

Enteropathogens associated with linear growth faltering in children in three sub-Saharan African countries after rotavirus vaccine introduction:

The Vaccine Impact on Diarrhea in Africa (VIDA) Study



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Background

- **The Global Enteric Multicenter Study (GEMS)**, a prospective, matched case-control study of moderate-to-severe diarrhea (MSD) in children <5 years old, conducted at 7 Asian and African sites during 2007-2011, reported significant linear growth faltering associated with infection with *Cryptosporidium*, enterotoxigenic *E. coli* producing heat stable toxin (ST-EPEC), typical enteropathogenic *Escherichia coli* (tEPEC) and *Shigella* not treated with WHO-recommended antibiotics.
- Rotavirus vaccine was introduced in three of the seven GEMS sites in 2013-14. The sites were in the Gambia, Mali and Kenya.
- **The Vaccine Impact on Diarrhea in Africa (VIDA) study** using comparable methods to GEMS, was conducted in 2015-18, following the introduction of rotavirus vaccine (RVV) in these three African sites.
- VIDA allowed us to re-examine the relationship between enteropathogens isolated from diarrheal stool with linear growth in children in Africa after RVV introduction.

Methods: Case-control enrollment

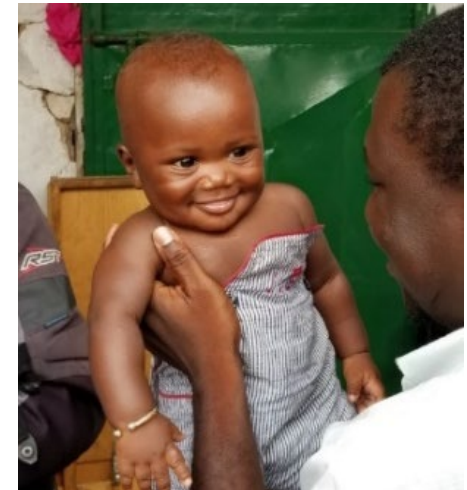
☐ Eligible cases from DSS sought care at SHC with a new (≥ 7 diarrhea-free days), and acute (< 7 days) diarrheal episode, with at least one of the following signs:

- Sunken eyes
- Loss of skin turgor
- Blood in stool
- Hospitalization
- IV rehydration



☐ 1-3 controls/case were enrolled from the community

- Randomly selected from the DSS population
- Did not have diarrhea for at least 7 days before enrollment
- Matched to cases by age, gender, residence, and within 14 days of index case enrollment



Data Collection

➤ Two visits: enrollment and follow-up visit ~60 days (range 50-90)

Enrollment visit:

- Epidemiological and clinical data
- A stool sample was tested for a wide variety of bacterial, viral and protozoal pathogens (conventional assays and quantitative PCR using TaqMan Array Card)
- Anthropometry data: length for 0-23 mos and standing height for 24-59 months



Follow-up visit:

- Epidemiological and clinical data
- Anthropometry data



Statistical methods

To determine the association of pathogens with linear growth among MSD cases:

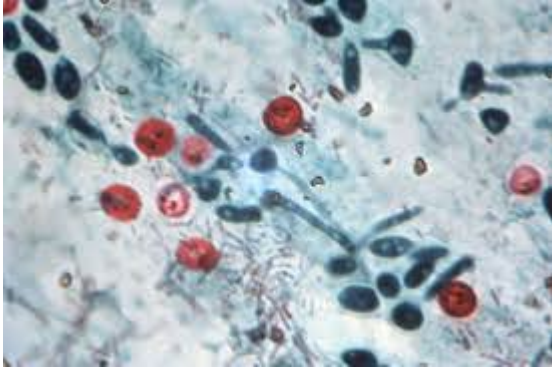
- Outcome variables: Δ HAZ (HAZ at follow up - HAZ at enrollment)
- Predictors:
 - ❖ 11 pathogens that were significantly associated with MSD in at least one age group and study site, including *Cryptosporidium*, *Shigella*, ST-EPEC, *Campylobacter* species, non-typhoidal salmonella, *Aeromonas*, rotavirus, norovirus G11, astrovirus, sapovirus, and adenovirus serotypes 40 and 41.
 - ❖ HAZ at enrollment, and duration of follow-up in days.
- Tested three-way interaction terms between each predictor, age stratum and study site
- We used multiple linear regression model to determine the association of pathogens with Δ HAZ
- An automatic backward model selection procedure was used to identify all predictors including interactions that were associated with the outcome at a significance level of 10% (i.e., p-value<0.1). If a higher-order interaction term is included in the final model, the corresponding lower-order interaction terms and main effect terms are also included.

Pathogens associated with change in HAZ between enrollment and follow-up (Δ HAZ) among MSD cases

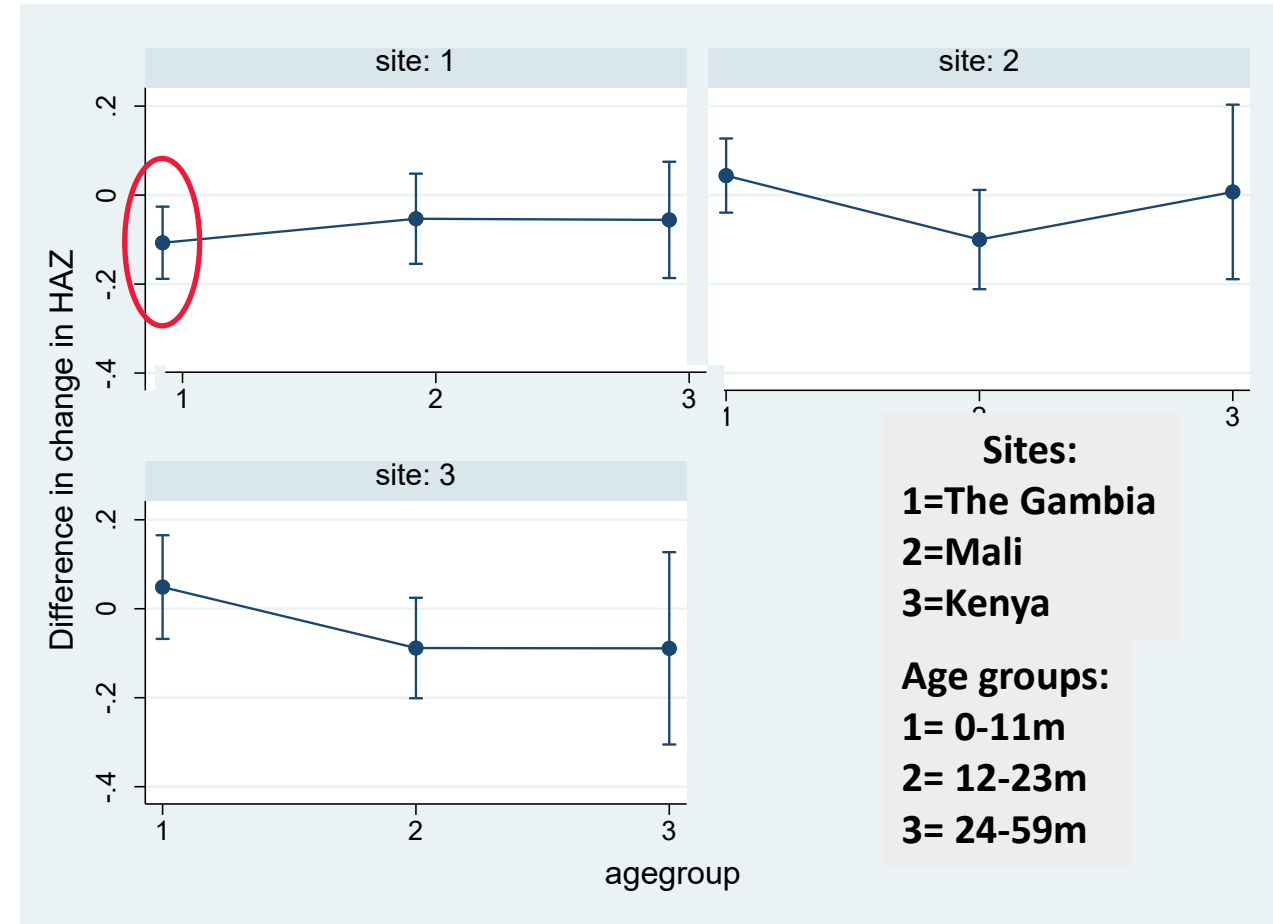
Five enteric pathogens among MSD cases were significantly associated with change of linear growth:

- *Cryptosporidium*
- ST-EPEC
- *Shigella*
- Rotavirus
- Astrovirus

Difference in linear growth in children with and without *Cryptosporidium*, by age and site



Tennessee Department of Health



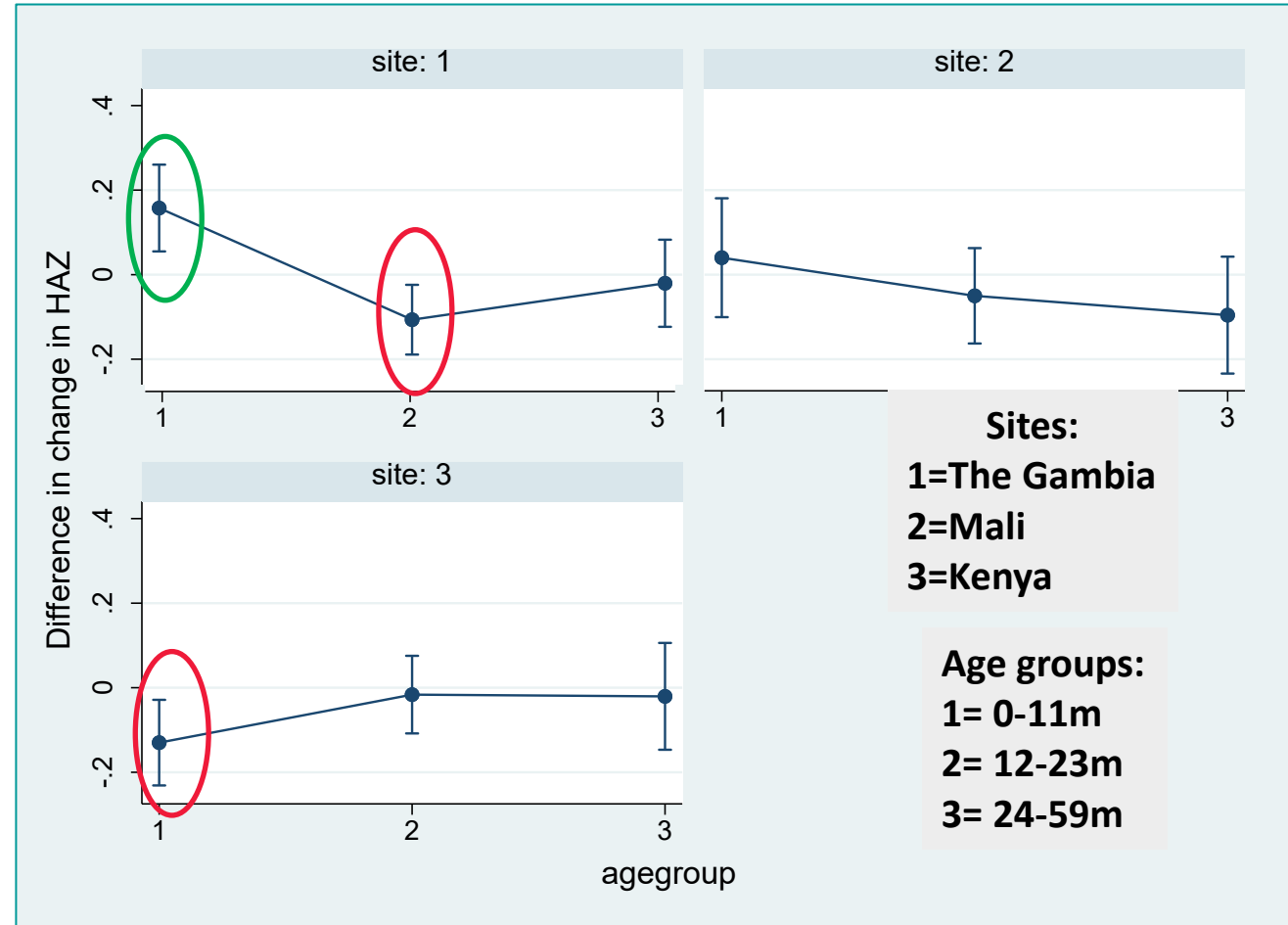
- Effect of *Cryptosporidium* on linear growth differed by age stratum and site.
- In 0-11 m in The Gambia, *Cryptosporidium* positive children had significantly greater decline in HAZ compared to those without *Cryptosporidium*.
 - $\Delta\text{HAZ} = -0.48$ with *Cryptosporidium* vs. -0.38 without *Cryptosporidium*
 - Difference in ΔHAZ [95% CI] = -0.11 [-0.19 , -0.03], $p = 0.01$)

Difference in linear growth in children with and without ST-ETEC, by age and site

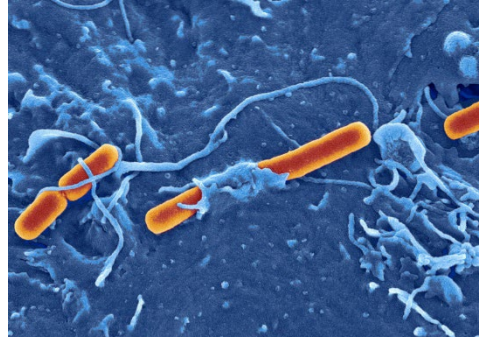


Alissa Eckert And Jennifer Oosthuizen/CDC

- Effect of ST-ETEC differed by age stratum and site
- Presence of ST-ETEC was associated with a greater decline in HAZ in
 - 12-23 m in the Gambia ($\Delta\text{HAZ} = -0.30$ vs. -0.19 ; difference in $\Delta\text{HAZ} = -0.11$ [$-0.19, -0.02$, **$P=0.01$**])
 - 0-11 m in Kenya ($\Delta\text{HAZ} = -0.32$ vs. -0.19 ; difference in $\Delta\text{HAZ} = -0.13$ [$-0.23, -0.03$, **$p=0.01$**])
- Presence of ST-ETEC was associated with smaller decline in linear growth in 0-11m in the Gambia ($\Delta\text{HAZ} = -0.24$ vs. -0.40 ; difference in $\Delta\text{HAZ} = 0.16$ [$0.06, 0.26$], **$p=0.003$**)



Effect of *Shigella* and antibiotic treatment on linear growth

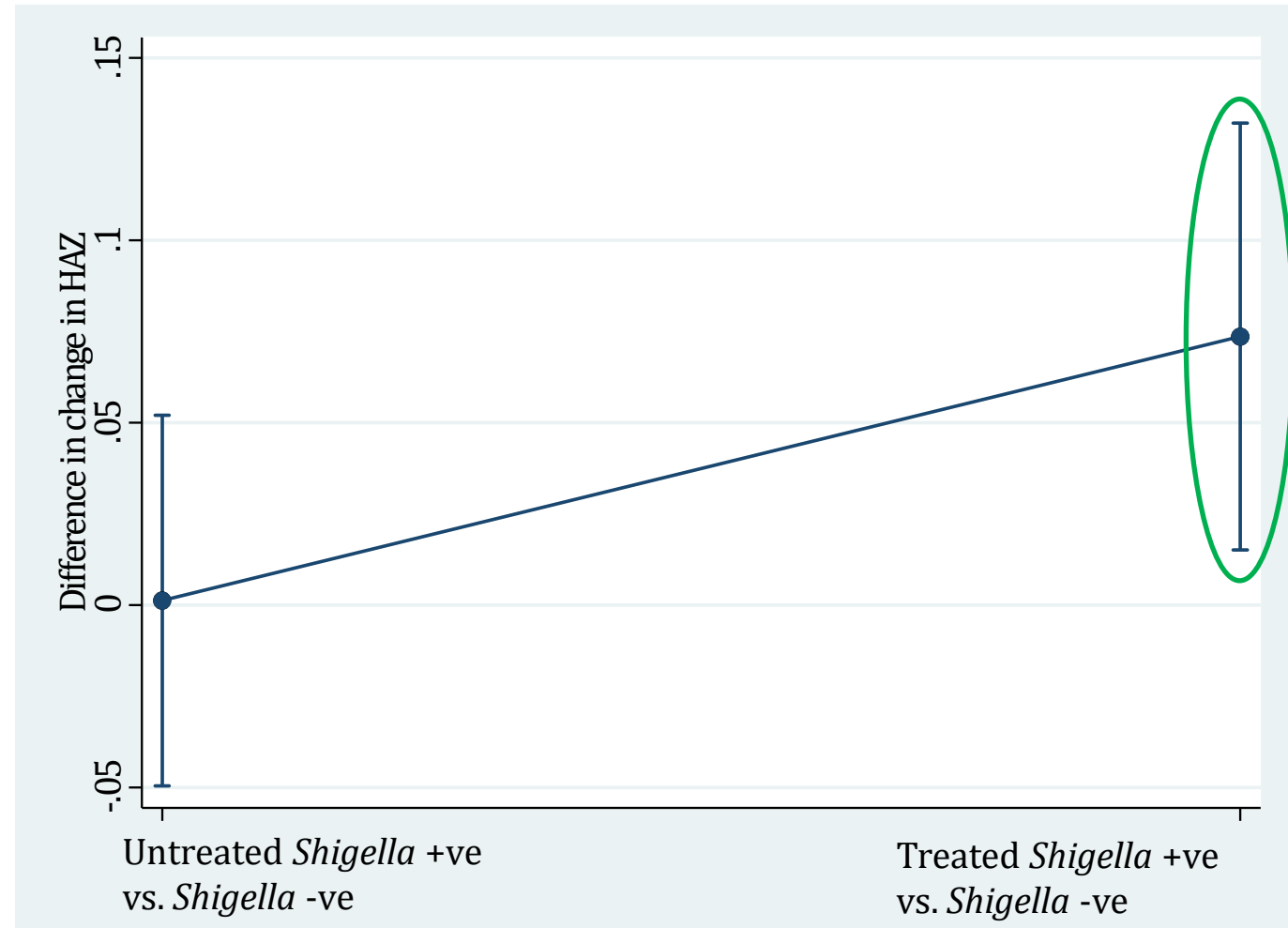


Shigella flexneri, invading an embryonic stem cell. © Wellcome Collection/David Goulding, Wellcome Trust Sanger Institute.

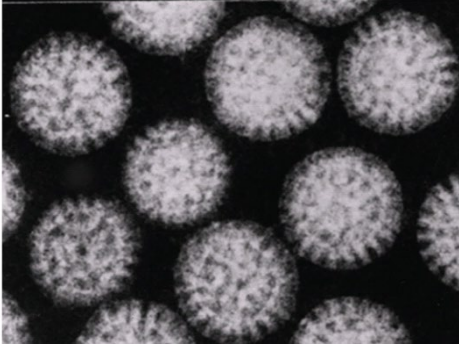
- Effect of *Shigella* and antibiotic treatment on Δ HAZ did not differ significantly by site or age (absence of significant interaction terms)
- Untreated *Shigella* positive MSD cases had no difference in Δ HAZ compared to *Shigella* negative cases:
 - Δ HAZ=-0.20 in untreated *Shigella* positive cases vs. -0.20 in *Shigella* negative cases
 - Difference in Δ HAZ [95% CI]=.001 [-0.52, 0.05], $p = 0.96$

Difference in linear growth in treated and untreated *Shigella* positive cases compared to *shigella* negative cases

- WHO recommended antibiotic treatment in *Shigella* positive cases was associated with a smaller decline in HAZ compared to *Shigella* negative cases.
 - $\Delta\text{HAZ} = -0.13$ in treated *Shigella* positive vs. -0.20 in *Shigella* negative cases
 - Difference in ΔHAZ [95% CI] = 0.07 [0.02, 0.13], **$p = 0.014$**
- Duration of diarrhea was significantly shorter in antibiotic treated shigella-positive cases compared to untreated shigella-positive cases.
 - Mean (SD): (6.0 ± 3.8 days) in treated shigella-positive cases vs. (7.0 ± 4.2) in untreated shigella-positive cases, **$p = 0.01$**

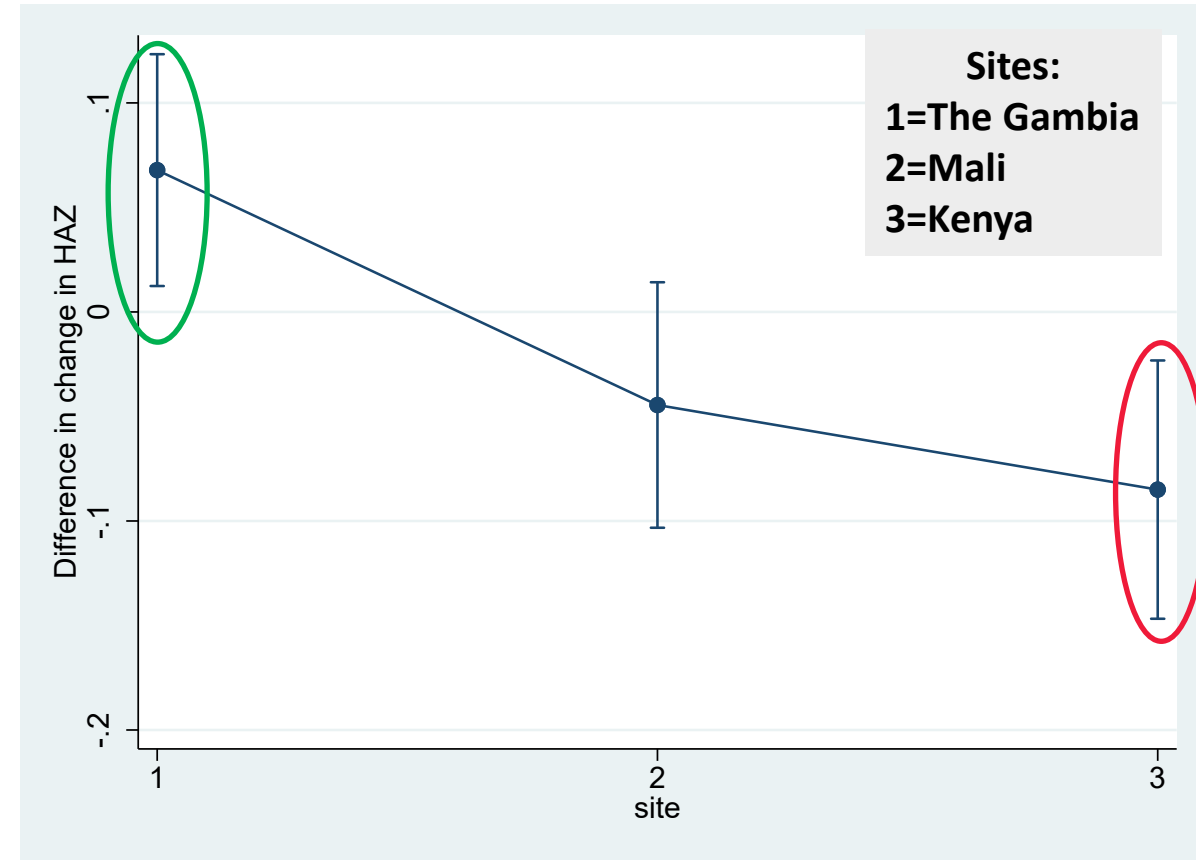


Effect of rotavirus on linear growth, by site

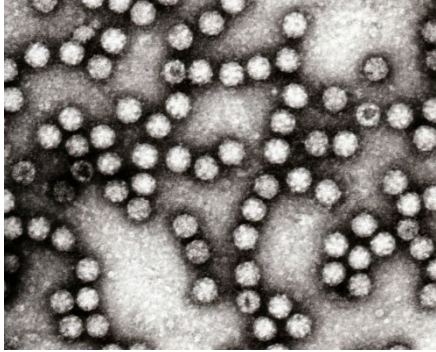


BVV Prasad

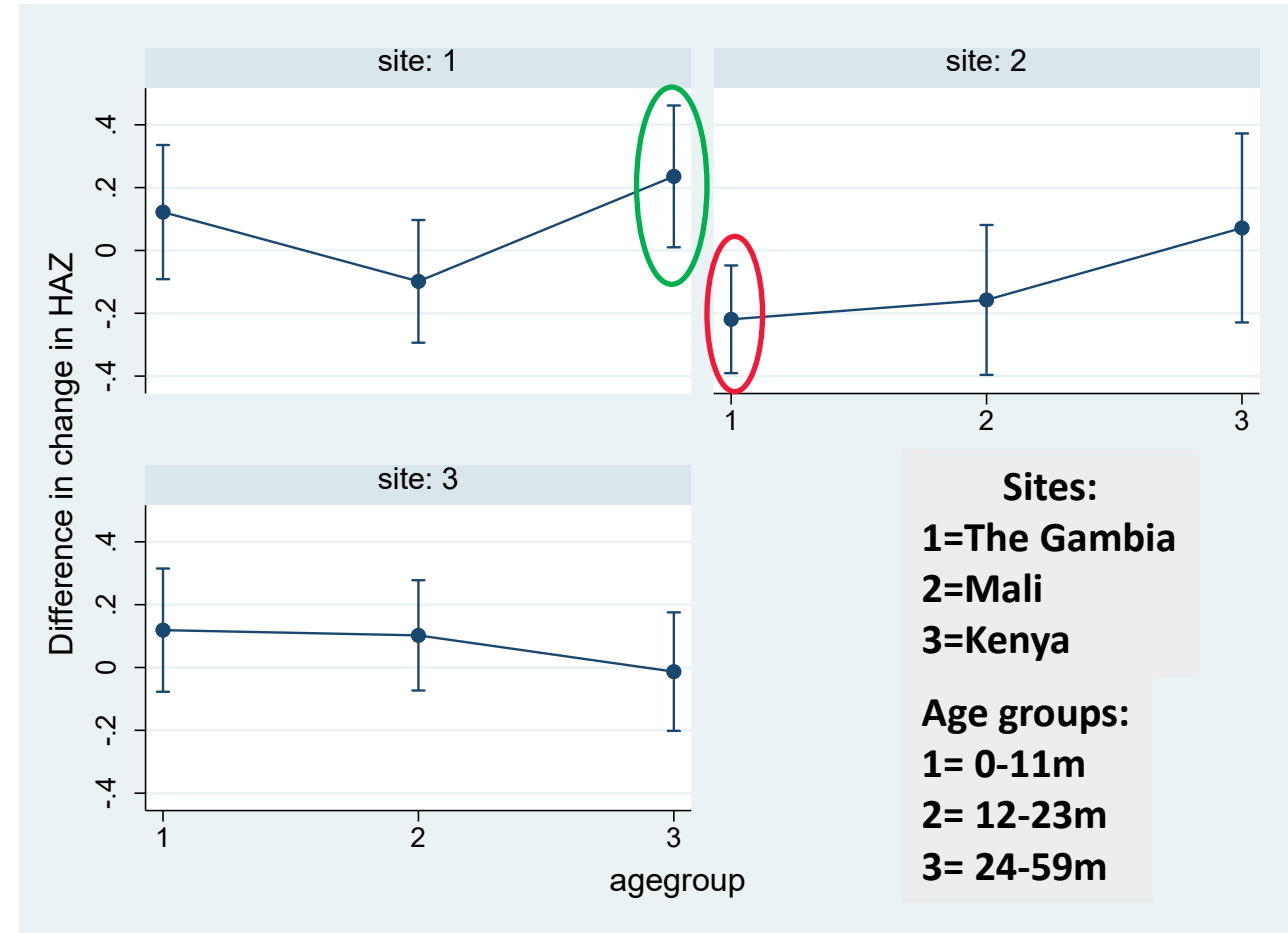
- Effect of rotavirus on linear growth significantly differed by site, but not by age strata.
- In Kenya, rotavirus positive cases had a larger **decline** in HAZ compared to rotavirus negative cases ($\Delta\text{HAZ} = -0.26$ vs. -0.17 ; difference in $\Delta\text{HAZ} = -0.08$, 95% CI $-0.15, -0.02$, $p=0.01$).
- In the Gambia, rotavirus positive cases had a smaller decline in HAZ compared to rotavirus negative cases ($\Delta\text{HAZ} = -0.19$ vs. -0.25 ; difference in $\Delta\text{HAZ} = 0.07$, 95% CI $0.01, 0.12$, $p=0.02$).



Effect of astrovirus on linear growth, by site and age stratum



- Effect of astrovirus on HAZ differed by age stratum and site.
- In Mali, astrovirus was associated with a significantly greater decline in HAZ among 0-11 m cases ($\Delta\text{HAZ} = -0.51$ vs. -0.29 ; difference in ΔHAZ [95% CI] = -0.22 [$-0.39, -0.05$], $p=0.01$)
- In the Gambia, among 24-59 m cases, astrovirus positive cases had an average of 0.12 increase in HAZ, while astrovirus negative cases had an average of 0.12 decline in HAZ (Difference in ΔHAZ [95% CI] = 0.24 [$0.01, 0.46$], $p=0.04$)



Conclusions

- Five diarrheal pathogens significantly associated with linear growth faltering in children younger than 5 years in Africa were *Cryptosporidium*, ST-EPEC, *Shigella*, rotavirus and astrovirus.
 - These same pathogens, with the exception of rotavirus and astrovirus, were associated with linear growth faltering in GEMS
 - Whereas *Cryptosporidium*, ST-EPEC, and *Shigella* demonstrated consistent adverse linear growth affects across sites, rotavirus and astrovirus had site-site variability.
- Treatment of *Shigella*-positive MSD cases with WHO-recommended antibiotics was associated with a shorter the duration of MSD and improved interim linear growth in the VIDA study.
 - These findings corroborate similar findings from GEMS (Nasrin D et al. *J Infect Dis* 2021).
 - In GEMS, antibiotics were found to confer a 4-fold reduction in linear growth faltering among *Shigella*-positive dysentery (p=0.03) and a similar, but statistically insignificant trend in *Shigella*-positive watery MSD. Although not currently recommended, the ability to identify the latter group would require low-cost rapid testing for *Shigella*.
- Our findings highlight the potential impact that could be conferred by development of safe and effective vaccines for enteric pathogens, particularly *Shigella* and *Cryptosporidium*, the major causes of MSD and associated growth faltering in African settings.

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