Shigella Vaccine Updates

Establishment of Shigella Vaccine Technical Advisory Group

Robert Kaminski, Ph.D.
WHO Consultant

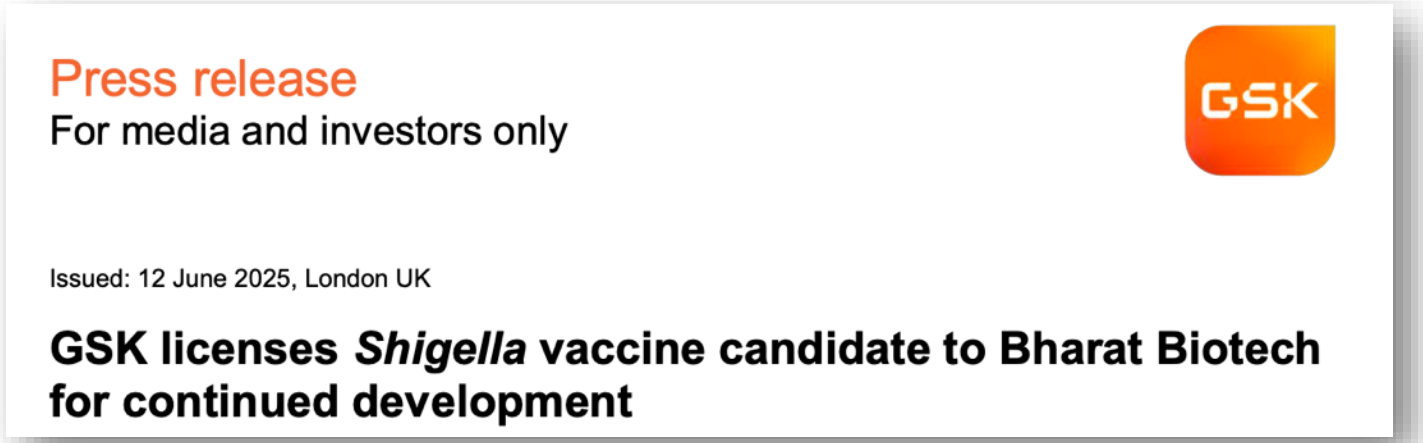
IVB

Shigella Vaccine Update

Partnerships and Upcoming Clinical Studies

Shigella Vaccine Licensing Agreements

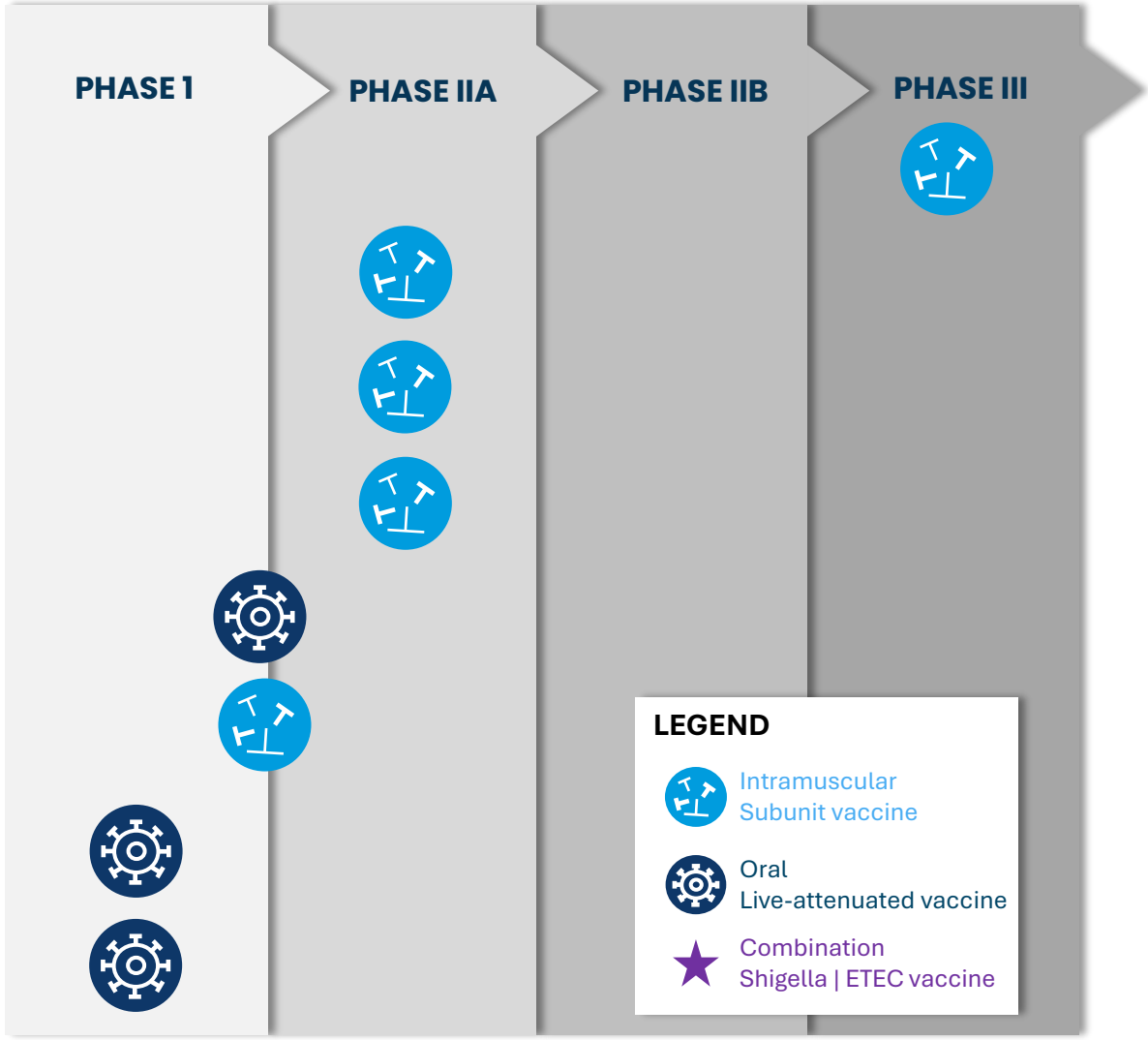
August 1, 2024
Valneva obtains exclusive worldwide license for LimmaTech's S4V Shigella vaccine candidate



June 12, 2025
GSK licenses Shigella GMMA vaccine to Bharat Biotech

Shigella Vaccine Clinical Landscape

Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd	**ZF0901** (Bivalent vaccine)	
Limmatech AG Valneva	**Shigella4V** (Quadrivalent vaccine)	
GSK Vaccines for Global Health (GVGH)	**altSonflex 1-2-3** (Quadrivalent vaccine)	
Institut Pasteur	**SF2a-TT15** (Monovalent vaccine)	
Eveliqure Biotechnologies	**ShigETEC** (Panvalent vaccine)	★
Walter Reed Army Institute of Research (WRAIR)	***S. flexneri* 2a Invaplex$_{AR-Detox}$** (Monovalent vaccine)	
Center for Vaccine Development University of Maryland	**CVD 1208S-122** (Monovalent vaccine)	★
NIAID | WRAIR	**WRSs2** (Monovalent vaccine)	



Shigella Vaccine Clinical Landscape

Target population (Infants in LMICs)

Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd	**ZF0901** (Bivalent vaccine)	
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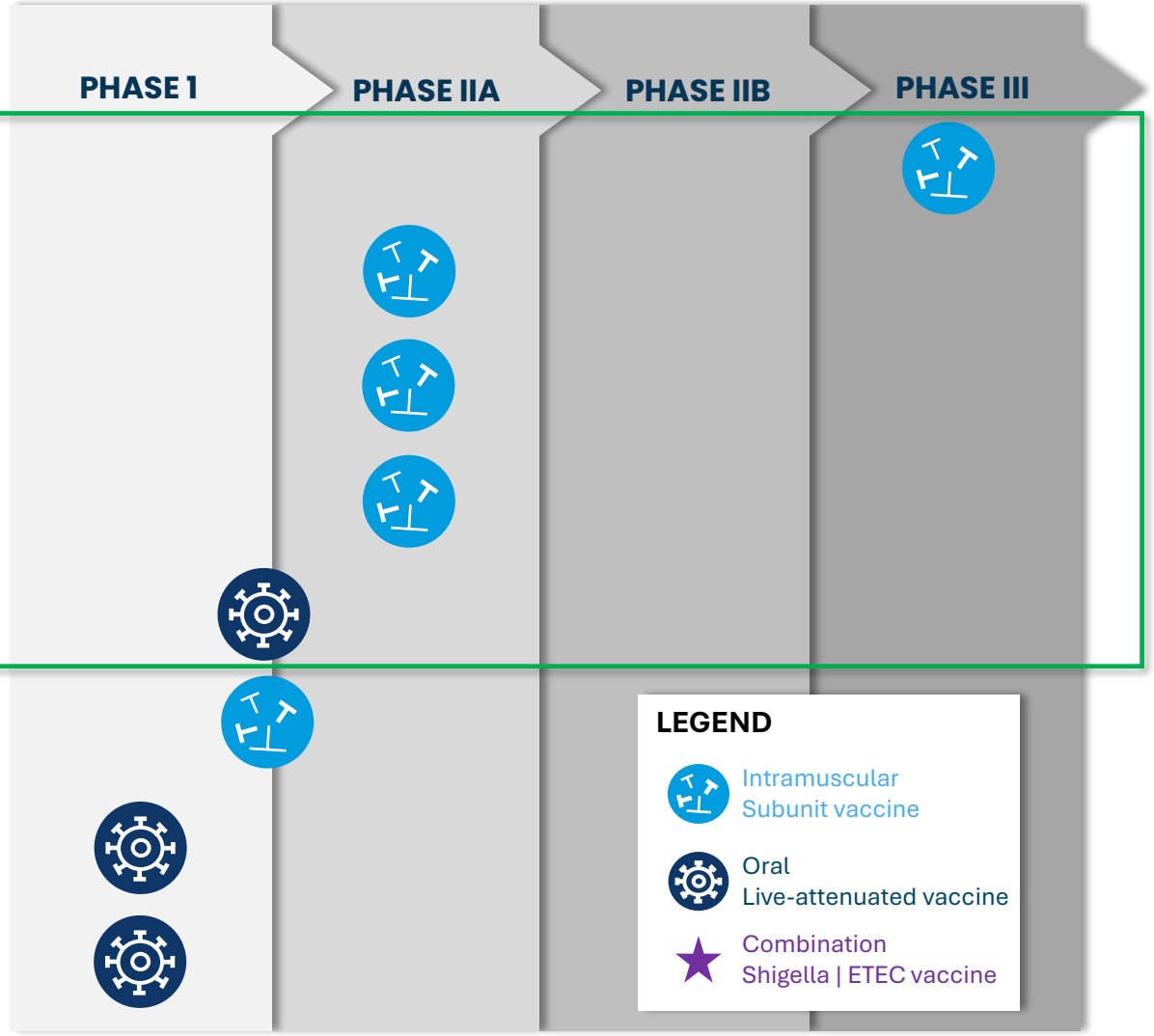


Upcoming Clinical Studies in LMIC Infant Populations

Developer	Vaccine	Location/ID	Brief Description
GSK Vaccines for Global Health (GVGH)	**altSonflex 1-2-3** (Quadrivalent vaccine)	**Kenya** NCT06663436	This study evaluates the **immune response** and **safety** of a multicomponent, **2-dose** Shigella vaccine in preventing shigellosis in African infants from **9 months** of age.
Beijing Zhifei Lvzhu Biopharmaceutical Co., Ltd	**ZF0901** (Bivalent vaccine)	**Bangladesh** NCT06838195	**Phase III** trial to evaluate the **protective efficacy** of S. flexneri-S. sonnei bivalent conjugate vaccine against diarrhea caused by Shigella infection in infants and children aged **6 months to 5 years** after 2 doses of vaccination.
Limmatech AG Valneva	**Shigella4V2** (Quadrivalent vaccine)	**Kenya** NCT06523231	The **second-generation** tetravalent bioconjugate candidate vaccine (Shigella4V2) will be tested to confirm data on its **safety** and **immunogenicity** in infants and to identify the best dose of in **9-month**-old infants.
Eveliqure Biotechnologies	**ShigETEC** (Multivalent vaccine)	**Bangladesh** NCT05987488	Clinical trial to test ShigETEC vaccine, a **combination vaccine** against Shigella and ETEC diarrhoea in Bangladeshi adults (aged 18-45 years) and paediatric participants of three different age groups (aged 2-5 years, 12-23 months and **6-11 months**).

Shigella Vaccine TAG

Technical Advisory Group to Advise WHO on Shigella vaccines

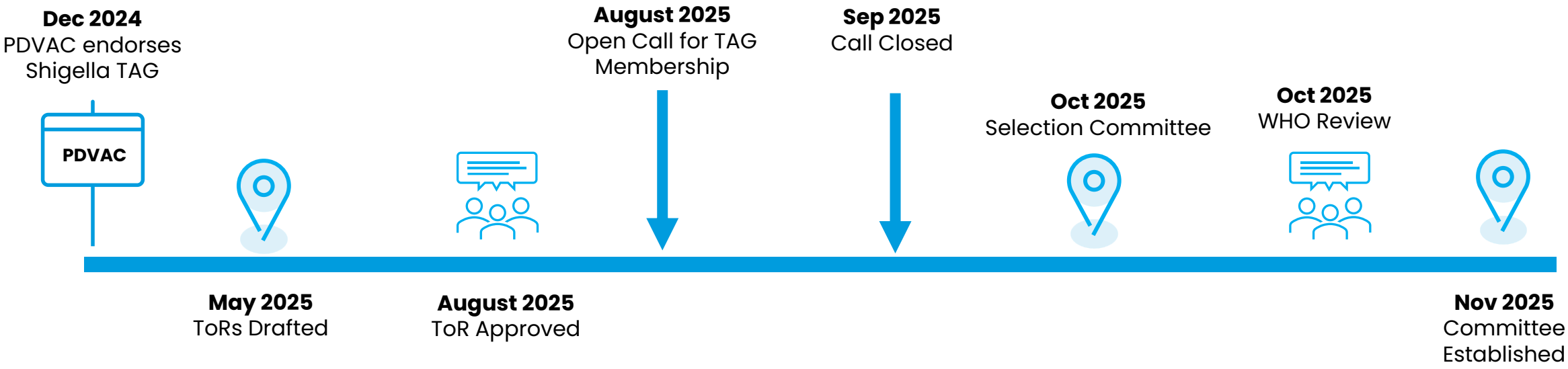
Shigella Vaccine TAG Functions

Review and provide expert technical advice to WHO on:

- Research and Development advances for Shigella vaccines;
- potential refinements to the Preferred Product Characteristics (PPC) for Shigella vaccines;
- the development of an Evidence Considerations for Vaccine Policy (ECVP);
- updated pipeline reviews of standalone and combination Shigella vaccines

Advise WHO on building consensus among global stakeholders, particularly with respect to product development strategy, including clinical endpoints and regulatory pathways for Shigella standalone and combination vaccines.

Overview of Shigella Vaccine TAG Establishment



Funder Acknowledgements

Gates Foundation

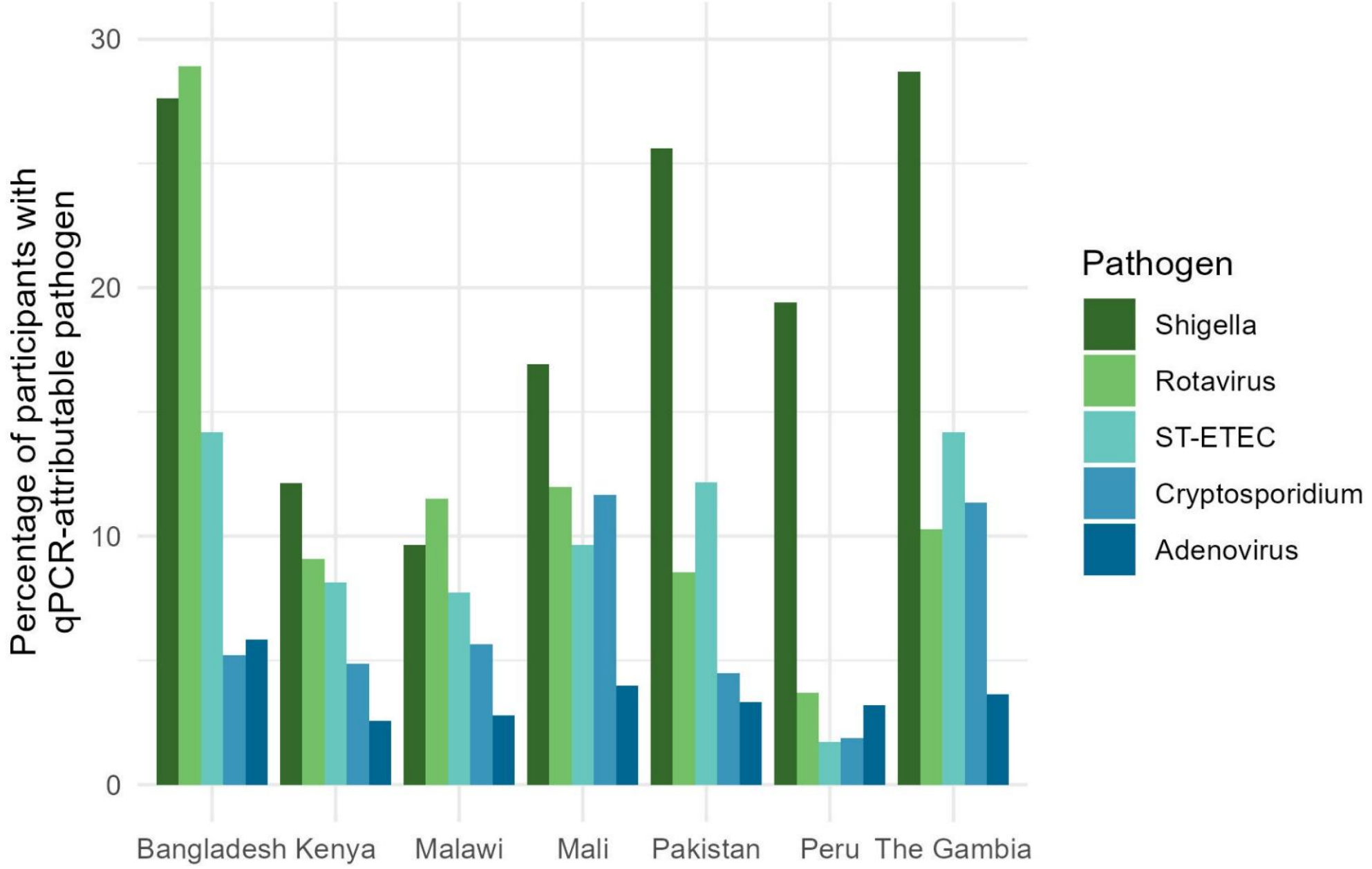

World Health Organization
Many thanks
IVB
11

Shigella epidemiology: Considerations towards lower age for protection/immunization

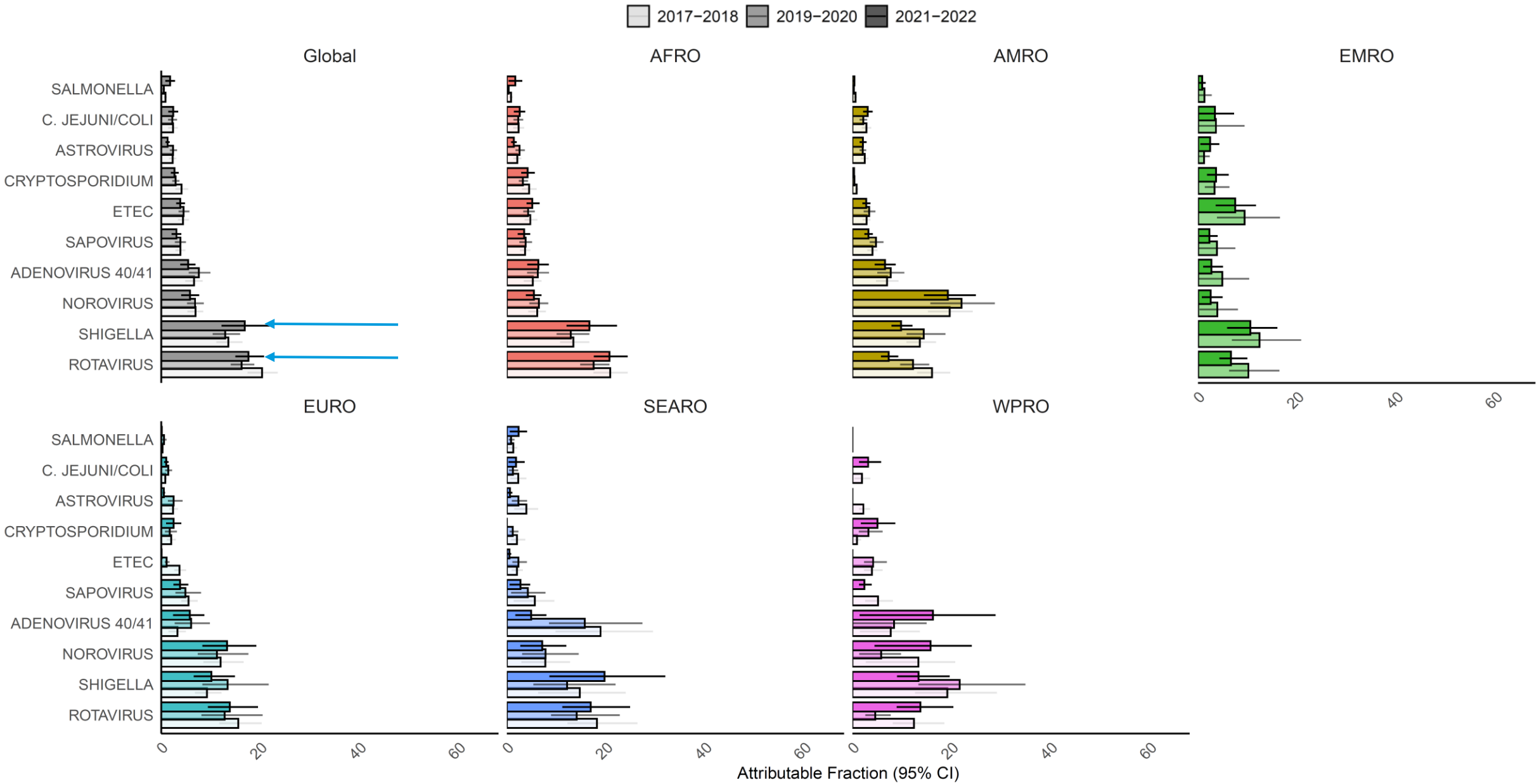
PDVAC – 6 October 2025

James Platts-Mills
Associate Professor of Medicine
Division of Infectious Diseases and International Health
University of Virginia

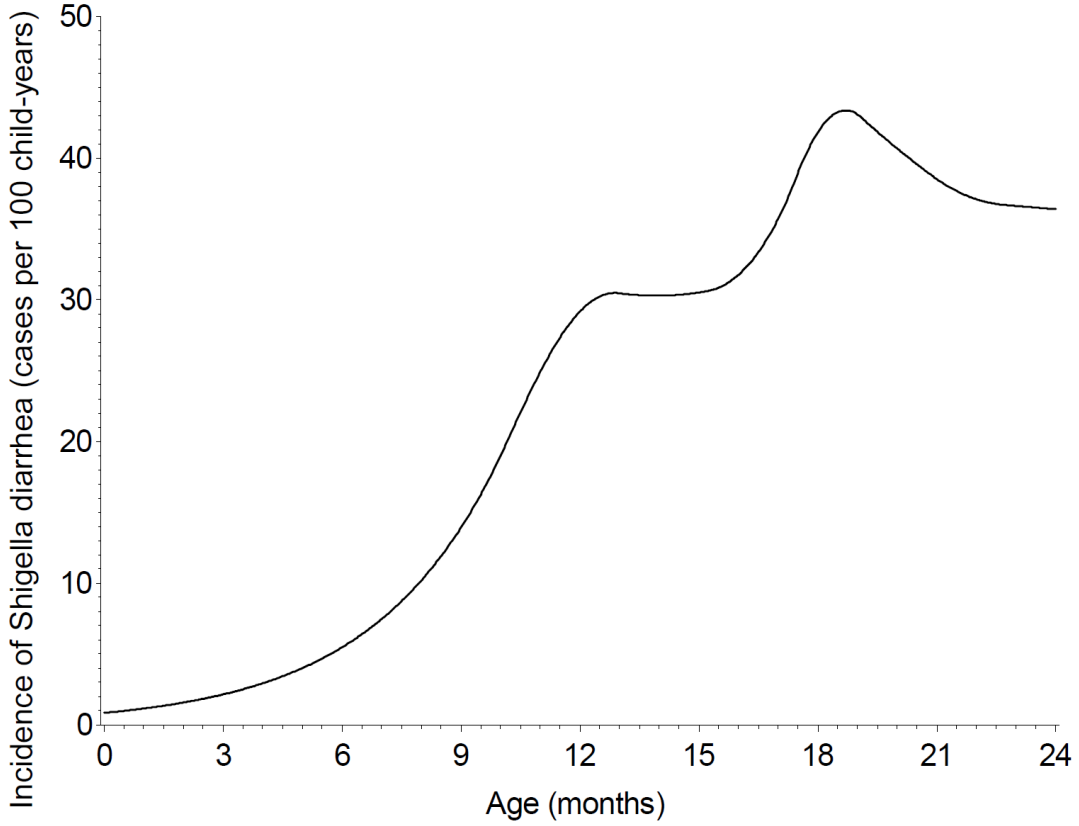
Shigella top cause of medically-attended diarrhea (EFGH)

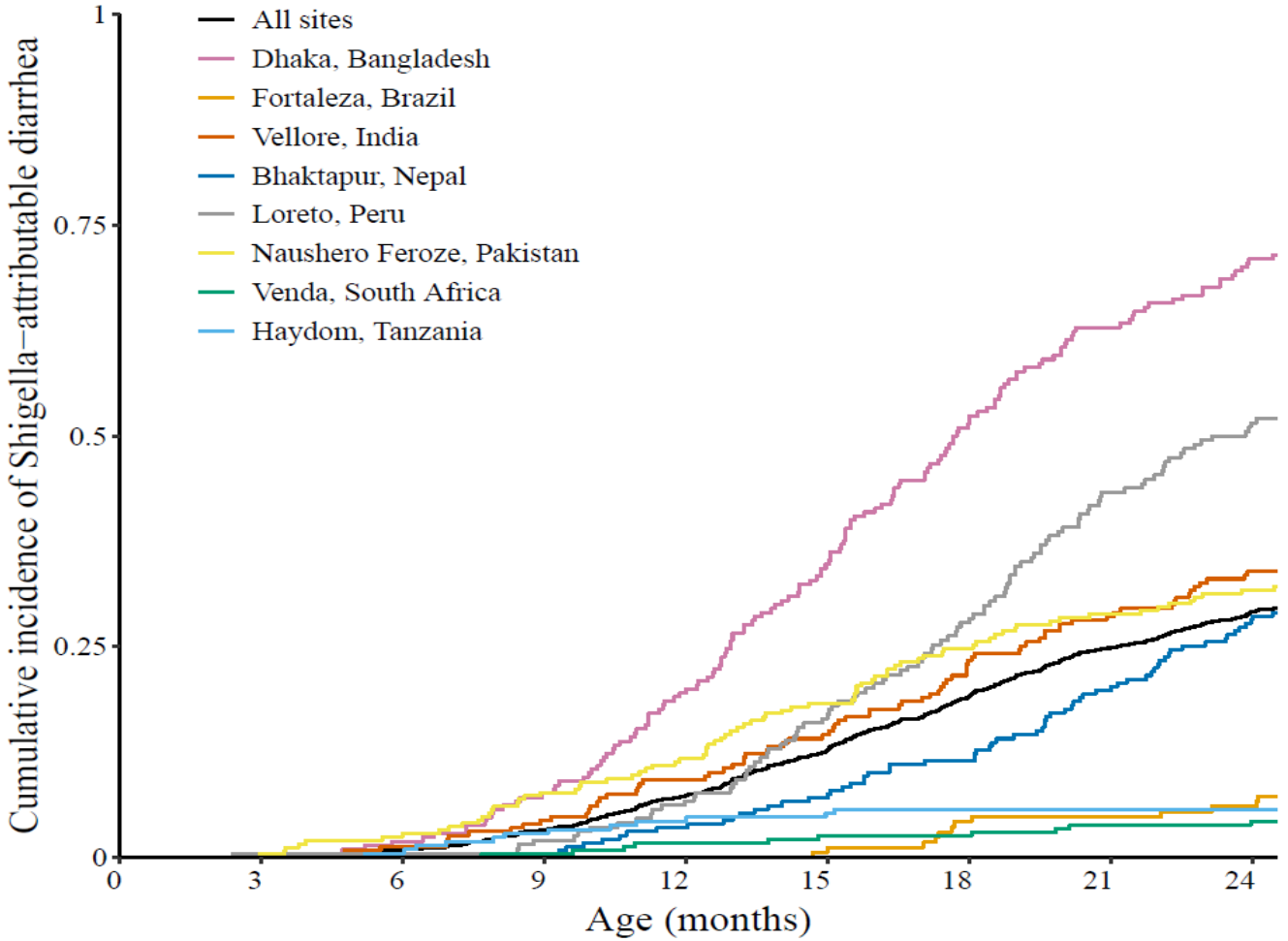


Burden of *Shigella* requiring hospitalization similar to rotavirus in LMICs that have introduced rotavirus vaccine (GPDS)



Most *Shigella* diarrhea of any severity is after 12 months of age (MAL-ED)





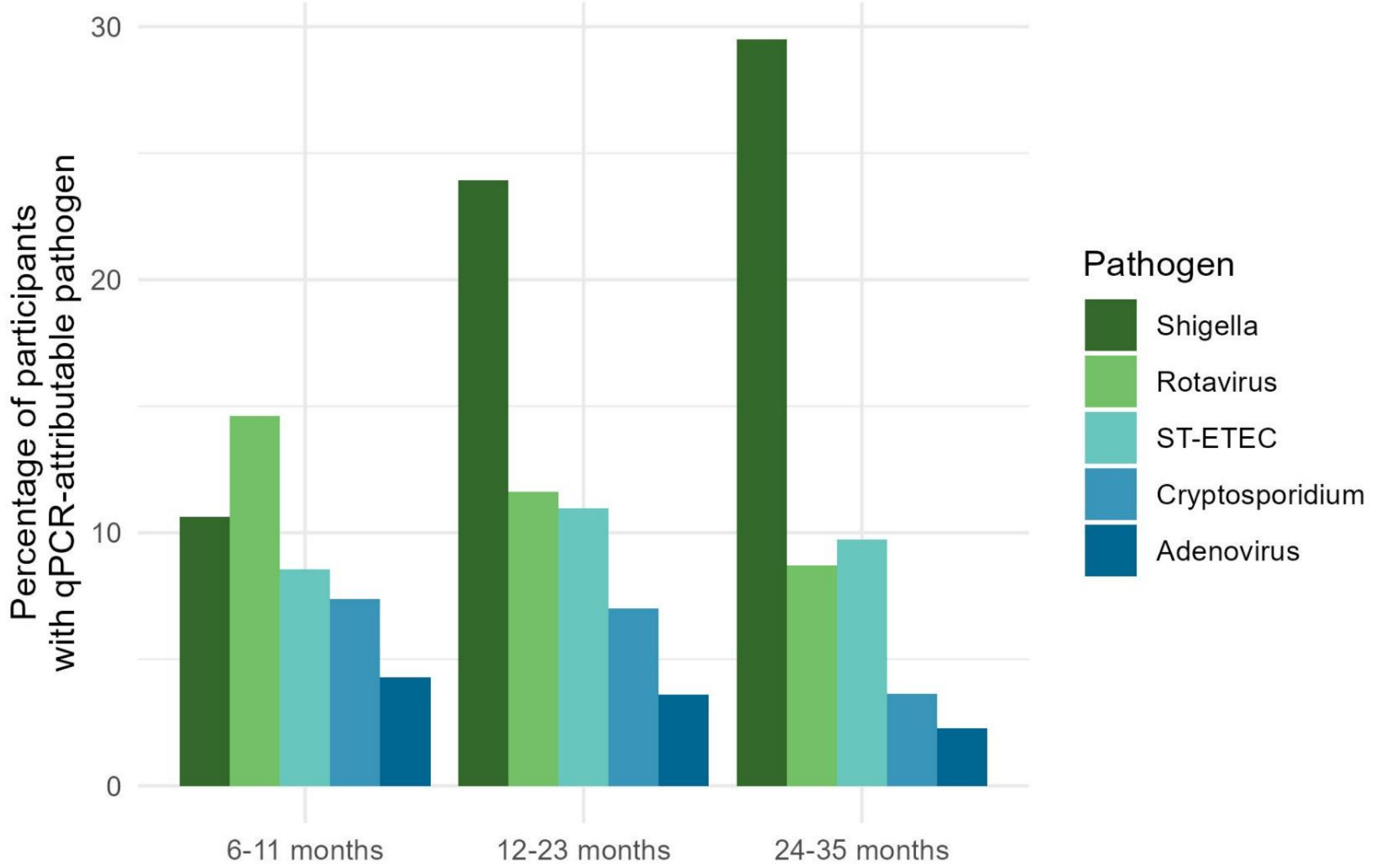
Rogawski McQuade et al, PLOS NTDs 2020

WHO PPC: Immunization goal is full protection by 12 months of age

Parameter	Preferred characteristic	Notes
Target population	Infants from 6 months and children up to 36 months of age. Data supportive of longer-term effectiveness in children up to 5 years of age will be of interest for policy and introduction decision-making.	Infants and children under 5 years of age experience the highest incidence of *Shigella* disease. The peak of incidence is between 12–24 months of age. Some country and regional variation (+/- 6 months) in peak incidence is expected. The immunisation goal is full protection of infants by 12 months of age, thus covering both peak incidence in the second year of life and the greatest burden in children up to 5 years of age in LMICs. Additional potential target populations include the following: immunocompromised children; children under 5 years in crowded communities with high birth rates and recurrent propagated *Shigella* epidemics (i.e. subnational deployment, outbreak response); children over 5 years of age; adolescents and adults living in LMICs; travellers; military; MSM; PLHIV; and elderly and institutionalized persons. However, the preferred product characteristics for vaccines targeted at these populations may differ.

WHO *Shigella* vaccine PPC 2021

Shigella was the second-leading cause in children aged 6-11 months (EFGH)



MSF Rotasiil Trial, Niger: High and early *Shigella* incidence

- We tested samples from 1729 episodes of diarrhea with Vesikari score >=7 (moderate to severe) from a phase 3 efficacy trial of Rotasiil in Niger, the country with the third highest diarrhea mortality in 2016 (IHME).
- *Shigella* was the leading etiology of diarrhea and the majority of shigellosis occurred in infants

	Any cause	*Shigella*	*Cryptosporidium*	Rotavirus	ST-ETEC	Adenovirus 40/41
Overall	43.4	**7.2 (5.2, 9.7)**	6.5 (5.8, 7.2)	6.4 (5.9, 6.7)	6.2 (3.1, 7.7)	4.0 (3.3, 4.5)
Age						
0-5 months**	54.6	2.5 (1.7, 3.3)	5.9 (5.2, 6.5)	6.6 (6.0, 6.9)	4.7 (2.1, 5.9)	4.8 (3.9, 5.5)
6-11 months	76.7	**12.8 (9.0, 17.3)**	13.6 (12.1, 14.9)	12.7 (11.8, 13.2)	11.9 (5.7, 14.8)	8.4 (7.0, 9.4)
12-17 months	26.4	6.0 (4.2, 8.3)	3.5 (3.1, 3.9)	4.9 (4.5, 5.1)	4.9 (2.2, 6.1)	2.5 (2.0, 2.8)
18-23 months	18.8	6.0 (4.2, 8.2)	2.8 (2.4, 3.1)	1.5 (1.4, 1.6)	3.1 (1.4, 3.9)	0.7 (0.5, 0.8)
Severity						
Severe	13	1.7 (1.2, 2.3)	2.6 (2.3, 2.9)	2.4 (2.2, 2.5)	1.9 (0.9, 2.4)	1.4 (1.2, 1.7)
< 12 months	22.9	2.2 (1.5, 3.0)	4.7 (4.2, 5.2)	4.0 (3.7, 4.2)	3.3 (1.5, 4.0)	2.7 (2.3, 3.1)
12-23 months	4.5	1.0 (0.7, 1.4)	0.8 (0.7, 0.9)	1.3 (1.2, 1.3)	0.8 (0.4, 1.0)	0.4 (0.3, 0.5)
Moderate	30.4	5.5 (4.0, 7.4)	3.9 (3.5, 4.3)	4.0 (3.7, 4.2)	4.3 (2.2, 5.4)	2.6 (2.1, 2.9)

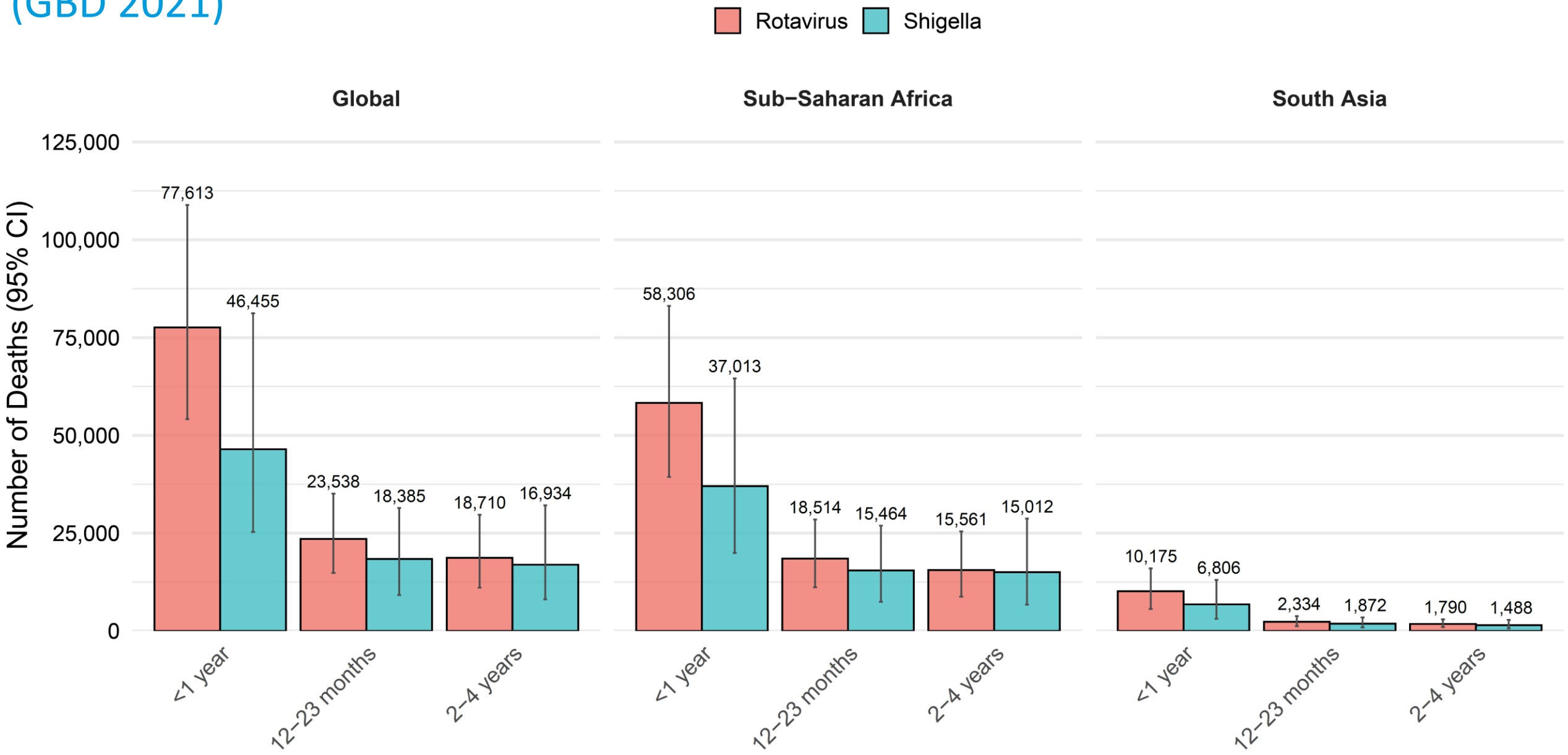
Age	*Shigella*-Attributable Episodes (Cumulative %)	Severe *Shigella*-Attributable Episodes (Cumulative %)	Rotavirus-Attributable Episodes (Cumulative %)	Severe Rotavirus-Attributable Episodes (Cumulative %)
1-3 months*	0.8 (0.1)	0.2 (0.2)	14.5 (2.9)	6.3 (3.4)
3-5 months	35.8 (6.7)	12.1 (9.7)	84.5 (20)	38.4 (24.3)
6-8 months	139.3 (32.1)	35.1 (37.2)	163.1 (53.1)	60.5 (57.1)
9-11 months	**124.9 (54.9)**	**29.7 (60.5)**	100 (73.3)	38.7 (78.1)
12-14 months	69.8 (67.7)	18.4 (75)	66 (86.7)	20.9 (89.4)
15-17 months	53.2 (77.4)	9.7 (82.6)	34.5 (93.6)	14.5 (97.3)
18-20 months	59.7 (88.3)	9.6 (90.1)	17.5 (97.2)	4 (99.5)
21-23 months	64.2 (100)	12.6 (100)	13.9 (100)	1 (100)

Platts-Mills JA et al. *J Pediatr Infect Dis Soc* 2021

Infants represent a significant proportion of under 5 *Shigella* diarrhea hospitalizations in LMICs (GPDS)

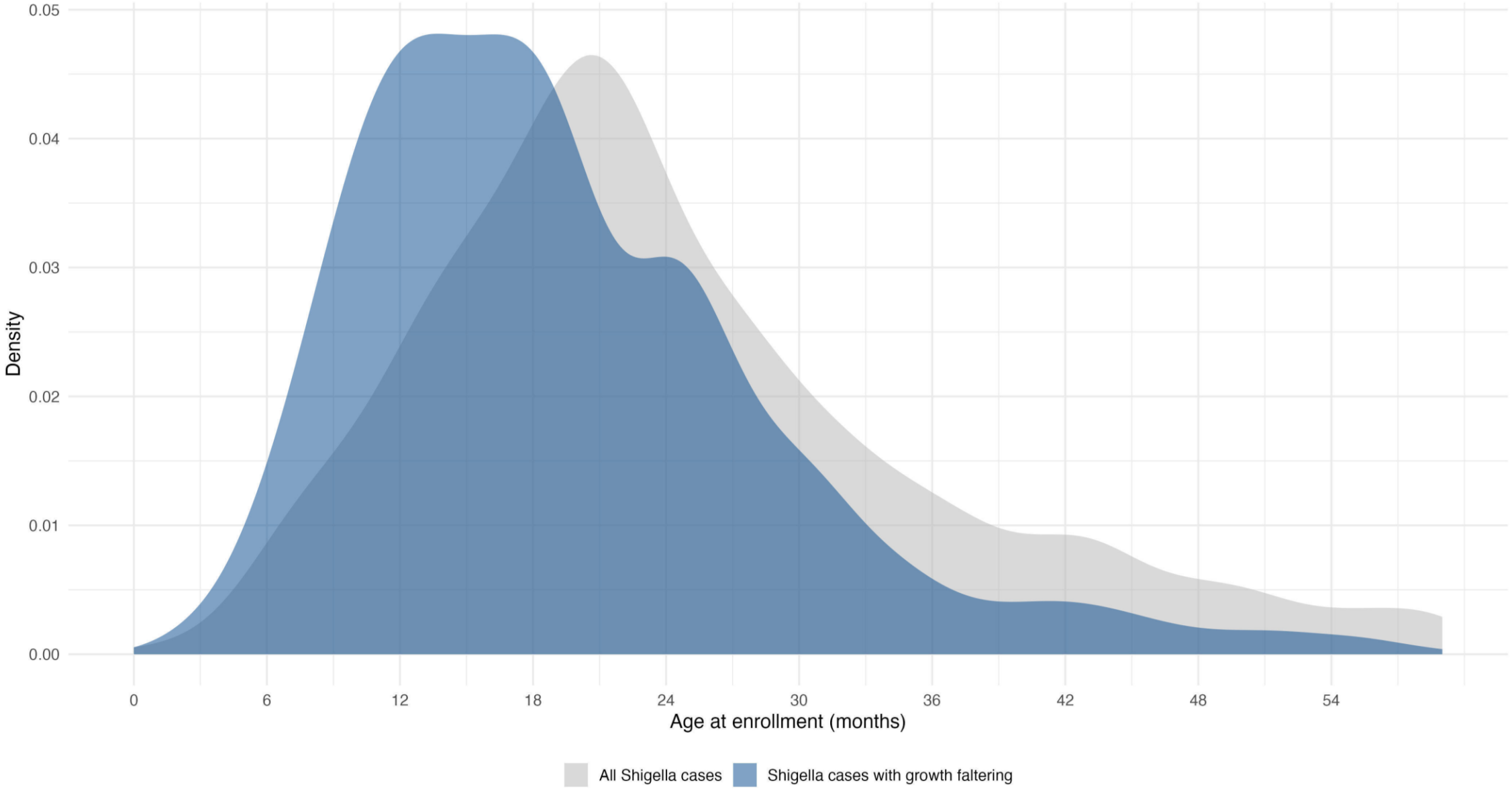
Geographic Region	6 months	9 months	**12 months**	15 months	18 months	24 months	36 months	48 months	60 months
Global	10.1	19.0	**27.1**	37.2	46.0	60.3	80.9	91.4	99.8
Central America	14.0	27.6	**34.2**	41.9	49.5	62.3	82.0	89.9	99.4
Central and Western Asia	7.4	13.8	**21.7**	31.7	41.1	56.7	81.7	92.1	100.0
East and Southern Africa	8.6	18.8	**30.4**	41.0	50.4	64.0	83.6	93.0	100.0
Eastern Europe	0.0	0.0	**0.6**	2.6	6.2	13.1	41.7	70.7	100.0
South America	2.5	4.0	**7.8**	13.9	21.5	36.6	65.3	87.9	100.0
South Asia	17.7	30.9	**41.3**	52.8	58.8	74.0	90.2	96.5	100.0
Southeast Asia and Oceania	7.2	14.4	**17.0**	31.0	39.7	53.1	72.1	83.7	98.9
West Africa	12.6	19.0	**28.3**	44.1	59.1	77.2	90.3	97.0	100.0

The majority of *Shigella* diarrhea deaths in children under 5 occurred in infants (GBD 2021)



IHME Global Burden of Disease study 2021 (https://vizhub.healthdata.org/gbd-results/)

Shigella in infants: ~25% of all cases vs. ~45% of cases with growth faltering (MALED, GEMS, VIDA, EFGH individual-level meta-analysis)



Note: Growth faltering defined as ≥0.1 decline in HAZ between enrollment and follow-up

Key points

- *Shigella* is consistently a leading etiology of diarrhea in a broad range of settings, and may become THE leading etiology of diarrhea, including severe diarrhea, with the ongoing introduction of rotavirus vaccine.
- The relative burden of *Shigella* diarrhea in infants may have been previously underappreciated, especially for more severe disease, including hospitalization and mortality. *Shigella*-associated growth shortfalls are also disproportionately observed in infants.
- It is critical to evaluate recent data to optimize the target age for full protection from a vaccine proposed in the PPC.

Thank you

UVA Division of Infectious Diseases & International Health

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GEMS

University of Maryland, Centro de Investigaçao em Saude da Manhiça Manhiça, Mozambique; Medical Research Council, The Gambia; Kenya Medical Research Institute, Kenya; Center for Vaccine Development, Mali; National Institute of Cholera and Enteric Diseases, India; International Center for Diarrheal Disease Research, Bangladesh; Aga Khan University, Pakistan

MAL-ED Network

Fogarty International Center, University of Virginia, Aga Khan University, Pakistan; Christian Medical College, India; International Center for Diarrheal Disease Research, Bangladesh; University of Venda, South Africa; Haydom Lutheran Hospital, Tanzania; Federal University of Ceará, Brazil; Associacion Benefica PRSIMA, Peru

Niger/MSF Epicentre

Sheila Isanaka, Rebecca Grais

GPDS Network

Sentinel surveillance hospitals and staff, Country Ministries of Health, WHO Country, Regional, and Global offices
National, Regional, and Global Reference Laboratories
Partners (University of Virginia, U.S. CDC)

EFGH

Patricia Pavlinac
University of Washington, University of Maryland, University of Virginia, Emory University
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PHASE III ENDPOINTS-CLINICAL DEFINITION(S)

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Shigella PPC- 2021

Case definition of MSD	Diarrhoea accompanied by dehydration, dysentery, or requiring hospitalization.	MSD is considered the most feasible measurement of desired vaccine impact for pivotal efficacy studies. Case ascertainment is therefore most practical in a medically attended context, where severity indicators can be systematically assessed and faecal samples collected.

This proposed case definition needs validation with stakeholders and harmonization across clinical studies. A scoring system, instead of the case definition proposed, may provide a greater spectrum of disease, and could differentiate moderate from severe diarrhoea.

March 2024 Shigella Vaccine Regulatory Science Meeting in Nairobi, Kenya

vaccines

MDPI

Conference Report

WHO Workshop Report: Regulatory Science to Inform Clinical Pathways for Shigella Vaccines Intended for Use in Children in Low- and Middle-Income Countries

Robert W. Kaminski [1,*], Patricia B. Pavlinac [2], James A. Platts-Mills [3], Elizabeth T. Rogawski McQuade [4], William P. Hausdorff [5,6], Richard A. Isbrucker [7], Kirsten S. Vannice [8], Marco Cavaleri [9], Sonali Kochhar [2,10], Kirsty Mehring-LeDoare [1], Godwin Enwere [11], Annelies Wilder-Smith [1], Karen L. Kotloff [12], Samba Sow [12,13] and Birgitte K. Giersing [1]

Discussion Domains	Issues/Complexities	Input/Next Steps
Clinical case definitions	• Two clinical case definitions were considered for a phase III *Shigella* vaccine study (MSD-GEMS and MSD by mVesikari ± dysentery). • MSD-GEMS does not easily account for various disease severities; some parameters are considered subjective. • mVesikari ± dysentery allows post hoc analysis of vaccine impact across a range of disease severities; it is not specifically tailored to Shigella disease.	• Evaluate the use of MSD-GEMS and mVesikari scoring systems using EFGH data sets. • Refine definition(s) to remove subjective measures and ensure robust alignment with Shigella disease. • Convene stakeholders, particularly regulators, to review recommended and refined case definitions.

GEMS moderate to severe diarrhea (MSD)

- **Dehydration:** some or severe by WHO criteria
- **Dysentery**: visible blood present in ≥1 stool
- **Admission to hospital with diarrhea of dysentery** (or who appears sufficiently ill to prompt the healthcare provider to recommend overnight admission to the hospital)

Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly.	***Pink:*** **SEVERE DEHYDRATION**	▪ If child has no other severe classification: ◦ Give fluid for severe dehydration (Plan C) OR **If child also has another severe classification:** ◦ **Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way** ◦ **Advise the mother to continue breastfeeding** ▪ **If child is 2 years or older and there is cholera in your area, give antibiotic for cholera**
Two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly.	***Yellow:*** **SOME DEHYDRATION**	▪ Give fluid, zinc supplements, and food for some dehydration (Plan B) ▪ **If child also has a severe classification:** ◦ **Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way** ◦ **Advise the mother to continue breastfeeding** ▪ Advise mother when to return immediately ▪ Follow-up in 5 days if not improving
Not enough signs to classify as some or severe dehydration.	***Green:*** **NO DEHYDRATION**	▪ Give fluid, zinc supplements, and food to treat diarrhoea at home (Plan A) ▪ Advise mother when to return immediately ▪ Follow-up in 5 days if not improving

WHO, IMCI, 2014

Modified Vesikari (MVS) moderate or severe diarrhea +/- dysentery

- **Moderate or Severe watery diarrhea**: 3 or more abnormally loose or water stools + modified Vesikari ≥9 points

Score Categories
Mild illness (0-8 points)
Moderate illness (9-10 points)
Severe illness (≥11 points)
[Total out of 20 points]

- **Dysentery**: 3 or more abnormally loose or watery stools with visible blood present in ≥1 stool

Score component	Modified Vesikari (rotavirus trials)	
Duration of diarrhea	1-4 days (1 point) 5 days (2 points) ≥6 days (3 points)	
Max # of stool in 24 hour period	1-3 diarrheal stools (1 point) 4-5 diarrheal stools (2 points) ≥6 diarrheal stools (3 points)	
Duration of vomiting	1 day (1 point) 2 days (2 points) ≥3 days (3 points)	
Max # of vomiting episodes in 24 hour period	1 (1 point) 2-4 (2 points) ≥5 (3 points)	
Max recorded temperature	Rectal: 37.1-38.4°C (1 point) 38.5°C-38.9°C (2 points) ≥39.0°C (3 points)	Axillary: 36.6-37.9°C (1 point) 38.0°C-38.4°C (2 points) ≥38.5°C (3 points)
Dehydration (based on WHO IMCI)	None (0 points) Some (2 points) Severe (3 points)	
Treatment	None (0 points) Rehydration (1 point) Hospitalization (2 points)	

Alternative severity definitions

Severity definitions		GEMS-MSD	MVS	MVS +/- dysentery	Clark	MAL-ED	*Shigella* mortality
		No criteria present = less-severe diarrhea Any criteria present = moderate-to-severe diarrhea (MSD)	Total Score: 0-8 = Mild 9-10 = Moderate ≥11 = Severe	MVS score of <9 and no dysentery = Mild with no dysentery MVS score of ≥9 or dysentery = Moderate/severe or dysentery	Total Score: 2-8 = Mild ≥9 = Moderate to severe	Total Score: <6 = Non-severe ≥6 = Severe	Total Score: <6 = Mild 6-8 = Moderate ≥9 = Severe
Severity indicator	**Description of severity indicator**						
Number of days of diarrhea	Number of days with diarrhea (3 or more loose stools) within the diarrhea episode		1-4 days = 1 5 days = 2 ≥6 days = 3	1-4 days = 1 5 days = 2 ≥6 days = 3	1-4 days = 1 5-7 days = 2 >7 days = 3	2-4 days = 1 5-7 days = 2 ≥8 days = 3	
Diarrhea duration prior to presentation	Number of days from diarrhea episode start to enrollment date (including day of enrollment)						1-3 days = 0 4-5 days = 2 ≥6 days = 3
Dysentery	Blood in stool reported by caregiver or clinician	Dysentery = MSD		Dysentery = Moderate/severe or dysentery			
Treatment	Rehydration: Oral rehydration solution (ORS) or IV rehydration given at enrollment Hospitalization: Participant received inpatient care from 12am-6am during the diarrhea episode	Hospitalization = MSD	Rehydration = 1 Hospitalization = 2	Rehydration = 1 Hospitalization = 2			Hospitalization = 5
Maximum number of loose stools	Maximum number of loose stools reported by caregiver in one day during diarrhea episode		1-3 stools = 1 4-5 stools = 2 ≥6 stools = 3	1-3 stools = 1 4-5 stools = 2 ≥6 stools = 3	2-4 stools = 1 5-7 stools = 2 >7 stools = 3	<5 stools = 1 5-7 stools = 2 ≥8 stools = 3	
Maximum number of times vomited	Maximum number of times vomiting reported by caregiver in one day during diarrhea episode		1 time = 1 2-4 times = 2 ≥5 times = 3	1 time = 1 2-4 times = 2 ≥5 times = 3	1-3 times = 1 4-6 times = 2 >6 times = 3		
Dehydration	Classified as none, some, or severe following WHO integrated management of childhood illness (IMCI) guidance	Some = MSD Severe = MSD	None = 0 Some = 2 Severe = 3	None = 0 Some = 2 Severe = 3		Some = 2 Severe = 3	None = 0 Some = 4 Severe = 8
Vomiting duration	Number of days of vomiting reported by caregiver during diarrhea episode		1 day = 1 2 days = 2 ≥3 days = 3	1 day = 1 2 days = 2 ≥3 days = 3	2 days = 1 3-5 days = 2 >5 days = 3	1 day = 1 2 days = 2 ≥3 days = 3	
Duration of fever	Number of days of fever or hot-to-touch reported by caregiver during diarrhea episode				1-2 days = 1 3-4 days = 2 ≥5 days = 3	≥1 day = 1	
Maximum axillary temperature	Maximum axillary temperature measured at enrollment or reported by caregiver during diarrhea episode		36.6-37.9 = 1 38.0-38.4 = 2 ≥38.5 = 3	36.6-37.9 = 1 38.0-38.4 = 2 ≥38.5 = 3			
Maximum rectal temperature	Maximum rectal temperature measured at enrollment or reported by caregiver during diarrhea episode				38.0-38.2 = 1 38.3-38.7 = 2 ≥38.8 = 3		
Confirmed Temperature	Temperature taken by clinician at enrollment					≥37.5 = 2	
Behavioral Signs	Assessed by clinician at enrollment				Irritable = 1 Lethargic = 2 Seizures = 3		

Data from EFGH

EFGH enrolled 9,476 children aged 6-35 months with medically-attended diarrhea between 2022 and 2024 in 7 countries:

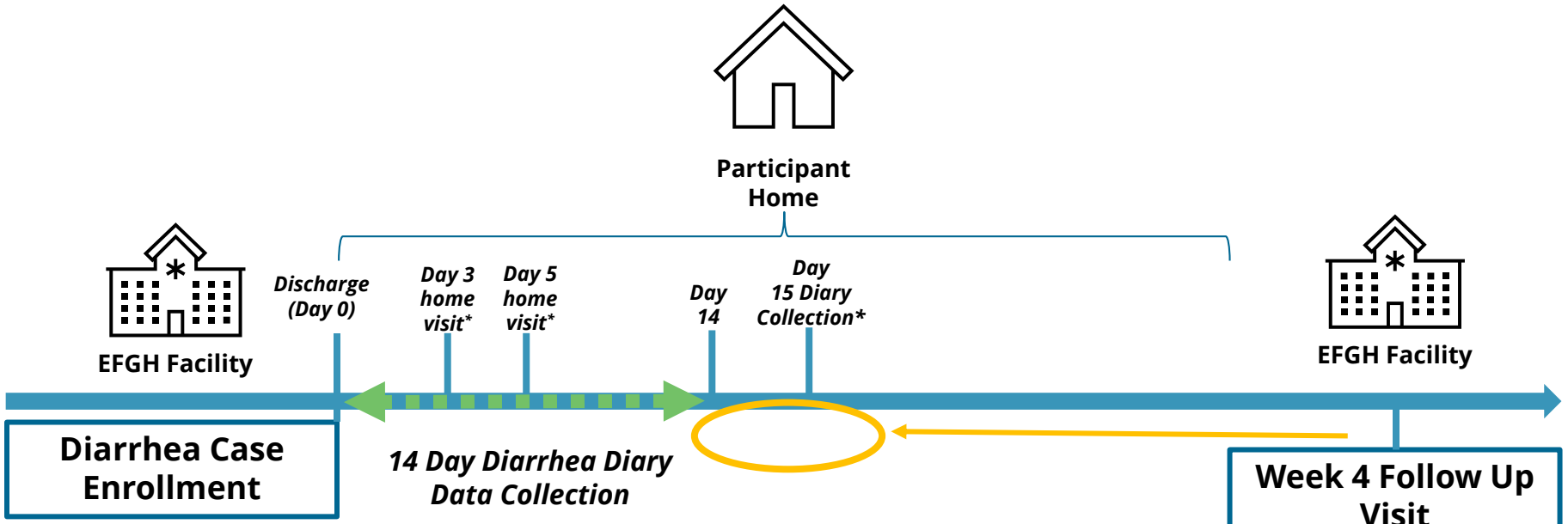
9.3% were *Shigella* culture positive

20.0% were *Shigella*-attributed by qPCR

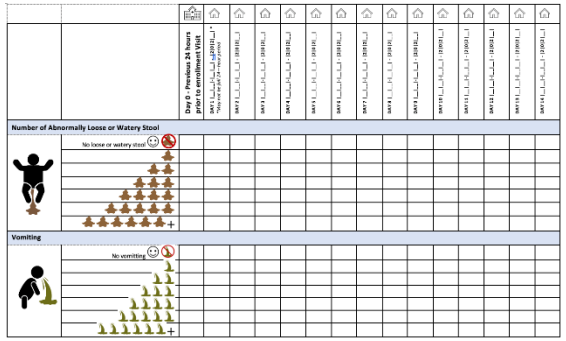
EFGH Protocol

EFGH Burden Pre-print

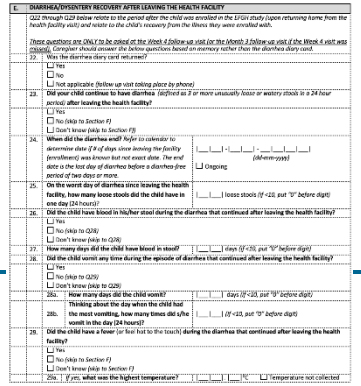
EFGH Diarrhea Diary



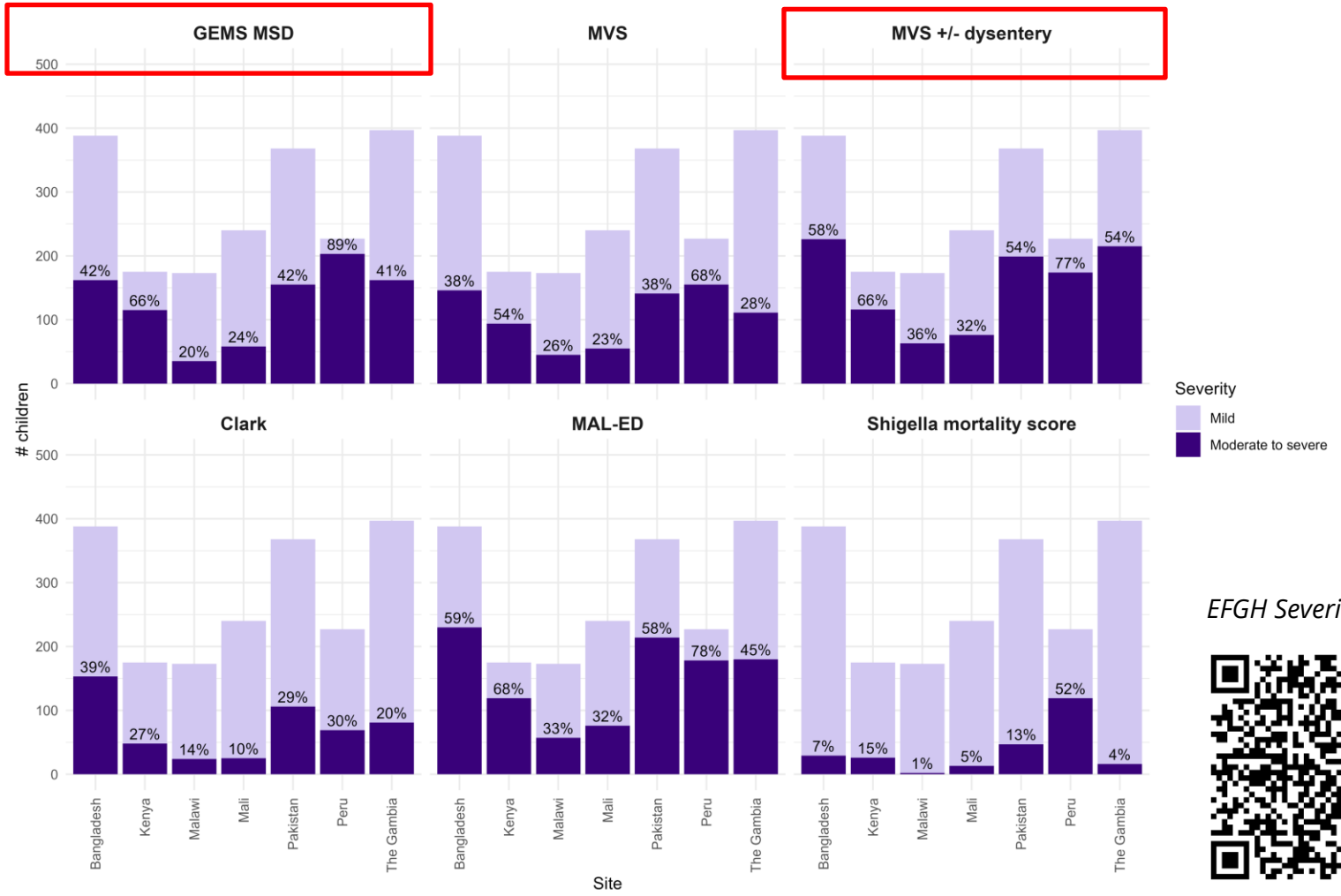
- *Caregiver Diarrhea Diary Training by Study Staff*
- *Practice entry completed by caregiver with staff*



- *Diarrhea Diary Return**
- *Diarrhea questions asked in CRF*



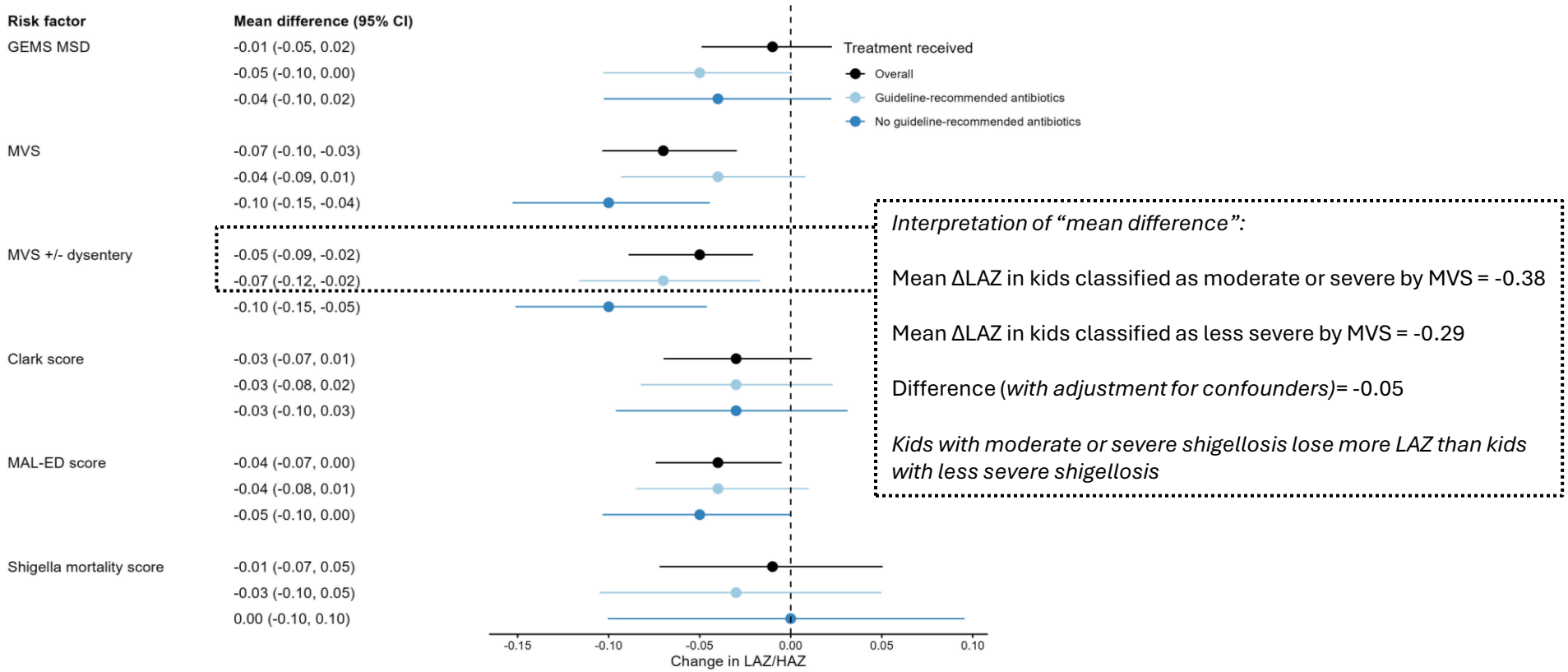
Severity of *Shigella*-attributable medically-attended diarrhea (n=1,968) by severity definition and site



EFGH Severity Pre-print

GEMS MSD: dehydration, dysentery, and/or indication for hospitalization
Moderate-or-severe MVS +/- dysentery: 9+ points by MVS or dysentery

Association between more severe diarrhea by dichotomized severity definitions and change in length-for-age z-score or height-for-age z-score (ΔLAZ/HAZ) from enrollment to 3-month follow-up among children with *Shigella*-attributable medically attended diarrhea



Interpretation of "mean difference":

Mean ΔLAZ in kids classified as moderate or severe by MVS = -0.38

Mean ΔLAZ in kids classified as less severe by MVS = -0.29

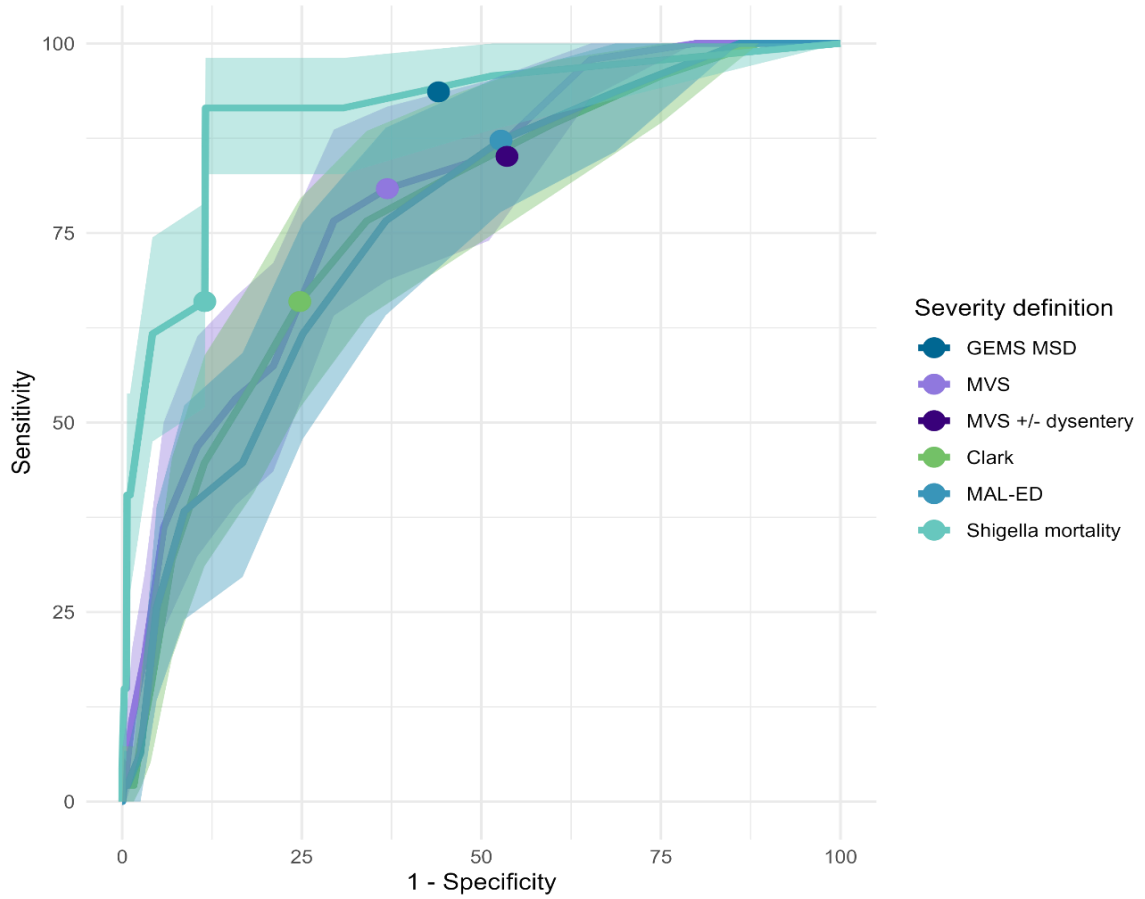
Difference (*with adjustment for confounders)*= -0.05

Kids with moderate or severe shigellosis lose more LAZ than kids with less severe shigellosis

Models adjusted for baseline LAZ/HAZ, site, and number of days

EFGH

Receiver operating characteristic (ROC) curves and 95% CIs of severity definitions on the outcome of death or hospitalization within 14 days of enrollment among 1,968 children with *Shigella*-attributable medically-attended diarrhea



March 2024 Shigella Vaccine Regulatory Science Meeting in Nairobi, Kenya

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Conference Report

WHO Workshop Report: Regulatory Science to Inform Clinical Pathways for Shigella Vaccines Intended for Use in Children in Low- and Middle-Income Countries

Robert W. Kaminski [1,*], Patricia B. Pavlinac [2], James A. Platts-Mills [3], Elizabeth T. Rogawski McQuade [4], William P. Hausdorff [5,6], Richard A. Isbrucker [7], Kirsten S. Vannice [8], Marco Cavaleri [9], Sonali Kochhar [2,10], Kirsty Mehring-LeDoare [1], Godwin Enwere [11], Annelies Wilder-Smith [1], Karen L. Kotloff [12], Samba Sow [12,13] and Birgitte K. Giersing [1]

Discussion Domains	Issues/Complexities	Input/Next Steps
Clinical case definitions	• Two clinical case definitions were considered for a phase III *Shigella* vaccine study (MSD-GEMS and MSD by mVesikari ± dysentery). • MSD-GEMS does not easily account for various disease severities; some parameters are considered subjective. • mVesikari ± dysentery allows post hoc analysis of vaccine impact across a range of disease severities; it is not specifically tailored to Shigella disease.	• Evaluate the use of MSD-GEMS and mVesikari scoring systems using EFGH data sets. • Refine definition(s) to remove subjective measures and ensure robust alignment with Shigella disease. • Convene stakeholders, particularly regulators, to review recommended and refined case definitions.

WHO IMCI Dehydration Classification-Subjective measures

- Sunken eyes
- Thirst

Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly.	***Pink:*** **SEVERE DEHYDRATION**	■ If child has no other severe classification: ○ Give fluid for severe dehydration (Plan C) OR **If child also has another severe classification:** ○ **Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way** ○ **Advise the mother to continue breastfeeding** ■ **If child is 2 years or older and there is cholera in your area, give antibiotic for cholera**
Two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly.	***Yellow:*** **SOME DEHYDRATION**	■ Give fluid, zinc supplements, and food for some dehydration (Plan B) ■ **If child also has a severe classification:** ○ **Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way** ○ **Advise the mother to continue breastfeeding** ■ Advise mother when to return immediately ■ Follow-up in 5 days if not improving
Not enough signs to classify as some or severe dehydration.	***Green:*** **NO DEHYDRATION**	■ Give fluid, zinc supplements, and food to treat diarrhoea at home (Plan A) ■ Advise mother when to return immediately ■ Follow-up in 5 days if not improving

WHO, IMCI, 2014

Alternative DHAKA Score

External validation of the DHAKA score and comparison with the current IMCI algorithm for the assessment of dehydration in children with diarrhoea: a prospective cohort study

Adam C Levine, Justin Glavis-Bloom, Payal Modi, Sabiha Nasrin, Bita Atika, Soham Rege, Sarah Robertson, Christopher H Schmid, Nur H Alam

Summary

Background Dehydration due to diarrhoea is a leading cause of child death worldwide, yet no clinical tools for assessing dehydration have been validated in resource-limited settings. The Dehydration: Assessing Kids Accurately

Lancet Glob Health 2016; 4: e744-51

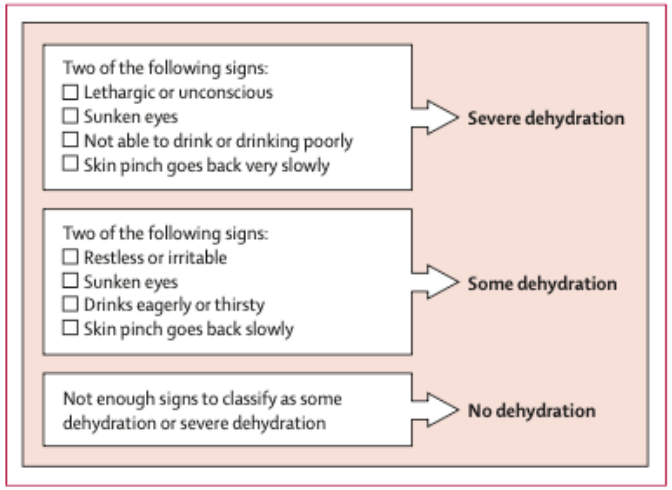

Figure 1: **IMCI algorithm**
IMCI=Integrated Management of Childhood Illness.

Clinical sign	Finding	Points
General appearance	Normal	0
	Restless/irritable	2
	Lethargic/unconscious	4
Tears	Normal	0
	Decreased	1
	Absent	2
Skin pinch	Normal	0
	Slow	2
	Very slow	4
Respirations	Normal	0
	Deep	2

Figure 2: **DHAKA score**
A score of 4 or more was deemed severe dehydration, a score of 2–3 as some dehydration, and a score of 0–1 as no dehydration. DHAKA=Dehydration: Assessing Kids Accurately.

	Sensitivity	Specificity	LR positive (95% CI)	LR negative (95% CI)
Some dehydration				
IMCI algorithm				
≥2 dehydration signs*	97%	26%	1·3 (1·2–1·4)	0·11 (0·05–0·23)
DHAKA score				
≥1	97%	30%	1·4 (1·3–1·5)	0·11 (0·05–0·22)
≥2*	93%	50%	1·9 (1·6–2·1)	0·14 (0·09–0·23)
≥3	89%	63%	2·4 (2·0–2·9)	0·18 (0·13–0·26)
≥4	78%	76%	3·3 (2·6–4·1)	0·29 (0·23–0·37)
≥5	74%	79%	3·6 (2·8–4·7)	0·32 (0·26–0·40)
≥6	70%	84%	4·3 (3·2–5·8)	0·36 (0·30–0·44)
≥7	69%	85%	4·6 (3·4–6·3)	0·37 (0·31–0·45)
≥8	57%	89%	5·3 (3·6–7·8)	0·48 0·41–0·56)
Severe dehydration				
IMCI algorithm				
≥2 severe signs*	77%	67%	2·3 (1·9–2·8)	0·34 (0·22–0·53)
DHAKA score				
≥3	94%	42%	1·6 (1·5–1·8)	0·14 (0·05–0·36)
≥4*	86%	54%	1·9 (1·6–2·1)	0·26 (0·15–0·47)
≥5	84%	58%	2·0 (1·7–2·3)	0·27 (0·16–0·47)
≥6	83%	63%	2·2 (1·9–2·6)	0·27 (0·16–0·46)
≥7	81%	64%	2·3 (1·9–2·7)	0·29 (0·18–0·48)
≥8	70%	71%	2·4 (2·0–3·0)	0·42 (0·29–0·60)
≥9	69%	75%	2·7 (2·2–3·4)	0·42 (0·30–0·60)
≥10	44%	86%	3·2 (2·2–4·6)	0·65 (0·52–0·80)

*Original cutoffs from the IMCI guidelines and the DHAKA derivation study. LR=likelihood ratio. IMCI=Integrated Management of Childhood Illness. DHAKA=Dehydration: Assessing Kids Accurately.

Table 3: **Test characteristics for the current IMCI algorithm and the DHAKA score by cutoffs**

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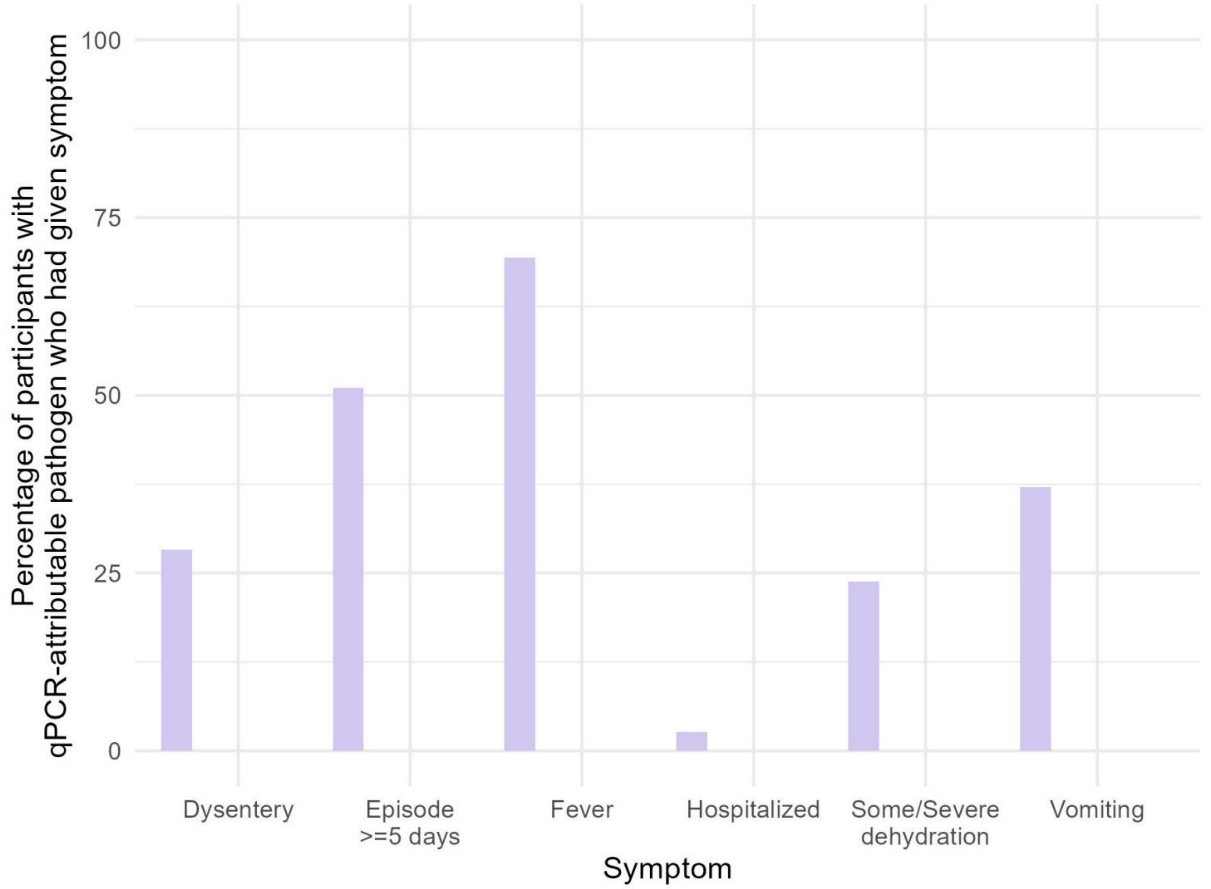
Clinical severity of children with *Shigella*-attributed diarrhea



Pathogen

- Shigella (n=1870)
- ST-ETEC (n=920)
- Cryptosporidium (n=614)
- Adenovirus (n=328)

	Dysentery (n=757)	Watery diarrhoea (n=288)
Fever	607 (80%)	207 (72%)
Abdominal cramps	616 (81%)	137 (48%)
Vomiting	136 (18%)	89 (31%)
WHO-defined dehydration	95 (13%)	134 (47%)
Tenesmus	511 (68%)	32 (11%)
Rectal prolapse	19 (3%)	4 (1%)

Data unpublished or from the Global Enteric Multicenter Study.[32]

Table: **Acute clinical manifestations of shigellosis among children younger than 5 years**

GEMS:

Shigellosis

Karen L Kotloff, Mark S Riddle, James A Platts-Mills, Patricia Pavlinac, Anita K M Zaidi

Shigellosis is a clinical syndrome caused by invasion of the epithelium lining the terminal ileum, colon, and rectum by *Shigella* species. Although infections occur globally, and in people of all ages, endemic infections among children aged

Published Online December 15, 2017

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Acknowledgements

We would like to acknowledge the EFGH PIs and their extraordinary teams:

- Maribel Paredes and Margaret Kosek (Peru)
- Nigel Cunliffe, Khuzwayo Jere, Jen Cornick (Malawi)
- Samba Sow and Karen Kotloff (Mali)
- Firdausi Qadri (Bangladesh)
- Jahangir Hossain and Karen Kotloff (The Gambia)
- Richard Omore and Karen Kotloff (Kenya)
- Farah Qamar (Pakistan)

With coordination support from:

- University of Washington
- University of Maryland, Baltimore
- University of Virginia
- Emory University

Gates Foundation:

- Kirsten Vannice
- Duncan Steele
- Cal MacLennan
- Gagandeep Kang

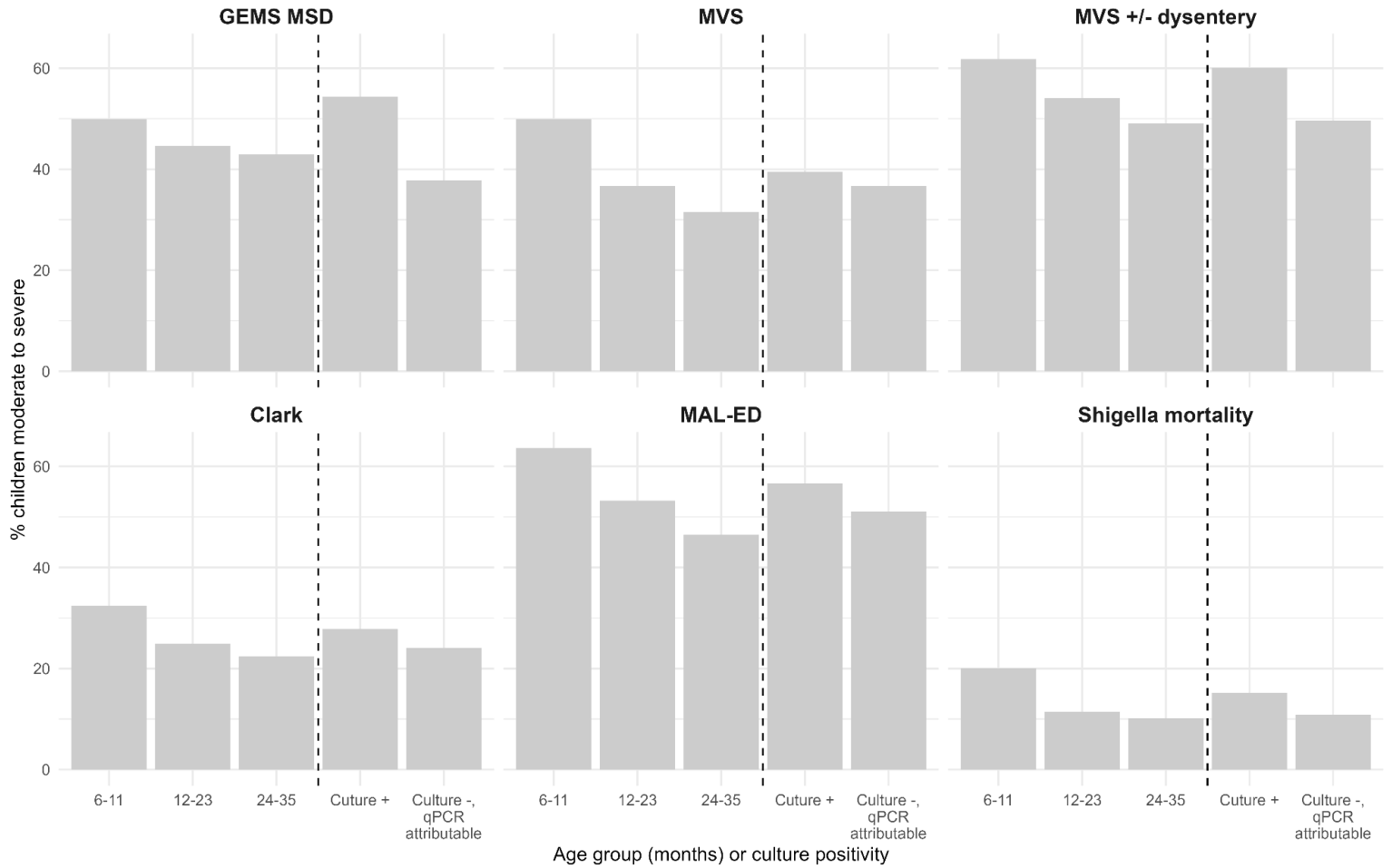
World Health Organization:

- Annelies Wilder-Smith
- Robert Kaminski

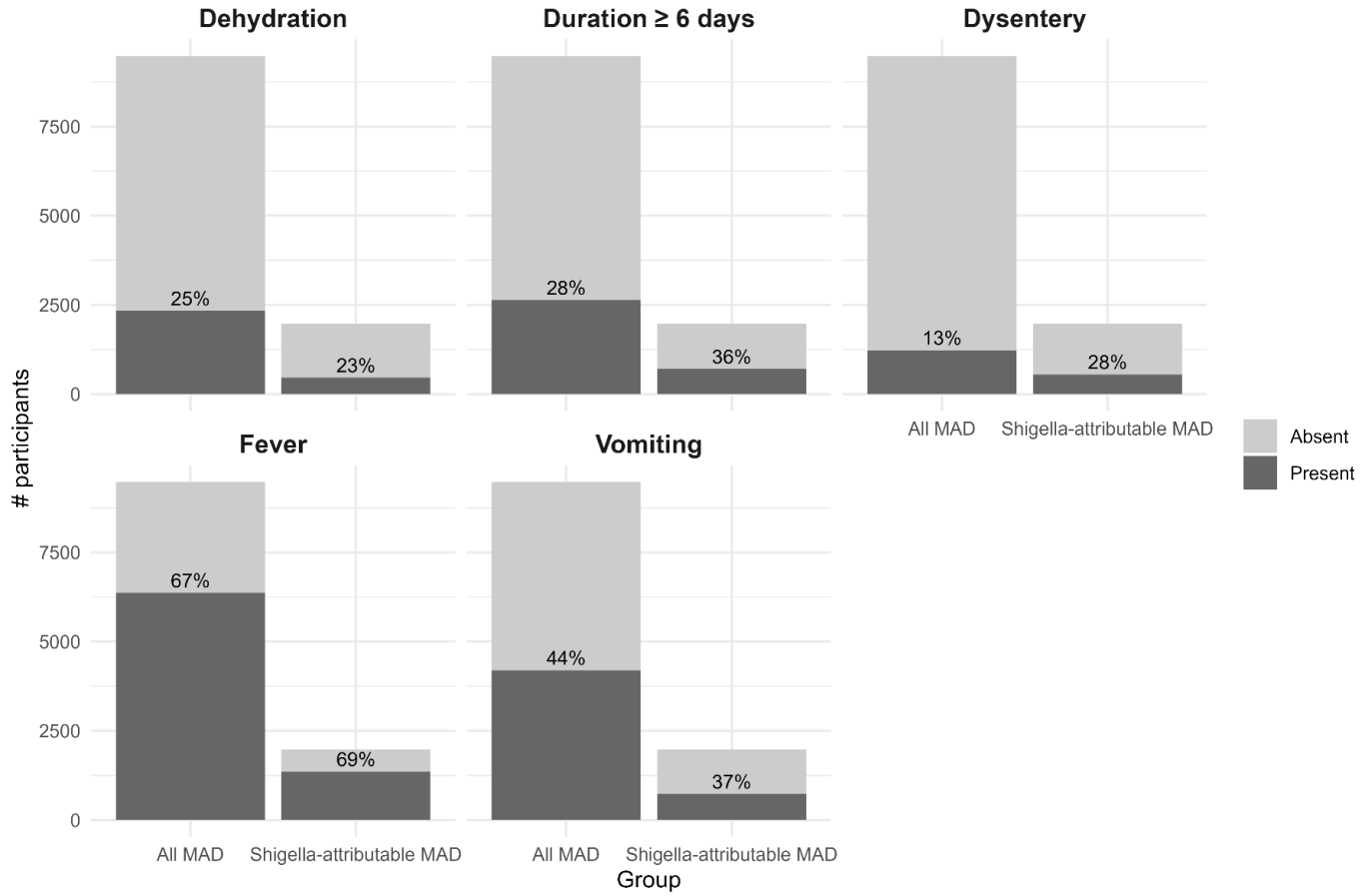
Thank you to the EFGH participants, families, and community members!

Appendix

Percentage of children with *Shigella*-attributable medically attended diarrhea classified as having moderate to severe diarrhea by each severity definition by age group and culture positivity.



Frequency of severity indicators among all medically-attended diarrhea (MAD) and *Shigella*-attributable MAD. Percentages indicate presence of indicator



Progress towards use of qPCR as a case detection method in Phase III studies

Eric Houpt MD
Professor and Chief
Division of Infectious Diseases and International Health
University of Virginia

Shigella are difficult to culture

APPLIED MICROBIOLOGY, Mar. 1970, p. 434-437
Copyright © 1970 American Society for Microbiology
Vol. 19, No. 3
Printed in U.S.A.

Comparison of Media for Direct Isolation and Transport of Shigellae from Fecal Specimens

GEORGE K. MORRIS, JUDITH A. KOEHLER, EUGENE J. GANGAROSA, AND ROBERT G. SHARRAR
Epidemiology Program, National Communicable Disease Center, Atlanta, Georgia 30333

Received for publication 5 December 1969

Xylose-lysine-deoxycholate (XLD) agar, SS agar, and MacConkey agar for isolating shigellae from fecal specimens were compared. XLD agar was superior to both SS agar and MacConkey agar for isolating *Shigella sonnei*, and both XLD and SS agar were superior to MacConkey agar for isolating *S. flexneri*. Direct plating of the fecal specimens in the field resulted in a greater yield of shigellae as compared to transporting specimens to the laboratory either in holding media or enrichment broth. Buffered glycerol saline was superior to other transport media evaluated, yielding 83% of shigella isolates when plated within 48 hr as compared to direct plating. The combination of XLD agar and SS agar is recommended for direct isolation of shigellae, and, whenever possible, these solid media should be taken to the bedside and inoculated directly.

INFECTION AND IMMUNITY, Apr. 1988, p. 1007–1009
0019-9567/88/041007-03$02.00/0
Vol. 56, No. 4

Nutritional Requirements of Shigellae for Growth in a Minimal Medium

ZIA U. AHMED,[1]* MAHFUZUR R. SARKER,[1] AND DAVID A. SACK[1,2]
International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh,[1] and Division of Geographic Medicine, The Johns Hopkins University School of Public Health, Baltimore, Maryland 21205[2]

Received 5 October 1987/Accepted 9 December 1987

APPLIED MICROBIOLOGY, Sept. 1968, p. 1387–1393
Vol. 16, No. 9
Printed in U.S.A.

Isolation of Shigellae

VI. Performance of Media with Stool Specimens

WELTON I. TAYLOR AND DOROTHY SCHELHART
West Suburban Hospital, Oak Park, Illinois 60302, and Lafayette Medical Laboratory, Lafayette, Louisiana 70504

Received for publication 29 April 1968

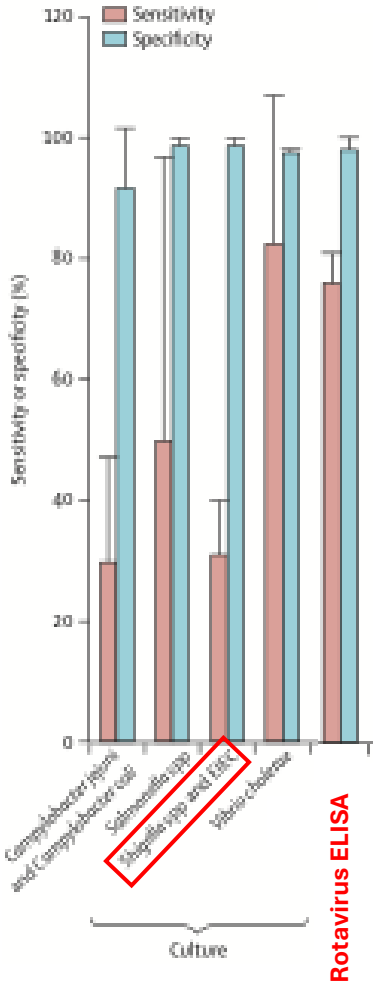
JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 1975, p. 281–286
Vol. 2, No. 4
Printed in U.S.A.

Effect of Temperature on Transport and Plating Media for Enteric Pathogens

WELTON I. TAYLOR[1] AND DOROTHY SCHELHART*
East Jefferson General Hospital, Metairie, Louisiana 70002

Received for publication 24 April 1975

PCR detects Shigella in fecal samples with greater sensitivity than culture



Liu et al, Lancet ID 2014

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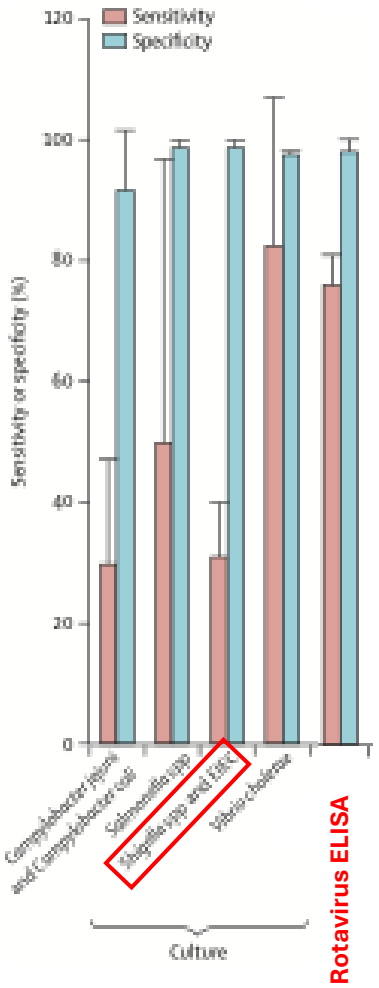
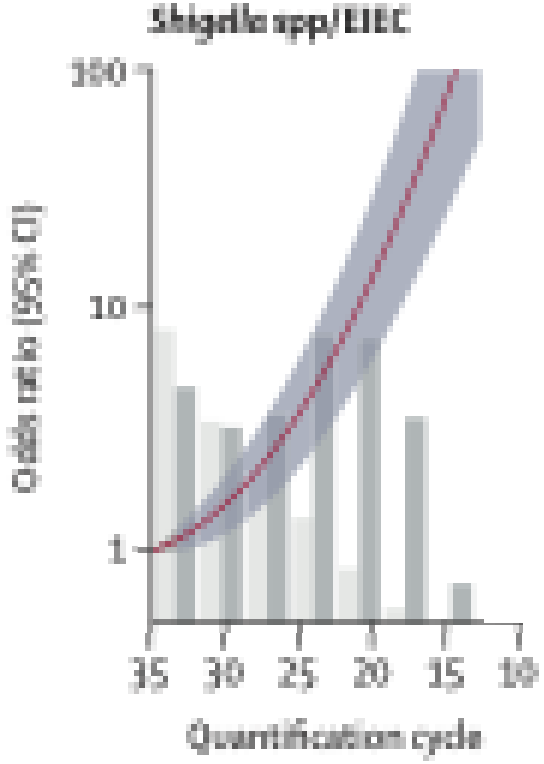


Liu et al, Lancet ID 2014

Some are low-level PCR detections that are not diarrhea associated (e.g., low odds ratio case control; Liu/Platts-Mills et al, Lancet 2016)



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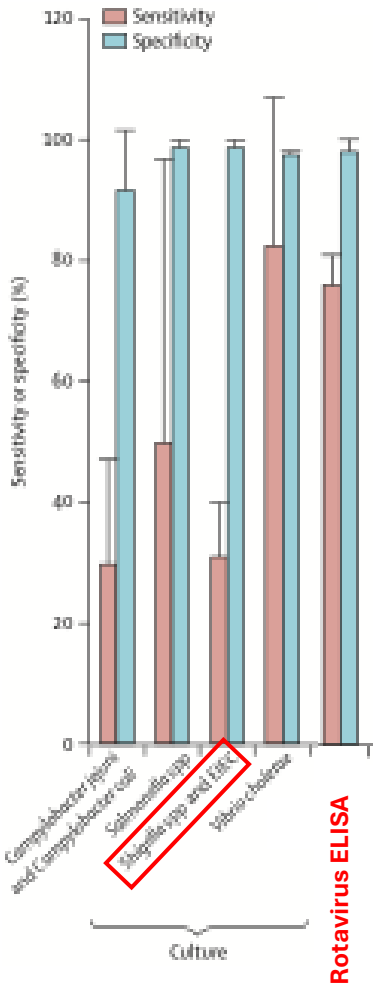

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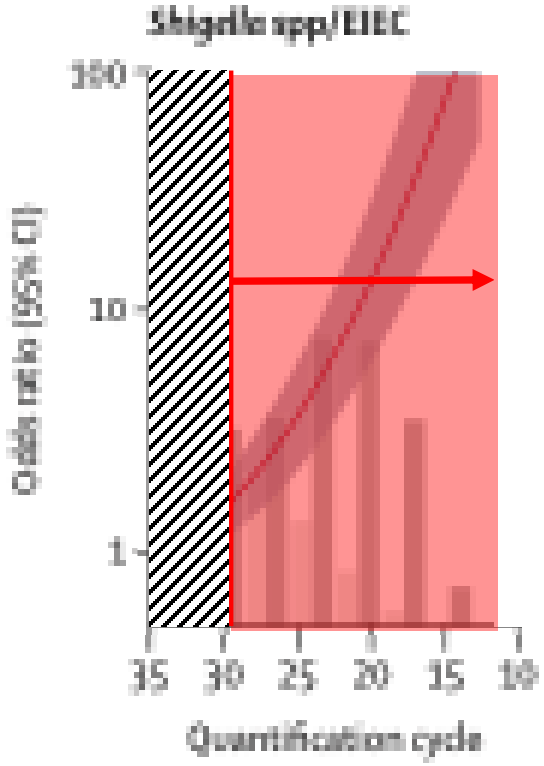

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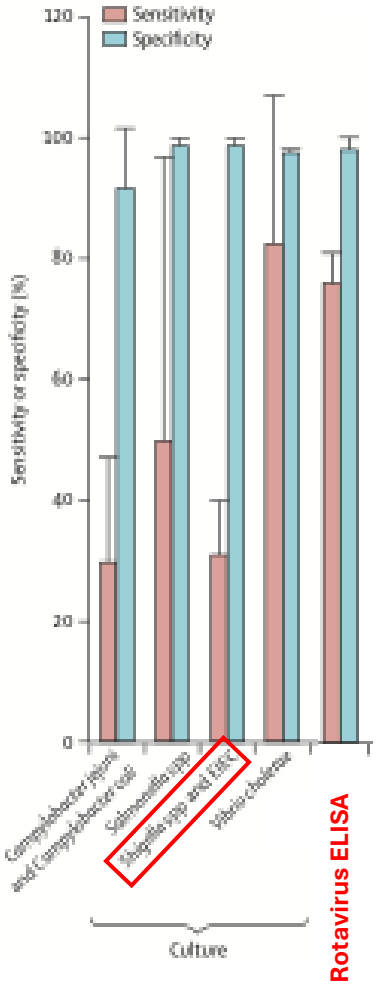

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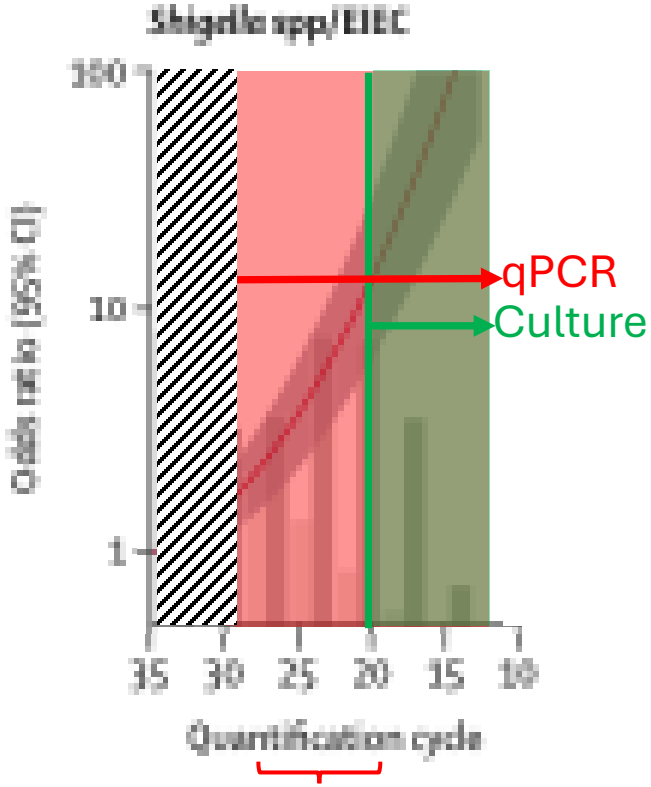

Culture-negative, PCR-positive, qPCR-attributable Shigella constitute the majority of the shigellosis burden and are clinically-important (Pavlinac CID 2021)

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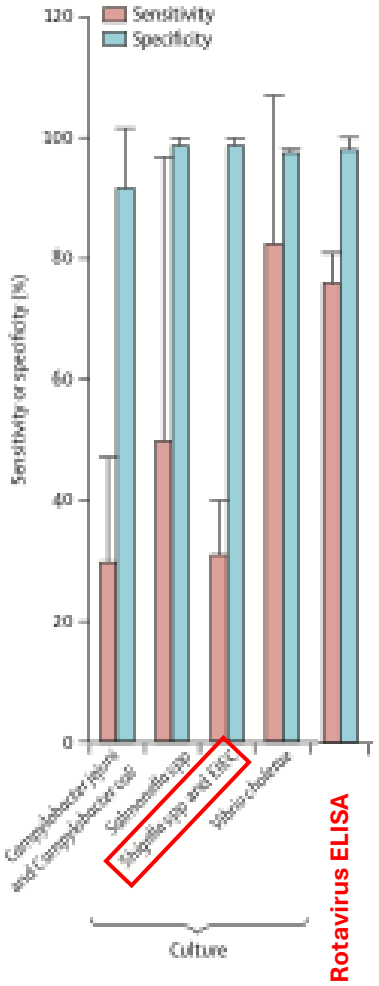

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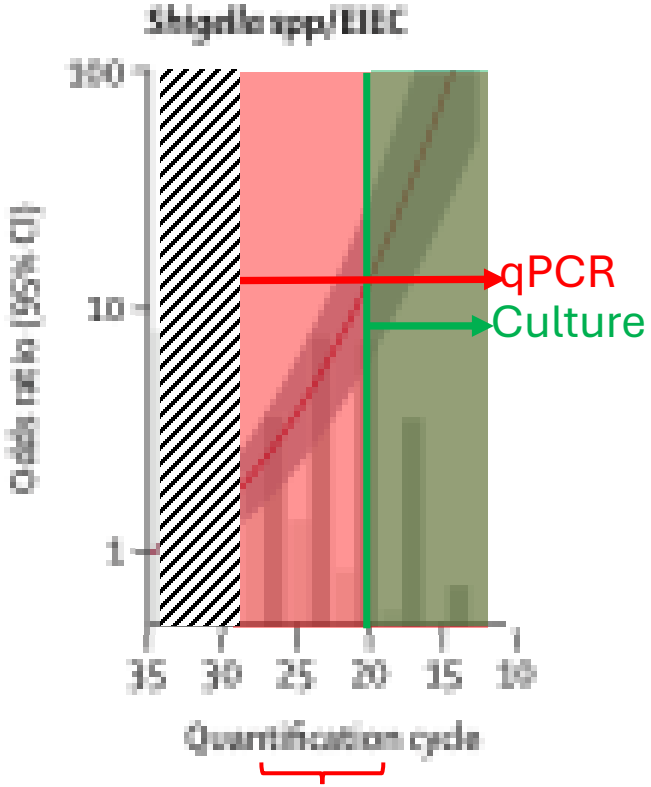
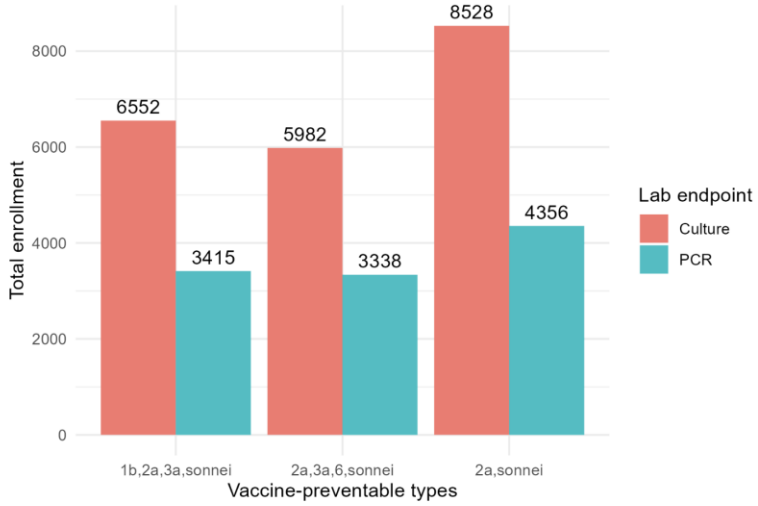


Using qPCR for a vaccine efficacy trial translates to smaller enrollment
Example:



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PCR issues to consider

- *ipaH* gene target is widely used by most molecular platforms
- Detects Shigella and Enteroinvasive E. coli
  - Less common in LMIC children than Shigella (e.g., 0.8% vs. 4.0% in MAL-ED study, Platts-Mills Lancet Global Health 2015)
  - Molecular assays can further specify Shigella sonnei and S. flexneri vaccine serotypes
- Co-detections and co-attributable detections of other enteropathogens occur
  - ~20-30%; True for Shigella (qPCR or culture), Rotavirus ELISA, etc.

Molecular assays can further detect Shigella sonnei and flexneri serotypes

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2011, p. 3766–3770 Vol. 49, No. 11
0095-1137/11/$12.00 doi:10.1128/JCM.01259-11

Development of a Multiplex PCR Assay Targeting O-Antigen Modification Genes for Molecular Serotyping of *Shigella flexneri*[▽]

TABLE 1. Serotype characteristics of *S. flexneri* reference strains by agglutination and multiplex PCR

Serotype	Agglutination										Multiplex PCR							
	Type						Group			MASF1c								
	I	II	III	IV	V	VI	3;4	6	7;8		*wzx*$_{1-5}$	*gtrI*	*gtrIC*	*gtrII*	*oac*	*gtrIV*	*gtrV*	*gtrX*
1a	+	–	–	–	–	–	+	–	–	–	+	+	–	–	–	–	–	–
1b	+	–	–	–	–	–	+	+	–	–	+	+	–	–	+	–	–	–
	–	–	–	–	–	–	–	+	–	+	+	+	+	–	+	–	–	–
2a	–	+	–	–	–	–	+	–	–	–	+	–	–	+	–	–	–	–
2b	–	+	–	–	–	–	–	–	+	–	+	–	–	+	–	–	–	+
3a	–	–	+	–	–	–	–	+	+	–	+	–	–	–	+	–	–	+
3b	–	–	+	–	–	–	–	+	–	–	+	–	–	–	+	–	–	–
4a	–	–	–	+	–	–	+	–	–	–	+	–	–	–	–	+	–	–
4b	–	–	–	+	–	–	–	+	–	–	+	–	–	–	+	+	–	–
5a	–	–	–	–	+	–	+	–	–	–	+	–	–	–	–	–	+	–
Y	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–
X	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	+

97.8% concordance, N=358 S. flexneri isolates

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PCR-Based Method for *Shigella flexneri* Serotyping: International Multicenter Validation

Silvina P. Brengi,[a] Qiangzheng Sun,[b] Hilda Bolaños,[c] Francisco Duarte,[c] Claire Jenkins,[d] Mariana Pichel,[a] Mohammad Shahnaij,[e] Evangeline G. Sowers,[f] Nancy Strockbine,[f] Kaisar A. Talukder,[e*] Gordana Derado,[g] María Rosa Viñas,[a] Kai Man Kam,[h] Jianguo Xu[b]

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BACTERIOLOGY

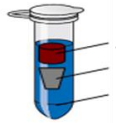
Evaluation of Molecular Serotyping Assays for *Shigella flexneri* Directly on Stool Samples

Jie Liu,[a] Suporn Pholwat,[a] Jixian Zhang,[a] Mami Taniuchi,[a] Rashidul Haque,[b] Masud Alam,[b] John Benjamin Ochieng,[c] Jennifer A. Jones,[d] James A. Platts-Mills,[a] Sharon M. Tennant,[d] Eric Houpt[a]

93% sensitive, 99% specific on stool compared to agglutination results of isolate

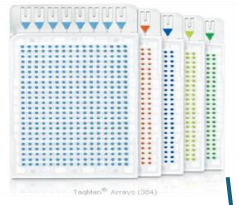
Molecular diagnostics on TaqMan Array Card format

TaqMan Array Card

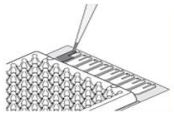


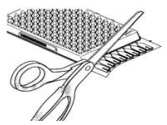
Sample
MS2 PhHV
Internal controls
Buffer

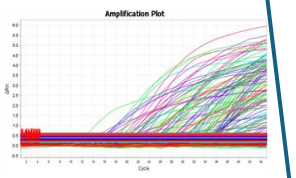
qPCR reagents



Load Spin Seal Trim Run Results







Example…

Port L	Port R	
Adenovirus 40/41	Astrovirus & Sapovirus V	Viruses
Norovirus GI & GII	Sapovirus I/II/IV	
Rotavirus	SARS-CoV-2	
Campylobacter jejuni&coli	C. upsaliensis & C. infans	Bacteria
Salmonella & H. pylori	Aeromonas & Plesiomonas	
Shigella/EIEC (ipaH)	V. cholerae	
S. flexneri 1a & 1b & 7 (gtrI&gtrC)	S. flexneri 2a & 2b & X (gtrII&gtrX)	
S. flexneri 3a & 3b & 5a & 5b (oac&gtrV)	S. flexneri 6 & 4a & 4b (wzx6&gtrIV)	
S. flexneri opt & Shigella (ipaH3)	S. sonnei (pm) & S. sonnei (rhs)	
EPECT_bfpA & eae	EAEC_aaiC & aatA	
ETEC_STh & STp	ETEC_LT	
ETEC_CFA/I & CS1	ETEC_CS2 & CS3	
ETEC_CS5 & CS6	STEC_stx1 & stx2	
18S	Bacterial 16S	Controls
MS2 & PhHV	MS2 & PhHV	
Cryptosporidium	Giardia	Protozoa
Cyclospora & Isospora	E. histolytica & E. bieneusi	
ermB & mphA	mefA & mphB	Antimicrobial resistance
ermA & ermC	msrA & msrD	
MCR1 & MCR2	Shigella/E.coli gyrA 83	
OXA-48	OXA-1 & OXA-9	
CTX-M1 & CTX-M8-M25	CTX-M2-M74 & CTX-M9	
SHV & SHV238-240SE-SK	TEM104E & 104K	
TEM164R & 164S-C	TEM238G & 238S	

Shigella

Molecular diagnostics on TaqMan Array Card format

- Minimizes manual steps and lab contamination risk
- Robust reproducible performance, wide use, multiple labs, many samples
  - GEMS (n=10,608), MAL-ED (n=37,323), WHO Global Pediatric Diarrhea Surveillance (n=6,343), VIDA (n=4,606), EFGH (n=9,476)
  - Rotasiil Niger (n=1,729), Rotavac India (n=1,507)
- We are assembling this existing Shigella assay data into a Qualification Plan (specificity, reproducibility, sample type, sample stability, etc.) so that Shigella vaccine developers and sponsors can adopt these molecular detection methods in vaccine trials if desired

PDVAC Question 1

As *Shigella* vaccines (stand alone or combinations) move towards Phase III evaluations, there remains a lack of consensus regarding case definitions and detection methods for the primary endpoint. Additionally, epidemiological data indicate substantial burden of *Shigella* in 6–12-month-olds and Shigella co-pathogens/co-infections warrant further consideration for Phase III study designs.

Does PDVAC agree with the four gaps (case definitions, case detection methods, lower age for protection, and impact of co-infections) and endorse engaging the *Shigella* TAG and convening a WHO Expert Consultation to inform potential refinements to the WHO PPC on these topics?