding determined considering the 24h recalls from 9 to 24 months of age for each child

A total of 29,120 recalls were analyzed!!

3 periods were considered:

- ✓ 9–12 months
- ✓ 13–18 months
- ✓ 19–24 months

TABLE 4 Intakes of energy and nutrients from complementary foods and nutritional status of children from the MAL-ED study at 24 mo of age[1]

	Underweight at 24 mo of age			Wasting at 24 mo of age			Stunting at 24 mo of age		
Nutrients	Yes ($n = 257$)	No ($n = 1179$)	Diff., %	Yes ($n = 63$)	No ($n = 1371$)	Diff., %	Yes ($n = 551$)	No ($n = 883$)	Diff., %
Energy, kcal/d	771 [482–1050][2]	959 [673–1184]	−19.6	695 [395–994][2]	938 [640–1170]	−25.9	925 [621–1171]	929 [617–1161]	−0.43
Macronutrients									
Protein, g/d	26.0 [23.6–28.1][2]	27.0 [23.4–30.8]	−3.7	25.7 [23.8–27.9]	26.5 [23.4–30.3]	−3.0	25.4 [22.3–28.5][2]	27.2 [24.2–31.9]	−6.6
Lipids, g/d	13.5 [10.6–15.4]	13.4 [10.4–16.1]	0.75	25.1 [23.0–28.3]	24.0 [19.0–28.1]	4.6	22.0 [14.7–26.3][2]	25.1 [20.8–29.1]	−12.4
Carbohydrates, g/d	146 [138–157]	145 [131–157]	0.69	145 [136–149]	145 [133–157]	0.00	150 [141–169][2]	142 [129–153]	5.6
Fiber, g/d	8.4 [6.4–11.3][2]	7.7 [3.7–13.1]	9.1	7.2 [6.0–9.2]	7.9 [4.2–13.1]	−8.9	9.5 [6.4–15.7][2]	6.9 [3.3–10.6]	37.7
Vitamins									
Folate, μg/d	101 [71.7–118][2]	109 [69.2–150]	−7.3	105 [86.9–117]	107 [69.0–142]	−1.9	96.3 [52.7–120][2]	115 [85.6–158]	−16.3
Niacin, mg/d	5.0 [3.8–6.3][2]	5.5 [4.2–8.0]	−9.1	5.0 [3.5–6.3]	5.4 [4.1–7.5]	−7.4	5.2 [4.0–6.6][2]	5.6 [4.1–8.3]	−7.1
Riboflavin, mg/d	0.74 [0.48–0.90]	0.78 [0.55–1.1]	−5.1	0.77 [0.51–0.91]	0.77 [0.54–1.0]	0.00	0.72 [0.45–0.90][2]	0.81 [0.59–1.1]	−11.1
Thiamin, mg/d	0.50 [0.35–0.60]	0.52 [0.37–0.76]	−3.9	0.49 [0.34–0.58]	0.52 [0.37–0.71]	−5.8	0.50 [0.35–0.62][2]	0.54 [0.37–0.77]	−7.4
Vitamin A, μg/d	258 [151–325]	271 [165–373]	−4.8	286 [221–349]	268 [163–361]	6.7	225 [106–314][2]	294 [202–419]	−23.5
Vitamin C, mg/d	23.6 [6.6–35.0]	25.7 [9.2–53.7]	−8.2	29.7 [8.9–37.2]	25.2 [8.9–47.4]	17.9	18.4 [2.5–35.1][2]	29.5 [13.2–61.7]	−37.6
Minerals									
Calcium, mg/d	331 [216–416]	312 [162–491]	6.1	346 [290–416][2]	313 [165–481]	10.5	267 [113–376][2]	357 [204–567]	−25.2
Iron, mg/d	5.7 [3.7–7.2][2]	6.3 [4.3–8.9]	−9.5	5.5 [2.9–6.9]	6.2 [4.3–8.6]	−11.3	6.2 [4.4–8.2]	6.3 [4.2–9.2]	−1.6
Magnesium, mg/d	137 [124–162][2]	130 [105–156]	5.4	131 [115–152]	132 [107–158]	−0.8	141 [120–265][2]	127 [102–148]	11.0
Potassium, mg/d	987 [877–1097]	966 [826–1131]	2.2	987 [867–1076]	969 [835–1127]	1.9	931 [809–1063][2]	1000 [860–1201]	−6.9
Phosphorus, mg/d	564 [490–623]	546 [422–648]	3.3	564 [504–622]	548 [431–645]	2.9	541 [433–615]	552 [432–673]	−2.0
Zinc, mg/d	4.1 [3.6–4.5][2]	4.3 [3.5–5.6]	−4.6	4.1 [3.4–4.5]	4.3 [3.5–5.2]	−4.7	4.2 [3.4–4.6][2]	4.3 [3.5–6.2]	−2.3

[1]Values are medians [IQRs], considering 24-h food recalls from 19 to 24 mo of age, unless otherwise indicated. Underweight was defined as when weight-for-age was < −2 *z* scores. Wasting was defined as when weight-for-length was < −2 *z* scores. Stunting was defined as when length-for-age was < −2 *z* scores. Diff. (%): differences in intake between the children with or without underweight, wasting, and stunting were expressed as percentages, considering children without underweight, wasting, and stunting as the reference value. MAL-ED, The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development.

[2]Mann–Whitney *U* test $P < 0.05$.

Maciel et al. J Nutr 2020;151(1):170–8.

The Journal of Nutrition
Commentary

See corresponding article on page 170.

Nutrients in Complementary Feeding Protect Against Wasting, but Not Stunting: Results from a Multi-Country Longitudinal Cohort Study

Daniel J Hoffman

Department of Nutritional Sciences, Program in International Nutrition; New Jersey Institute for Food, Nutrition, and Health, Center for Childhood Nutrition Research; Rutgers, the State University of New Jersey, New Brunswick, NJ, USA

Hoffman DJ J Nutr 2020; 151(1):5-6.

Maciel et al. J Nutr 2020;151(1):170–8.

The strength of the work by the MAL-ED Network investigators is rooted in the saying “data render a problem visible” and, despite these data being intuitive to many nutrition professionals, data also render a solution visible. The noble goal of ending world hunger continues to remain elusive given ongoing geopolitical challenges that impede poverty reduction, challenges that are now complicated by a global pandemic that has disrupted food systems, caused widespread economic distress, and created greater food insecurity throughout the world, especially in lower-income countries. Still, having specific dietary data from a diverse cohort of children strengthens the ability to address at least 1 aspect of world hunger, providing optimal CF for children in all parts of the globe. However, this knowledge must be paired with efforts to provide sustainable dietary solutions to world hunger, such as diversifying crops, combating climate change, and promoting community food production and poverty eradication. Perhaps most important, it is essential to address structural racism and poverty and work toward improvements in healthcare delivery, gender and racial equality, and maternal education. Without these broader systemic changes, dietary recommendations are provided in a vacuum and advancement toward reducing the global prevalence of the double burden of malnutrition will remain out of reach.

Experimental work...

Samilly A. Ribeiro

Ribeiro et al. J Nutr. 2024 Feb 10:S0022-3166(24)00052-X

Experimental work...

Murine model based on the diet of children from the MAL-ED birth cohort study

Samilly Albuquerque Ribeiro

Nutrients	Stunting at 24 mo of age		Diff., %
	Yes ($n = 551$)	No ($n = 883$)	
Energy, kcal/d	925 [621–1171]	929 [617–1161]	– 0.43
Macronutrients			
Protein, g/d	25.4 [22.3–28.5][2]	27.2 [24.2–31.9]	– 6.6
Lipids, g/d	22.0 [14.7–26.3][2]	25.1 [20.8–29.1]	– 12.4
Carbohydrates, g/d	150 [141–169][2]	142 [129–153]	5.6
Fiber, g/d	9.5 [6.4–15.7][2]	6.9 [3.3–10.6]	37.7
Vitamins			
Folate, μg/d	96.3 [52.7–120][2]	115 [85.6–158]	– 16.3
Niacin, mg/d	5.2 [4.0–6.6][2]	5.6 [4.1–8.3]	– 7.1
Riboflavin, mg/d	0.72 [0.45–0.90][2]	0.81 [0.59–1.1]	– 11.1
Thiamin, mg/d	0.50 [0.35–0.62][2]	0.54 [0.37–0.77]	– 7.4
Vitamin A, μg/d	225 [106–314][2]	294 [202–419]	– 23.5
Vitamin C, mg/d	18.4 [2.5–35.1][2]	29.5 [13.2–61.7]	– 37.6
Minerals			
Calcium, mg/d	267 [113–376][2]	357 [204–567]	– 25.2
Iron, mg/d	6.2 [4.4–8.2]	6.3 [4.2–9.2]	– 1.6
Magnesium, mg/d	141 [120–265][2]	127 [102–148]	11.0
Potassium, mg/d	931 [809–1063][2]	1000 [860–1201]	– 6.9
Phosphorus, mg/d	541 [433–615]	552 [432–673]	– 2.0
Zinc, mg/d	4.2 [3.4–4.6][2]	4.3 [3.5–6.2]	– 2.3

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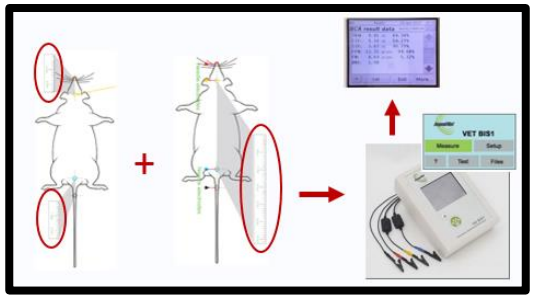
Experimental work...

C57BL/6
(aged 21 days)



Control
(AIN-93M diet)

Undernourished
(MAL-ED diet)

7 days | 14 days | 21 days | 28 days

Daily measurements of length and weight

Body composition assessment – electrical bioimpedance

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Experimental work...

C57BL/6
(aged 21 days)

Control
(AIN-93M diet)

Undernourished
(MAL-ED diet)

0 — 7 days — 14 days — 21 days — 28 days

Daily measurements of length and weight

Body composition assessment – electrical bioimpedance

Gastrointestinal barrier function:
L/M test (7d and 28d)
Morphometric and histopathological analysis (7d and 28d)
Ussing chamber
(challenge with glutamine, alanyl-glutamine and glucose) (7d)
Gene transcription and protein expression of tight junctions and intestinal transporter proteins - jejunal mucosa (7d)

Metabolome (urine samples):
Nuclear magnetic resonance (1H NMR)

Table 1- Nutritional composition of the MAL-ED and control diets.

	Control Diet	MAL-ED Diet	Difference (%)
Energy (Kcal)	391.69	360.22	-8.03
Macronutrients			
Carbohydrate (g)	61.89	65.66	5.93
Protein (g)	21.25	13.29	-37.46
Lipid (g)	6.57	4.98	-24.20
Fibers	2.9	4.21	45.17
Micronutrients			
Zinc (mg)	35.0	31.21	-10.83
Ingredients			
Semola grits (g)	-	54.90	
Casein (81% protein)/14% (g)	16.40	9.60	
Dextrinized starch (g)	15.50	0.00	
Sucrose (g)	10.00	0.00	
Soy oil (g)	4.00	5.10	
Cellulose MC-101 (g)	5.00	26.00	
Mineral mix (g)	3.50	3.50	
Vitamin mix (g)	1.00	1.00	
L-cysteine (g)	0.18	0.30	
Choline Bitartrate (g)	0.25	0.25	
Tert-butylhydroquinone (g)	0.0008	0.0014	

Values referring to the analysis of the centesimal composition of the MAL-ED diet and control diet (AIN-93M), as well as the amount of ingredients used to formulate each diet.

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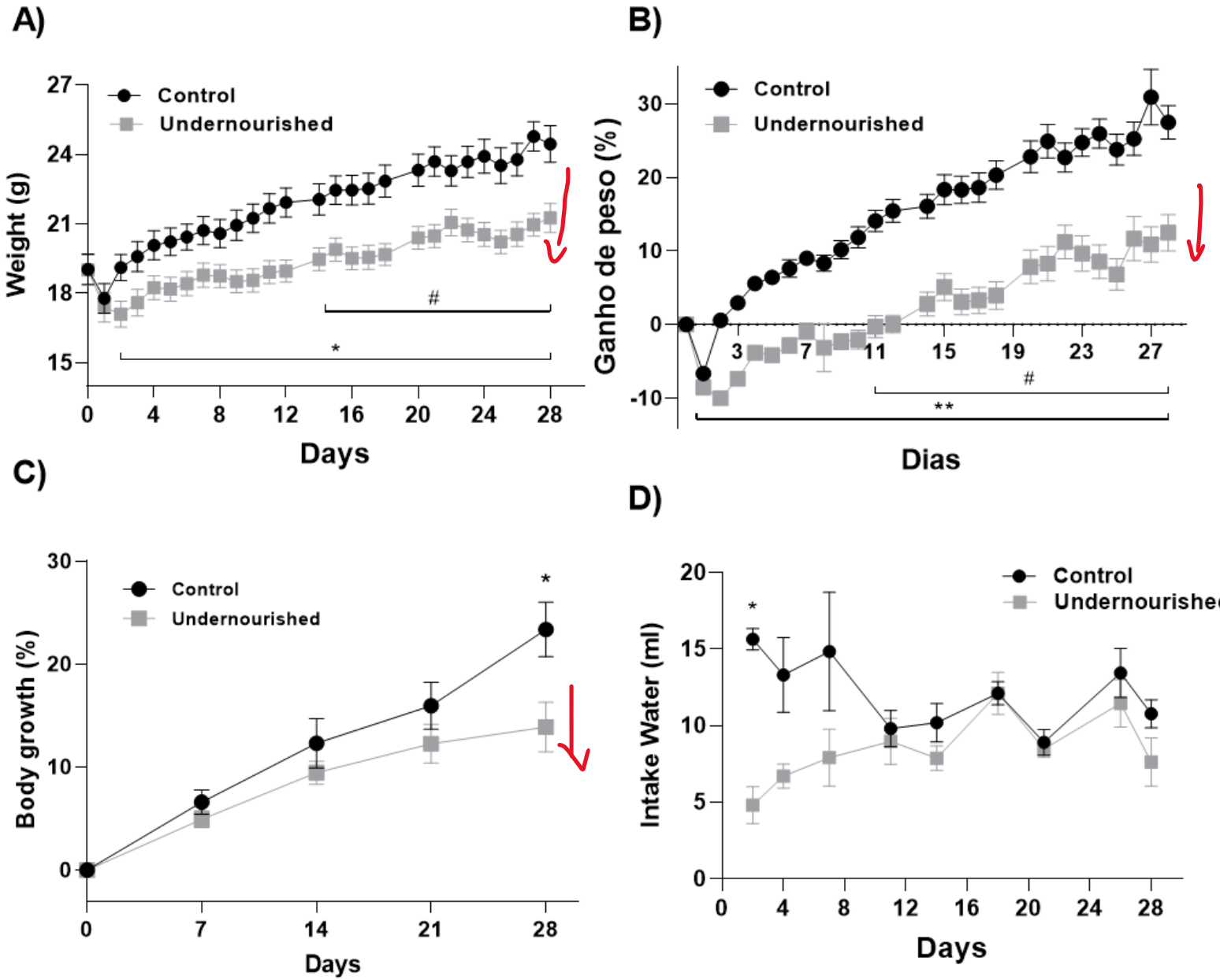

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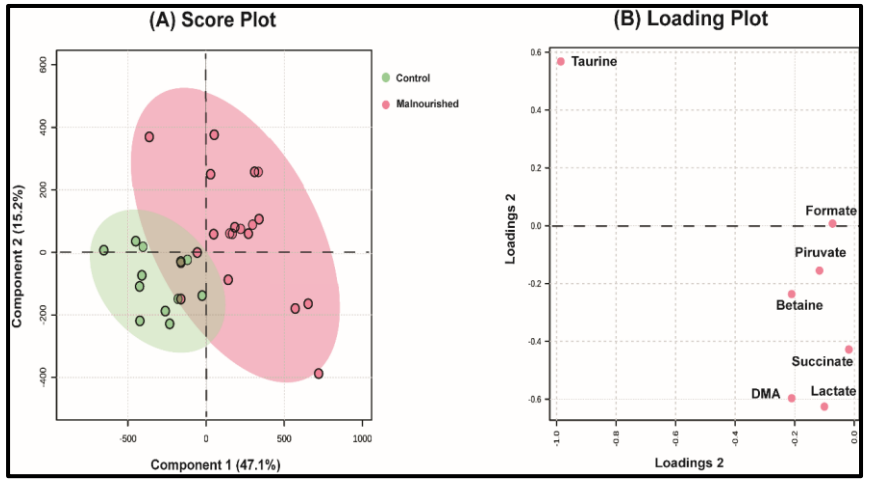

Metabolomic analysis revealed that consumption of the MAL-ED diet in the chronic period was associated with increased dimethylamine and reduced taurine.

- ✓ **Dimethylamine:** metabolite derived from choline degradation by the intestinal microbiota. Protein undernutrition in mice is reported to increase metabolites derived from the intestinal microbiota, including dimethylamine.
- ✓ **Taurine:** nitrogenous compound → several physiological, including carbohydrate and lipid metabolism, anti-inflammatory action, antioxidant, increased muscle contraction, important role in the central nervous system (neurotransmitter). The low excretion of taurine in undernutrition animals may indicate metabolic dysfunction of various body systems.

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