Association between enteric pathogens and diarrhea and child growth shortfalls: insights from the application of molecular diagnostics

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Livestock, Sanitation, Hygiene, and Child Growth: Exploring the complex underlying causes of child stunting

March 1, 2018

Overview

1. Molecular diagnostics have substantially revised estimates of the etiology and burden of childhood diarrhea in low resource settings
2. These same diagnostics have recently been applied to longitudinal studies evaluating the impact of early enteric infections on child growth
3. Findings from these studies most clearly and consistently implicate inflammatory bacterial pathogens
4. Extension of these diagnostics to interventional studies with child growth as the primary outcome may serve as an important secondary endpoint which can help elucidate the reasons for the impact (or lack thereof) of these interventions

The standard work-up for diarrhea: expensive, complicated, and variably sensitive

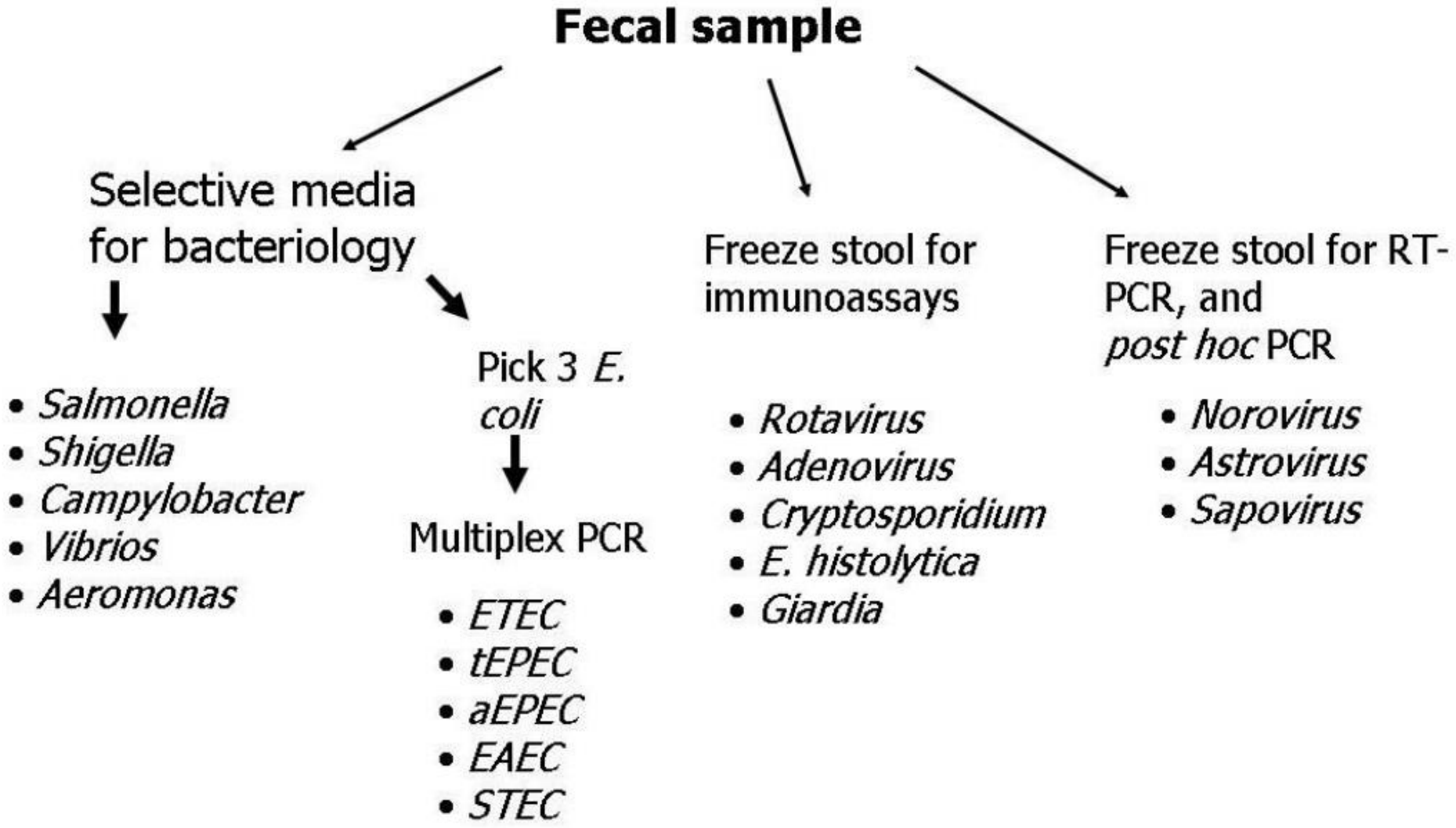
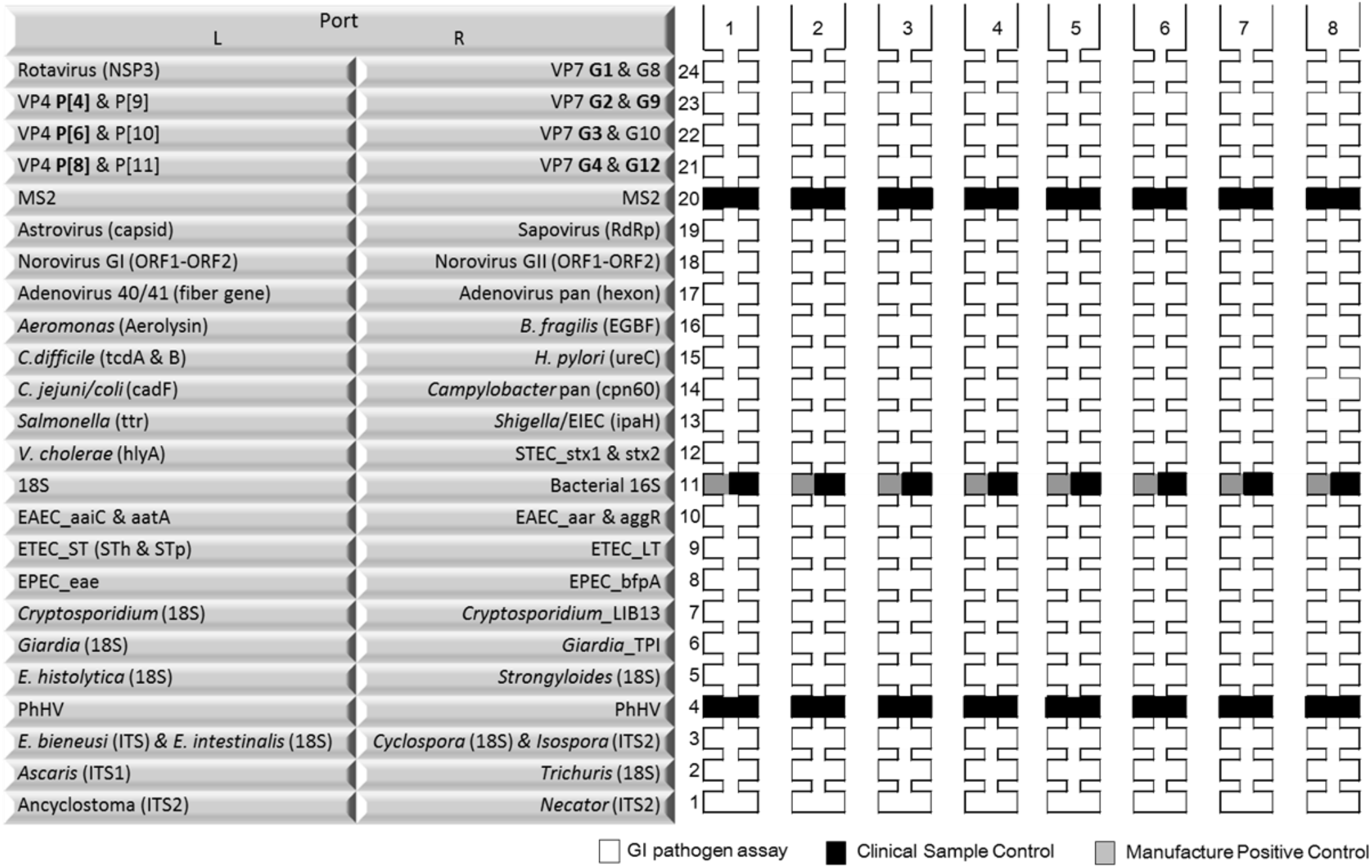
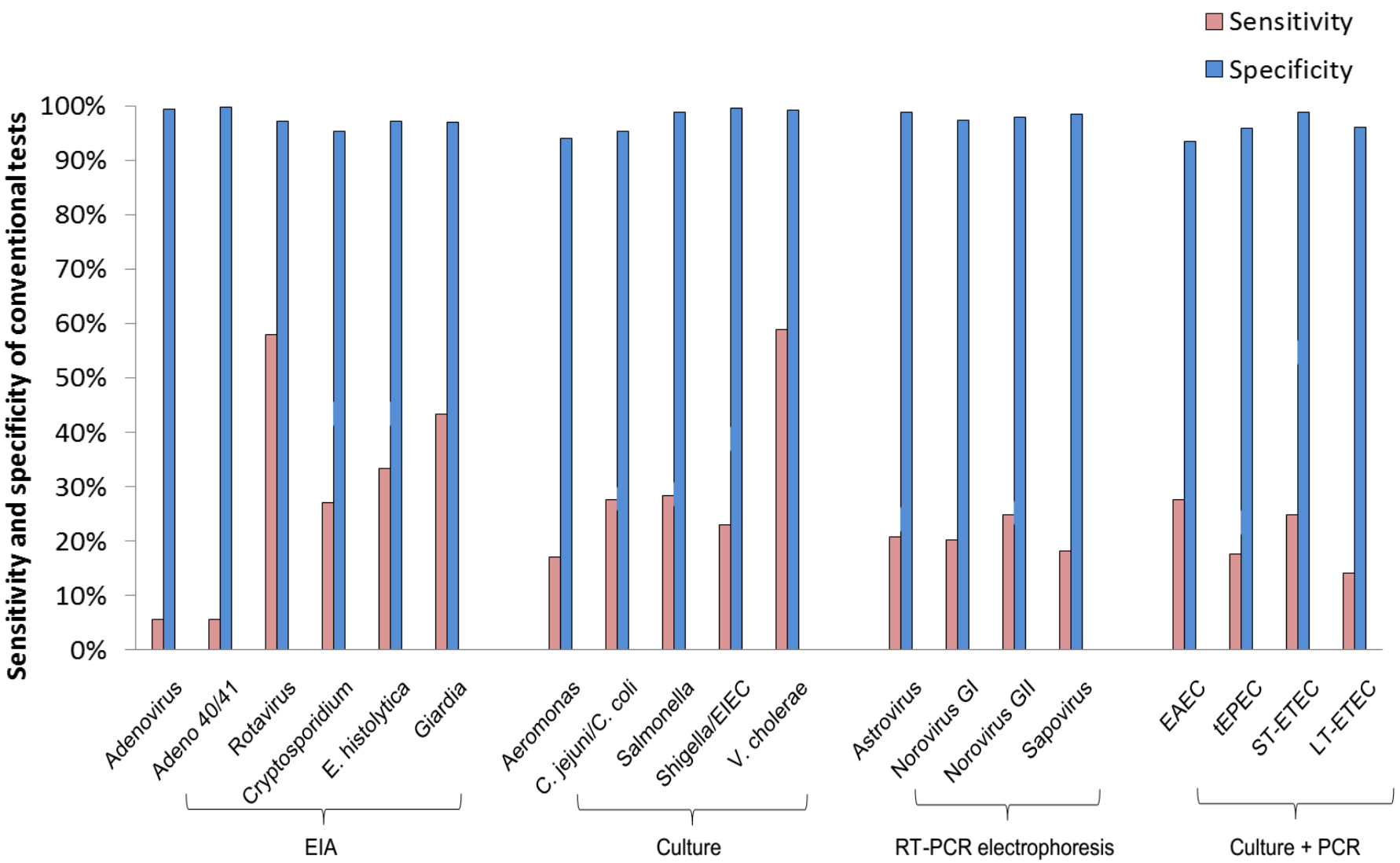


Figure courtesy of Mike Levine

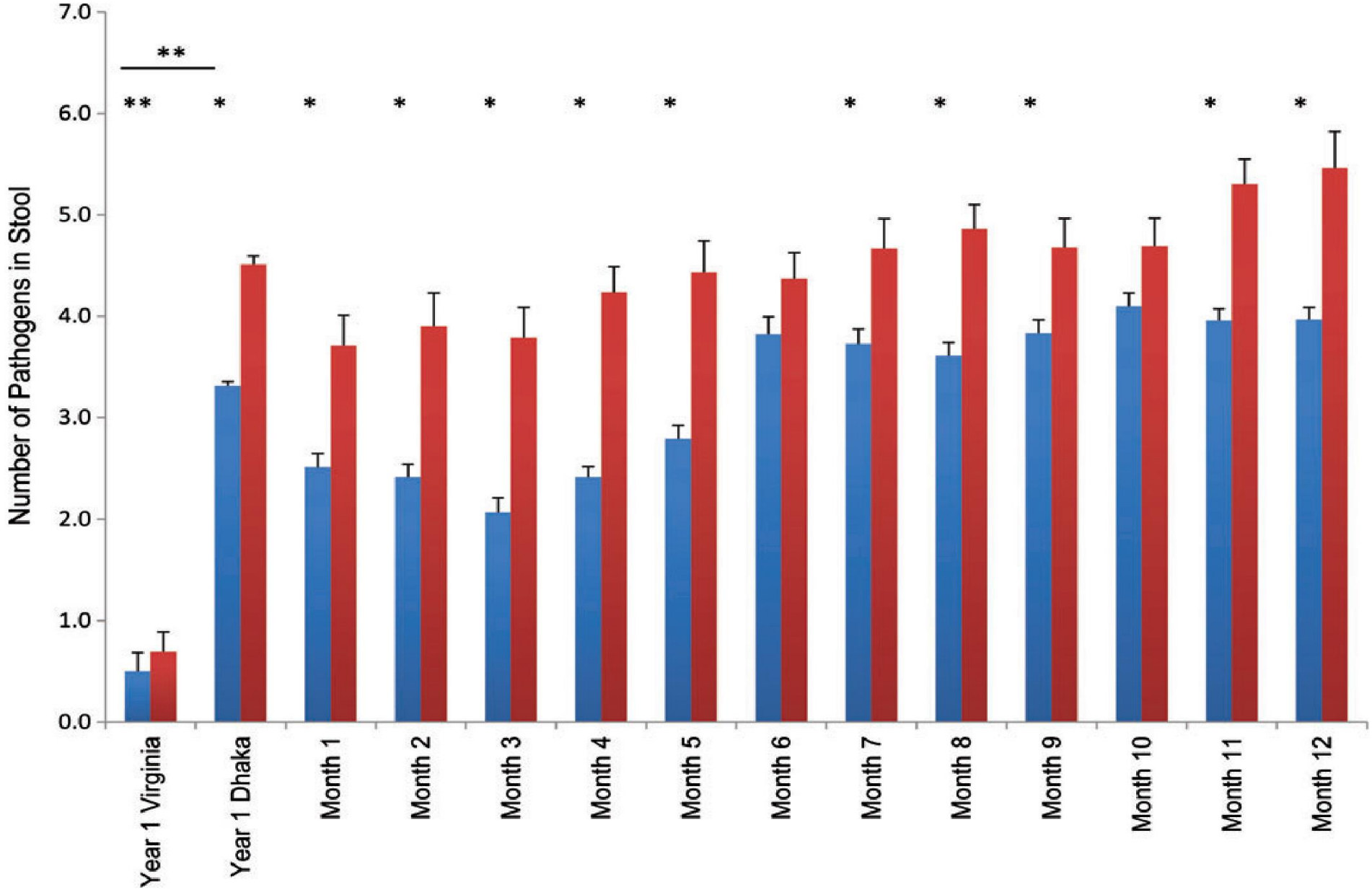
The TaqMan Array Card: simultaneous quantitative PCR for a broad range of enteropathogens



The TaqMan Array Card: test characteristics vs. standard microbiologic studies



Sensitive molecular diagnostics yield many pathogens



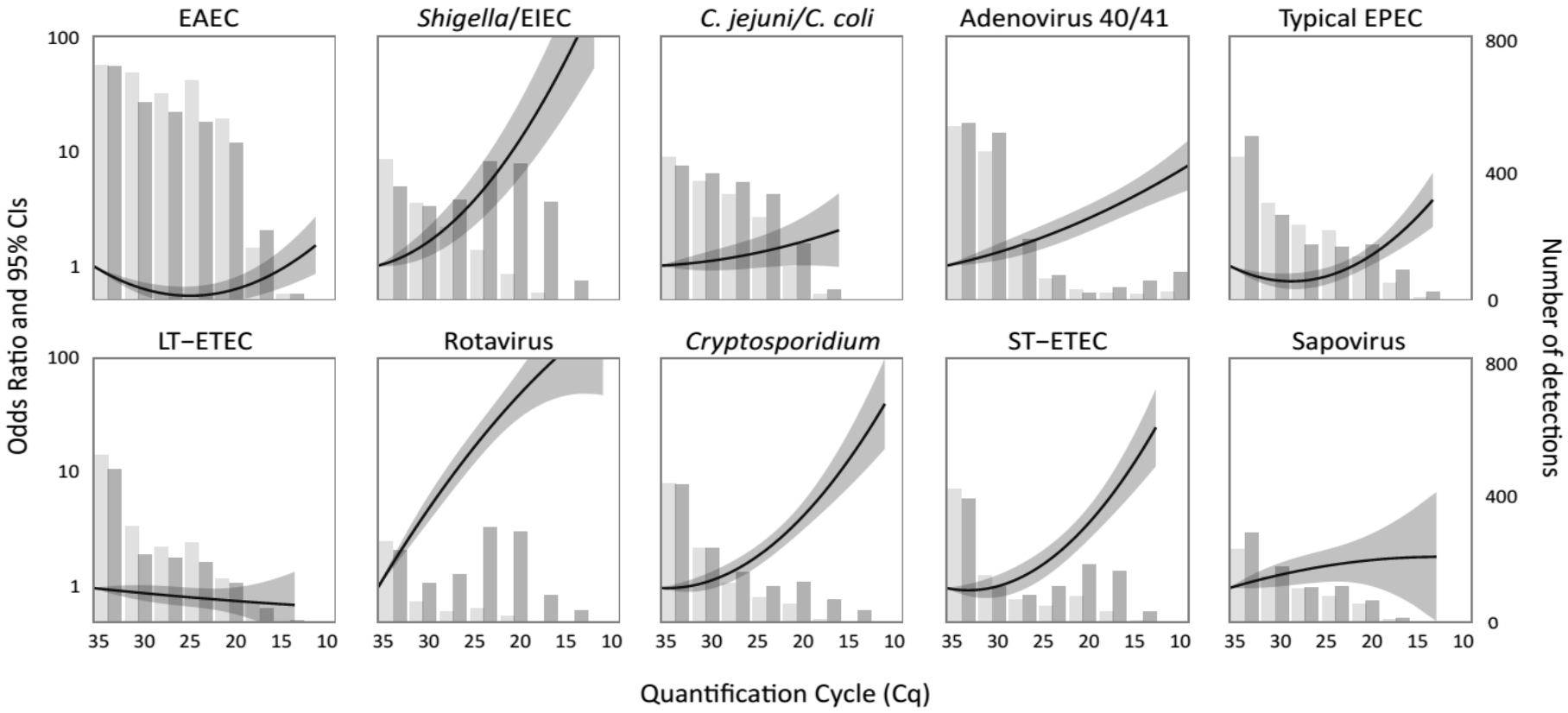
Taniuchi M, et al. JID 2015

A common drinking water source in Haydom, Tanzania

Photo by Jean Gratz

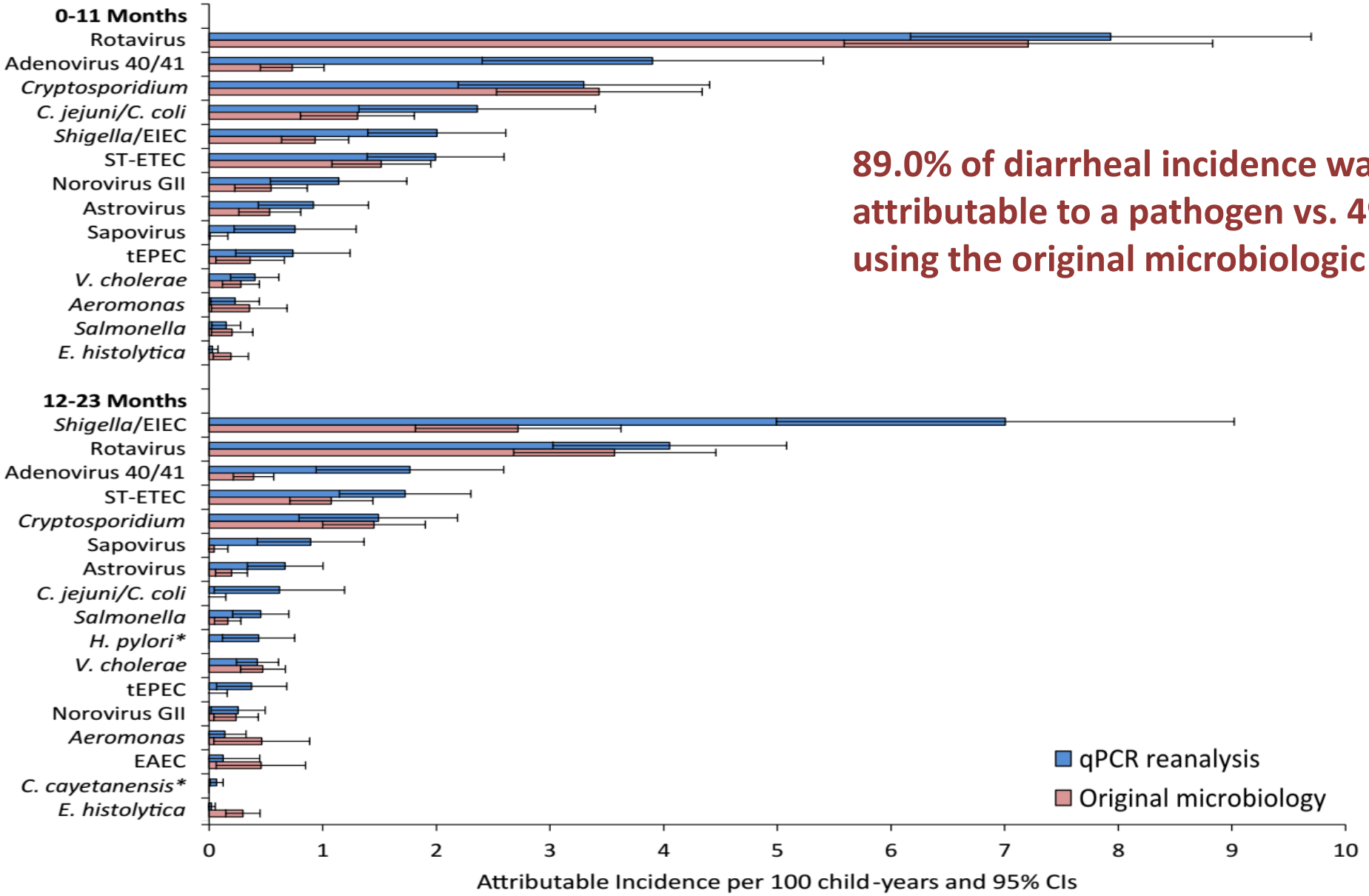
GEMS: Etiology of moderate to severe childhood diarrhea in low-resource settings

	GEMS	PROVIDE	MAL-ED
Location	**Africa and Asia**	Bangladesh	South America, Africa, Asia
Study design	**Case-control (moderate to severe diarrhea)**	Birth cohort	Birth cohort
Sample size	**5304 cases and matched controls**	603 children from single site	1469 children from 7 sites
Age range	**0-59 months**	0-12 months	0 – 24 months
PCR testing	**5304 diarrheal and 5304 non-diarrheal stools**	1741 diarrhea episodes	4975 diarrheal and 30,647 non-diarrheal stools



Kotloff K, et al. Lancet

GEMS: qPCR re-analysis of pathogen-specific burdens of diarrhea



89.0% of diarrheal incidence was attributable to a pathogen vs. 49.8% using the original microbiologic work-up

Liu J and Platts-Mills JA, et al. Lancet 2016

Diarrhea and growth shortfalls – a moving target

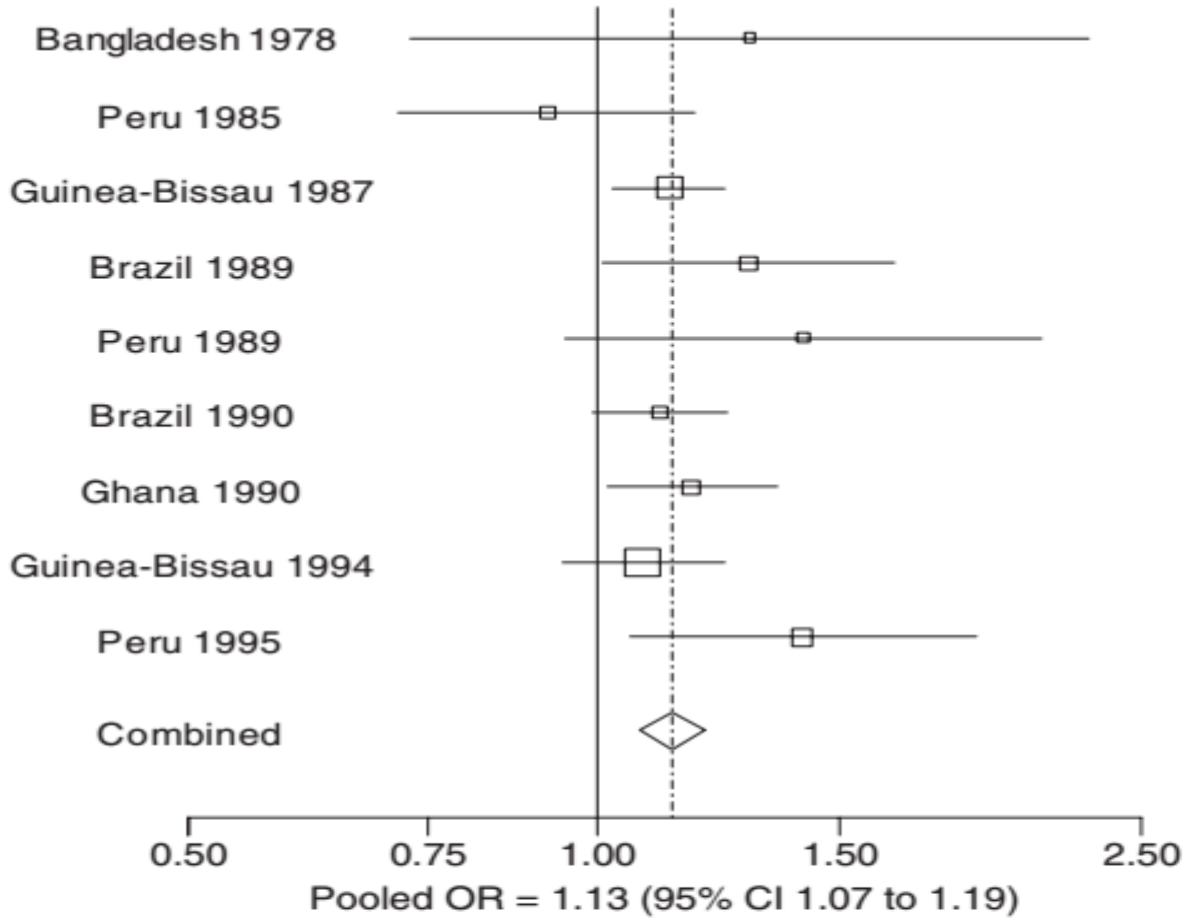


Figure 3 Effect of diarrhoeal incidence prior to 24 months on stunting at 24 months of age. Point estimates of the effect of diarrhoeal incidence on stunting at 24 months are shown for each study. The size of the square around the point estimate is proportional to sample size. The lines represent 95% CI. In the pooled estimate, represented by a diamond, the odds of stunting at 24 months increased by 1.13 when diarrhoeal incidence prior to 24 months increased by five episodes (95% CI 1.07 to 1.19)

Checkley W, et al. Int J Epidemiol 2008;37:816-830
Lee, G et al. Ped Infect Dis J 2014;33:1004-9

PROVIDE: Association between all-cause and etiology-specific diarrhea and linear growth

	GEMS	**PROVIDE**	MAL-ED
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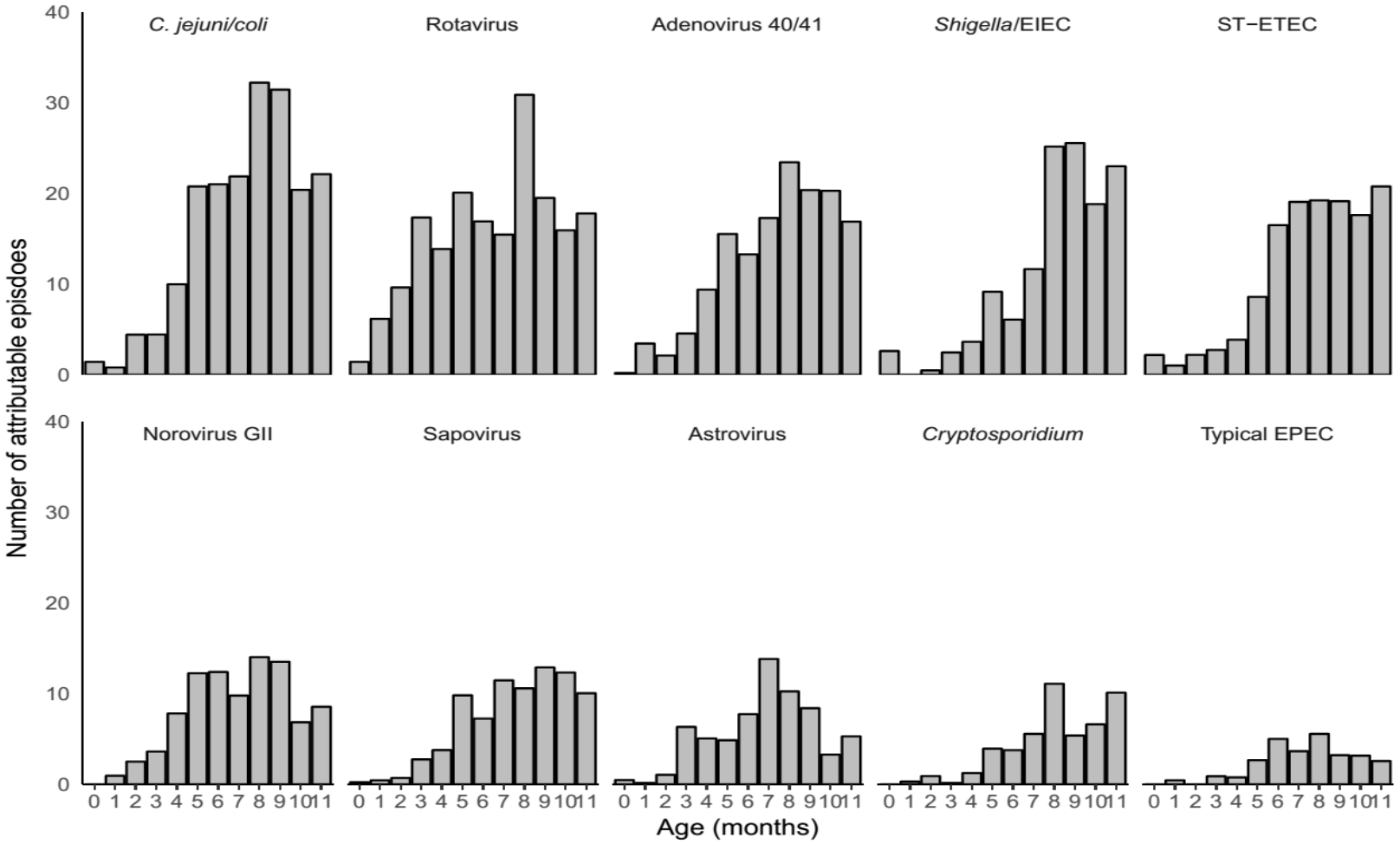
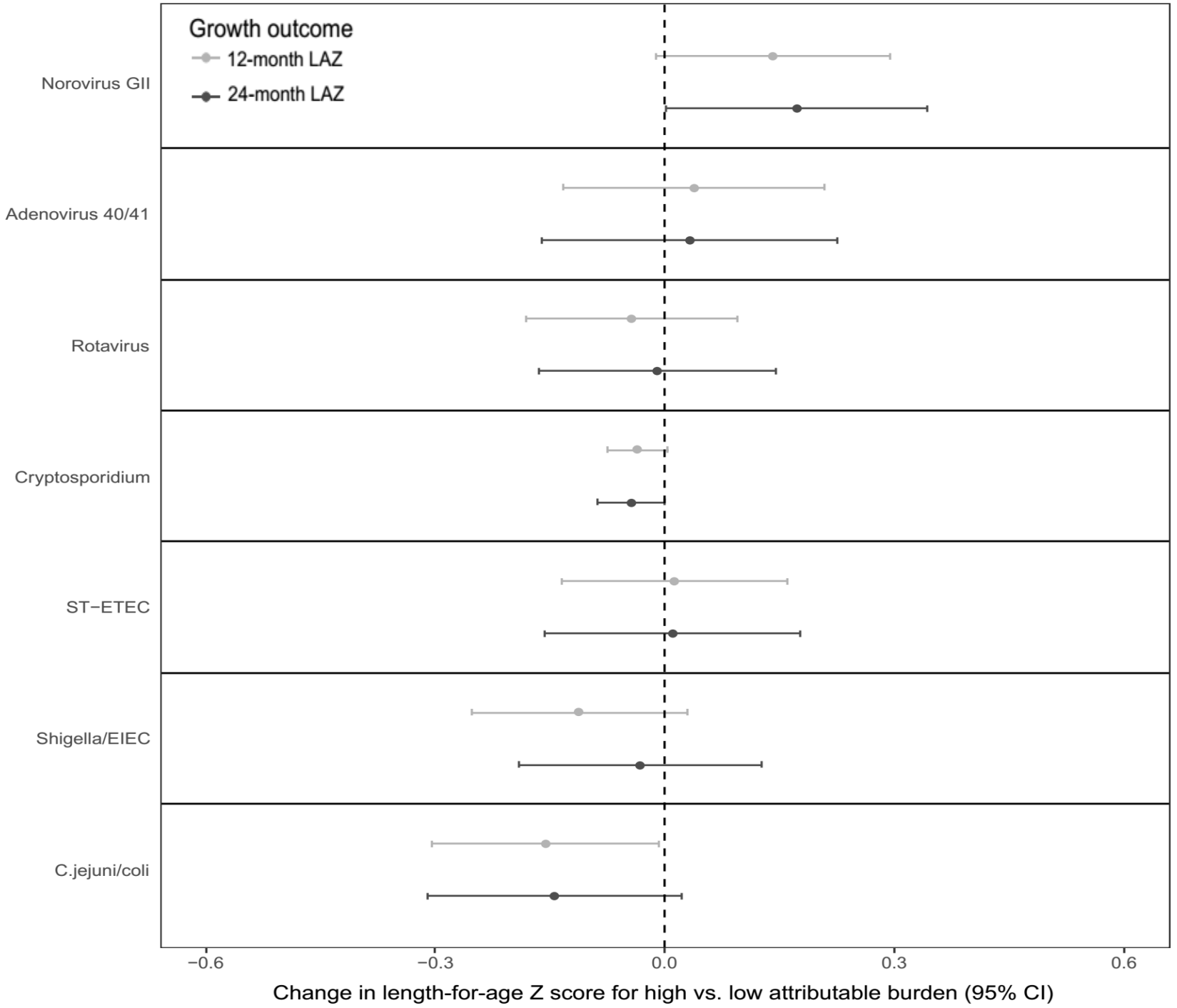
No relationship between all-cause diarrhea and length at 12 months (-0.01 decrease in 12-month LAZ per episode; 95% confidence interval: -0.06, 0.03)

Bacteria (-0.09 decrease in 12-month LAZ per attributable episode; 95% CI: -0.16, -0.01) and protozoa (-0.24; 95% CI: -0.49, 0.01) were more strongly associated with linear growth deficits than viruses (-0.01; 95% CI: -0.11, 0.08)



PROVIDE: Etiology-specific diarrhea and linear growth attainment in 603 Bangladeshi infants – effect for high (90th percentile) vs. low (10th percentile) attributable burden



Maternal and Child Health Clinic outside of Haydom

MAL-ED: Impact of early enteropathogen infections and child growth and development

	GEMS	PROVIDE	**MAL-ED**
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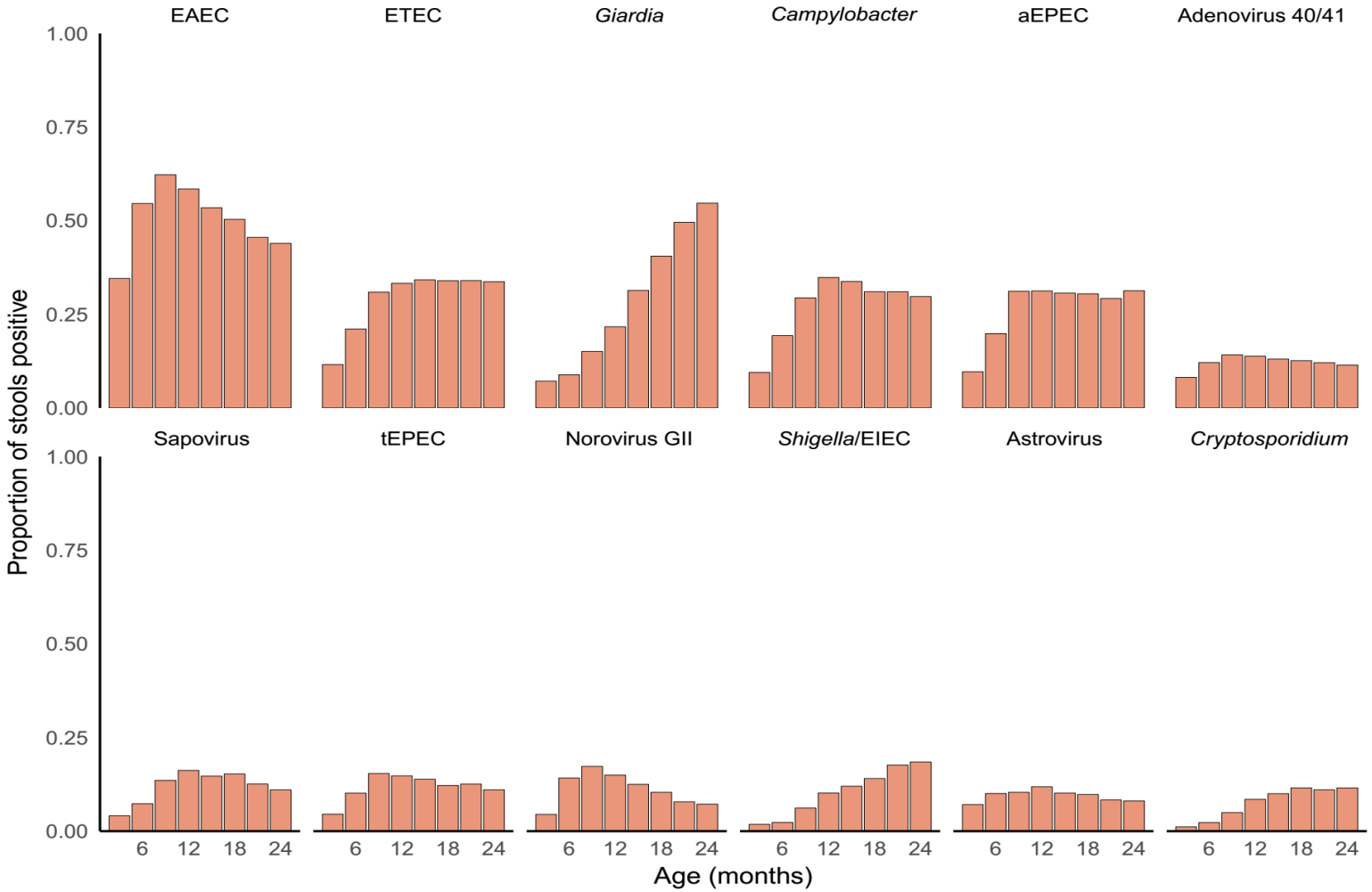
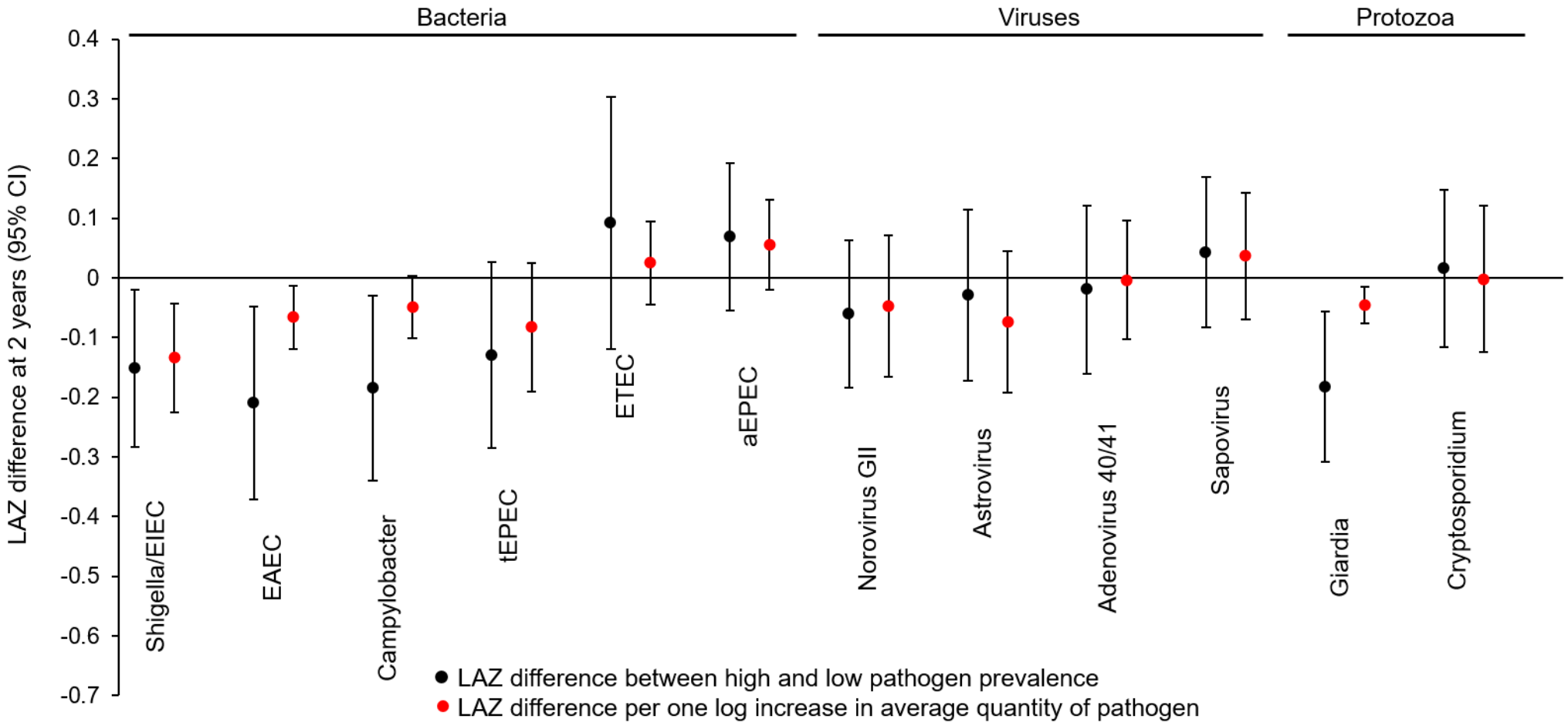
LAZ difference per diarrhea episode: -0.00, 95% CI: -0.02, 0.01.

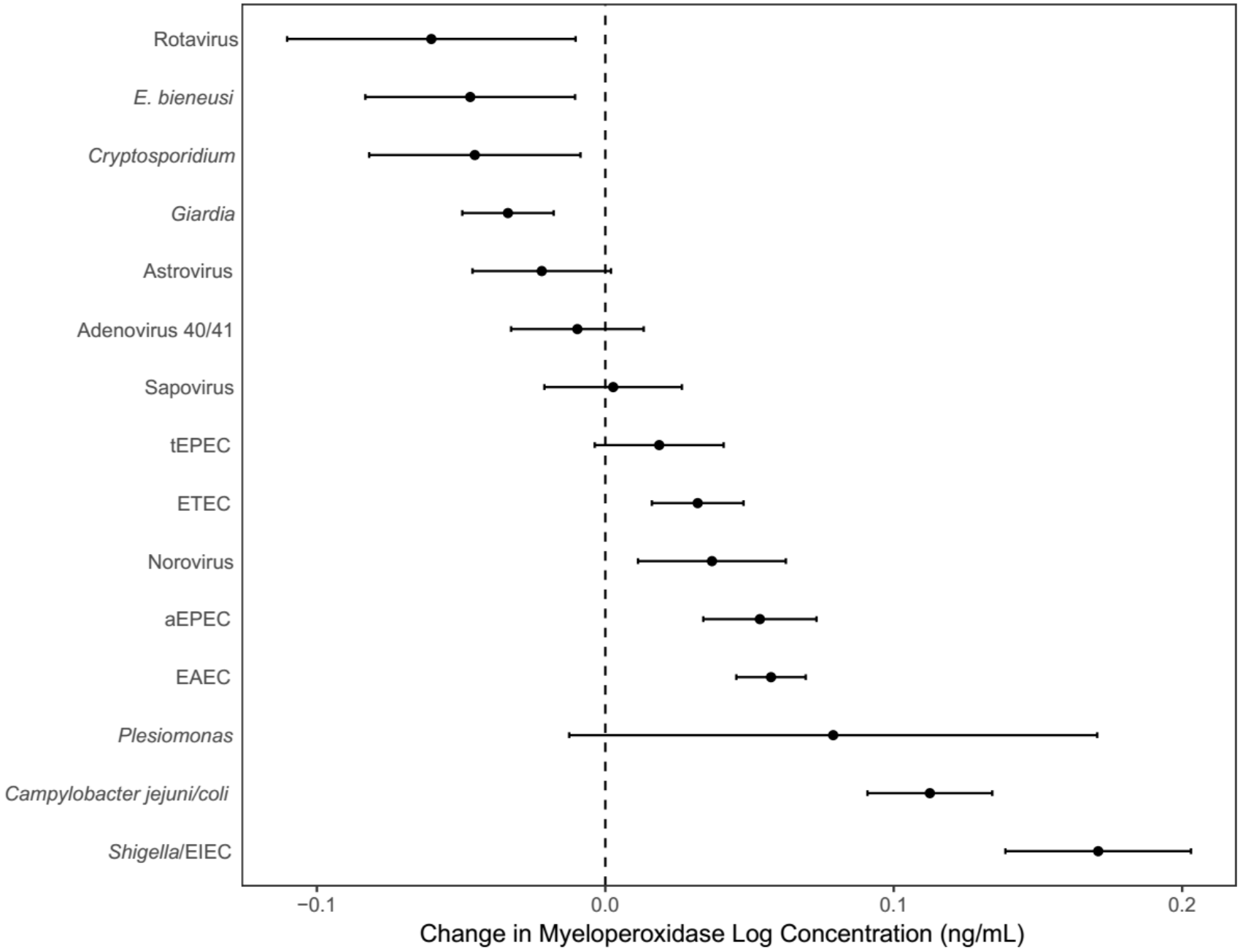
Parasitic (LAZ difference: -0.12, 95% CI: -0.25, 0.01) and bacterial (-0.04, 95% CI: -0.08, 0.01) diarrhea were more strongly associated with decrements in LAZ than viral diarrhea (0.02, 95% CI: -0.02, 0.06).



MAL-ED: Subclinical enteropathogen burden and linear growth at 2 years of age



MAL-ED: Enteric pathogen detection in non-diarrheal stools and gut inflammation (MPO)



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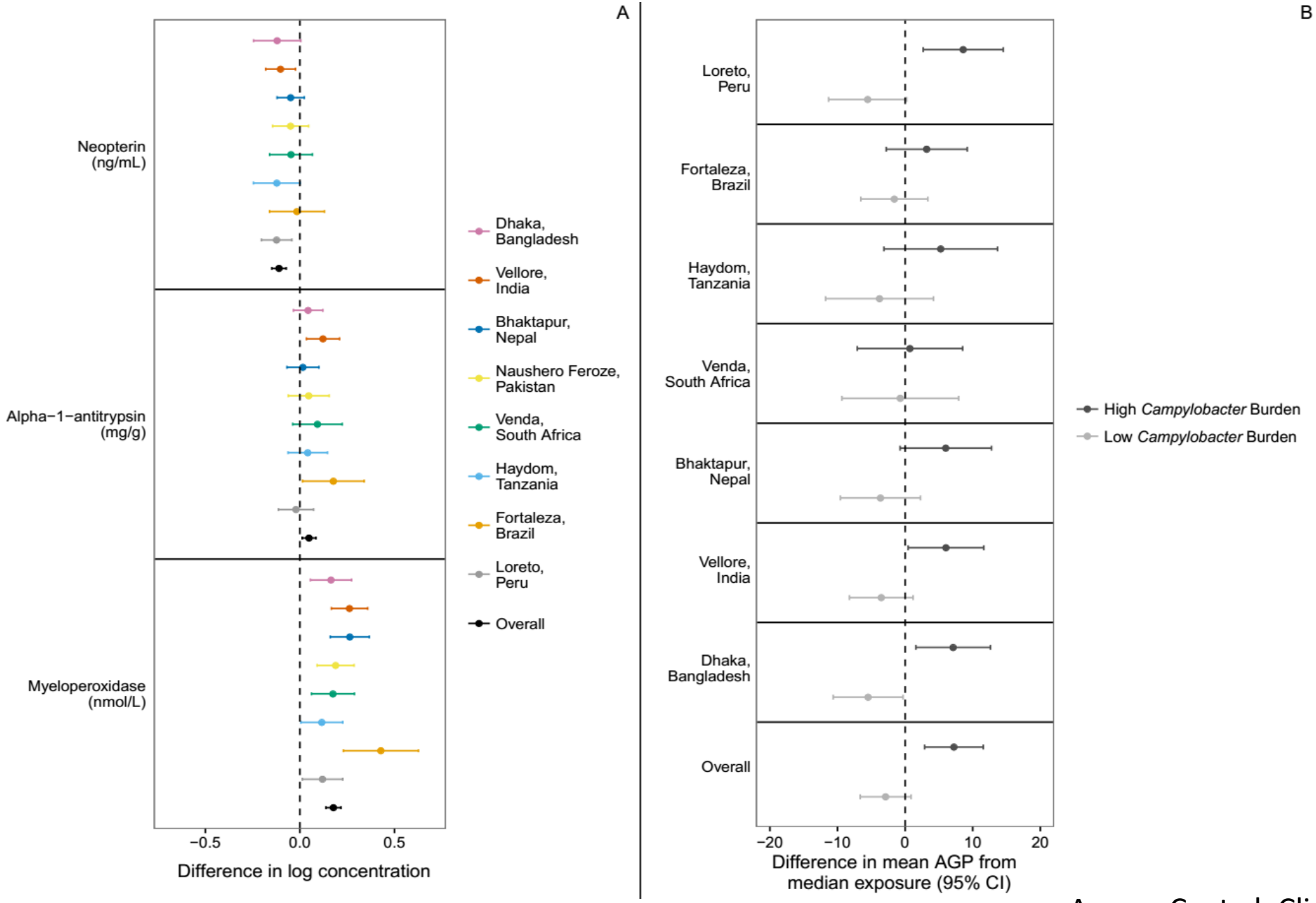
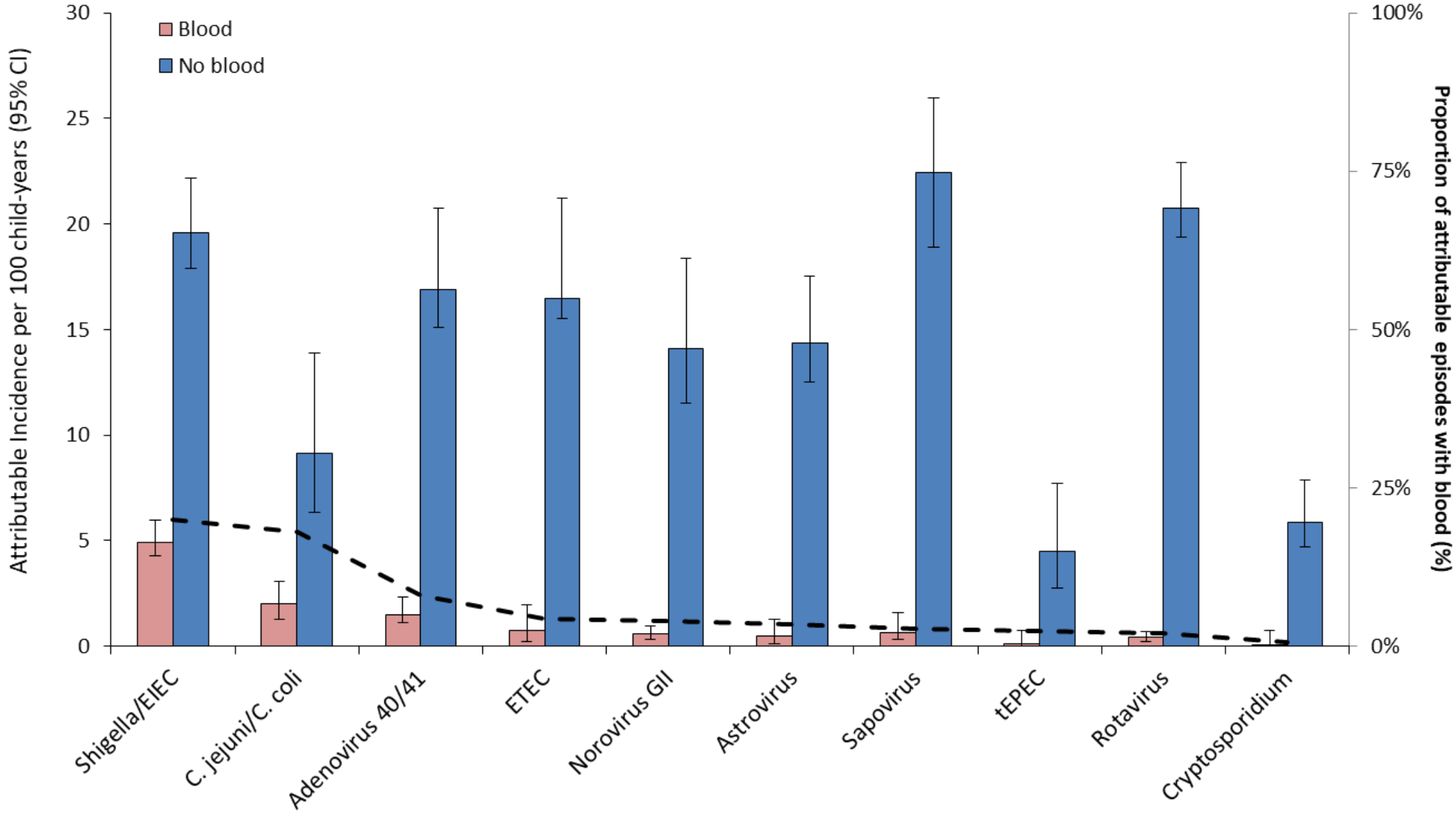


Amour C, et al. Clin Infect Dis 2016

MAL-ED: Etiology of watery diarrhea vs. dysentery



WHO guidelines for treatment of childhood diarrhea

THE TREATMENT OF DIARRHOEA

A manual for physicians and other senior health workers

World Health Organization

2.6 Use of antimicrobials

Antimicrobials should not be used routinely. This is because, except as noted below, it is not possible to distinguish clinically episodes that *might* respond, such as diarrhoea caused by enterotoxigenic *E. coli*, from those caused by agents unresponsive to antimicrobials, such as rotavirus or *Cryptosporidium*. Moreover, even for potentially responsive infections, selecting an effective antimicrobial requires knowledge of the likely sensitivity of the causative agent, information that is usually unavailable. In addition, use of antimicrobials adds to the cost of treatment, risks adverse reactions and enhances the development of resistant bacteria.

Antimicrobials are reliably helpful *only* for children with bloody diarrhoea (probable shigellosis), suspected cholera with severe dehydration, and serious non-intestinal infections such as pneumonia. Anti-protozoal drugs are *rarely* indicated.

What is the role of antimicrobial therapy for non-dysenteric diarrhea?

A Quiet Revolution in the Treatment of Childhood Diarrhea

Global Health

By DONALD G. McNEIL Jr. AUG. 10, 2015

WHO is rethinking the decades-old recommendation that only febrile, bloody diarrhea requires antibiotic therapy. A 15,000 child multisite mortality and growth co-primary endpoint clinical trial of azithromycin vs. placebo is planned (now underway).

Extending molecular diagnostics to interventional studies

1. **Water, Sanitation, and Hygiene**: the most comprehensive studies done to date (WASH Benefits, SHINE) have not shown clear growth benefits of WASH interventions. Did these interventions fail to reduce enteric pathogen exposure, carriage, and the development of EED? If so, why?
2. **Diagnosis and management of diarrhea**: does broadening the treatment indications for childhood diarrhea improve child growth? If so, who to treat: a) syndromic treatment that is broader than bloody diarrhea; b) POC test – either pathogen diagnostic or test for inflammation? c) based on child risk? (MAL-ED, ABCD)
3. **Treatment of subclinical enteropathogen burden**: does scheduled macrolide therapy improve child growth (and does it do so by reducing infection with invasive bacterial enteropathogens?)(ELICIT, CHAIN, MORDOR)
4. **Other therapies**: Micro/macronutrients, colostrum, microbiota-targeted therapeutics, novel gut therapeutics…

Acknowledgements

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PROVIDE: William Petri, Mami Taniuchi, Amanda Schnee, Beth Kirkpatrick, Rashidul Haque, Jashim Uddin

MAL-ED: Elizabeth Rogawski, Rosemary Nshama, Buliga Mujaga, Irene Araujo Maciel, Alex Havt, Shahida Qureshi, Furqan Kabir, Md. Ohedul Islam, Ira Praharaj, Revathi Rajendiran, Pablo Peñataro Yori, Mery Salas, Shaila Sharmeen Khan, Paphavee Lertsethtakarn, Arinao Murei, Fatima Aziz, Adil Kalam, Imran Rizvi, Pimmada Sakpaisal, Sasikorn Silapong, Jessica Seidman, Dennis Lang, Michael Gottlieb, Aldo A.M. Lima, Amidou Samie, Pascal Bessong, Estomih Mduma, Jose Paulo Leite, Ladaporn Bodhidatta, Carl Mason, Nicola Page, Ireen Kiwelu, Najeeha Iqbal, Tahmeed Ahmed, Zulfiqar Bhutta, Gagandeep Kang, Rashidul Haque, Margaret N. Kosek, Eric R. Houpt, and the MAL-ED Network Investigators

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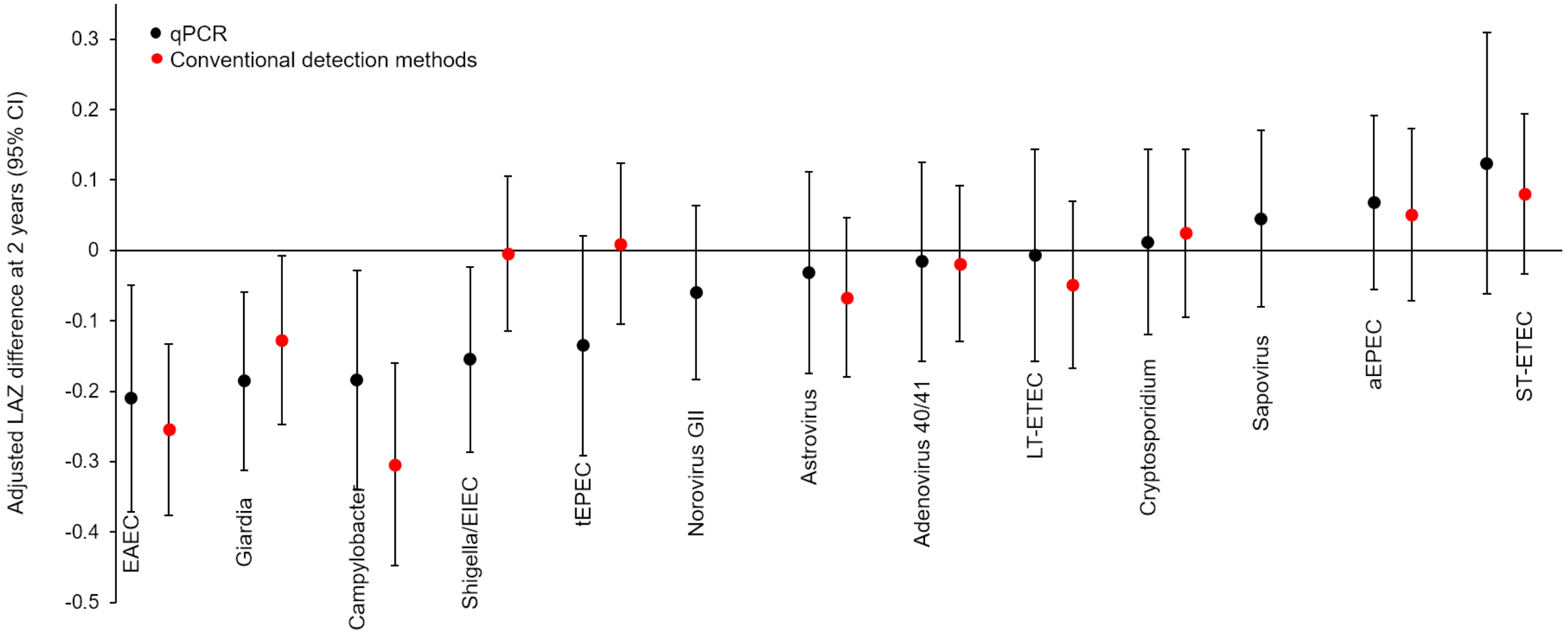
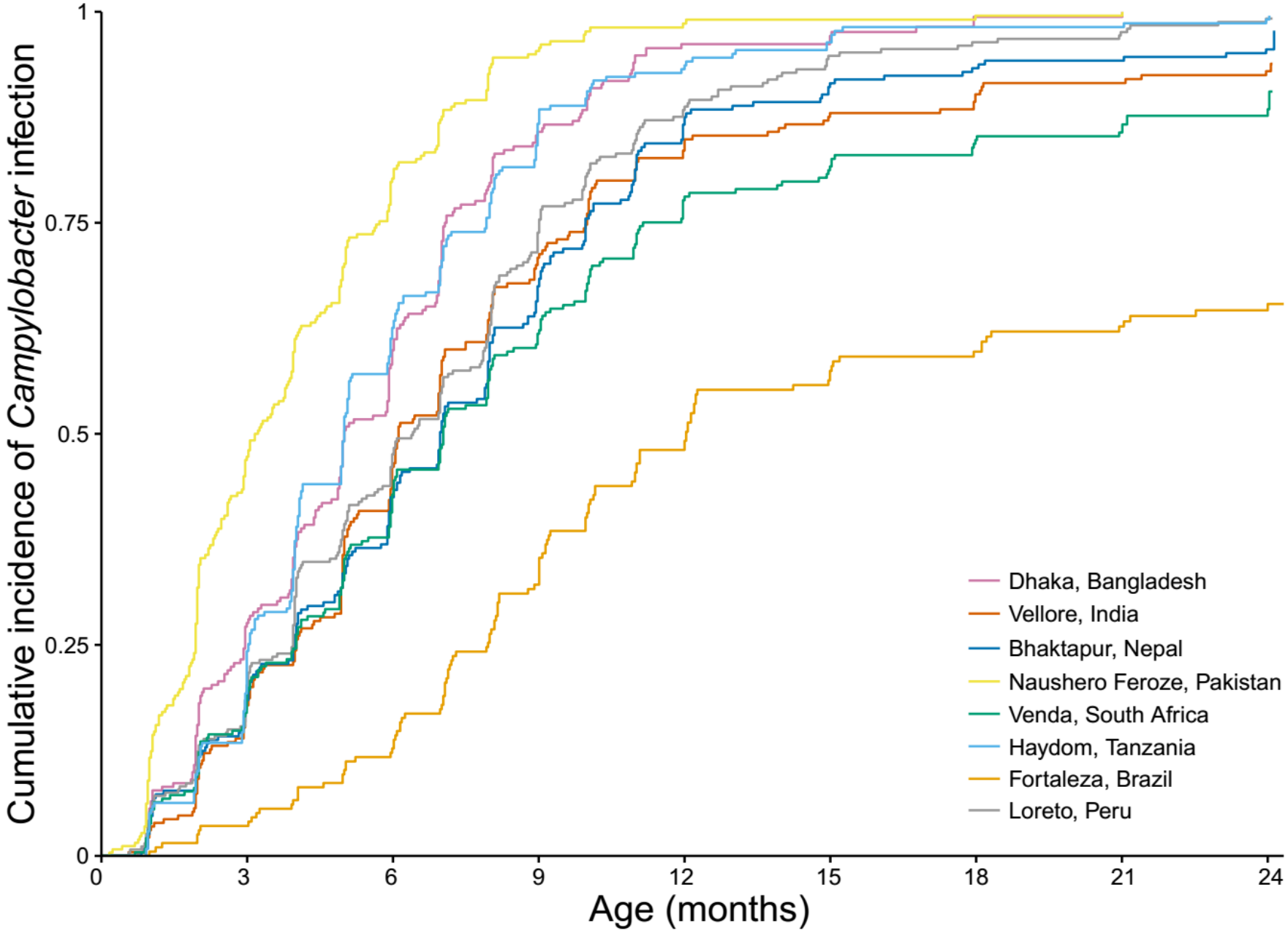
MAL-ED: Comparison between original microbiology and qPCR



MAL-ED: Campylobacter burden



Amour C, et al. Clin Infect Dis 2016

MAL-ED: Campylobacter species?

Campylobacter species detected by ProSpecT EIA	Approximate frequency of detection by PCR/sequencing in TZH, BGD, PEL
C. jejuni/coli	~70%
C. hyointestinalis	~5-15%
C. troglodytis	~5-15%
C. upsaliensis	<5%
C. concisus	<5%