Update on *Shigella* burden

PDVAC – 11 December 2024

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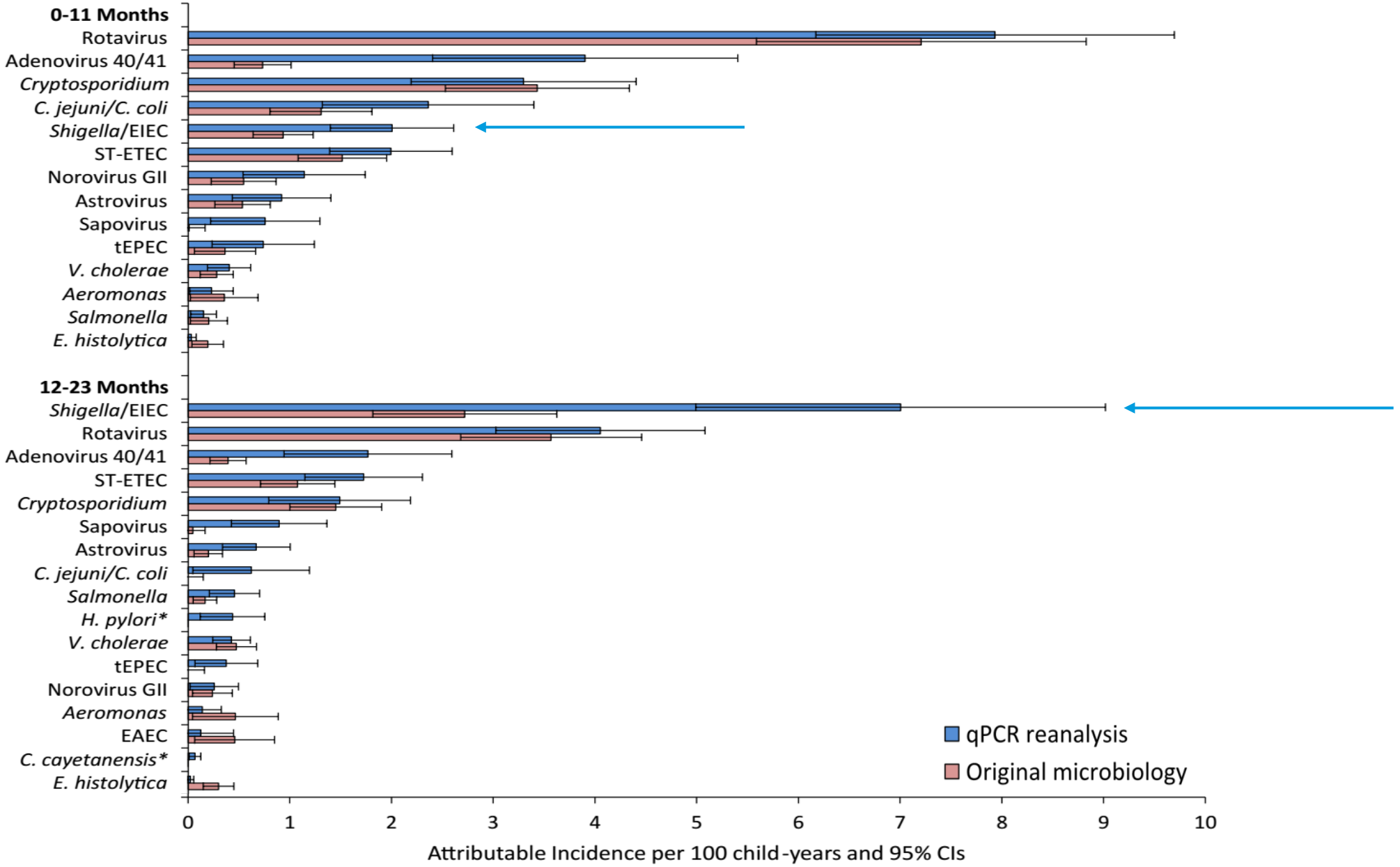
Multiple multisite studies of diarrhea have been conducted over the last 20 years

	GEMS	MAL-ED	EFGH	GPDS
Study setting	Health center	Community	Health center	Hospital
# of Sites	7	8	7	~30
Dates	2008-2011	2009-2014	2022-2024	2017-present
Location	Africa and Asia	South America, Africa, Asia	South America, Africa, Asia	Low- and middle-income countries across all WHO regions
Rotavirus vaccine introduced	No	Mixed (3/8 sites)	Most (6/7 sites)	Most (21/33 in 2017-2018 and increasing since)
Ages	0 – 60 months	0 – 24 months	6-35 months	0 – 60 months
Diarrhea definition/ Enrollment criteria	Acute moderate-to-severe diarrhea (diarrhea with dehydration, dysentery, hospitalization)	Diarrhea or dysentery	Acute diarrhea or dysentery	Diarrhea or dysentery
Controls	Age-, sex-, residence-, and time-matched	Longitudinal non-diarrheal stools	None (cutoffs generated from GEMS/MAL-ED to assign etiology)	None (GEMS AWD models used to produce AFs)
Case mortality	0.8%	~0%	<0.5%	1.2%

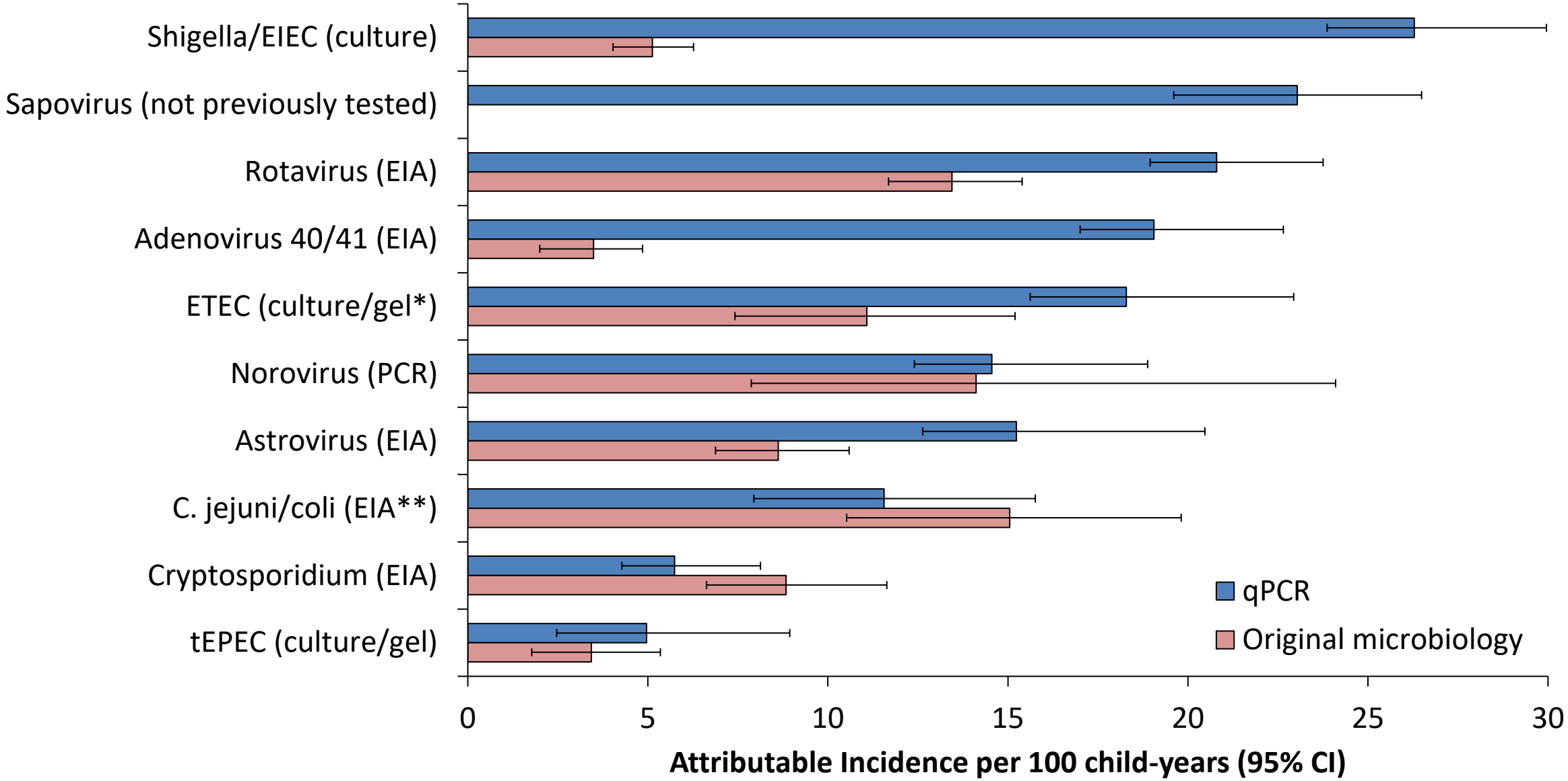
qPCR diagnostics substantially increased *Shigella* attributable incidence (GEMS)



Kotloff et al, Lancet 2013

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

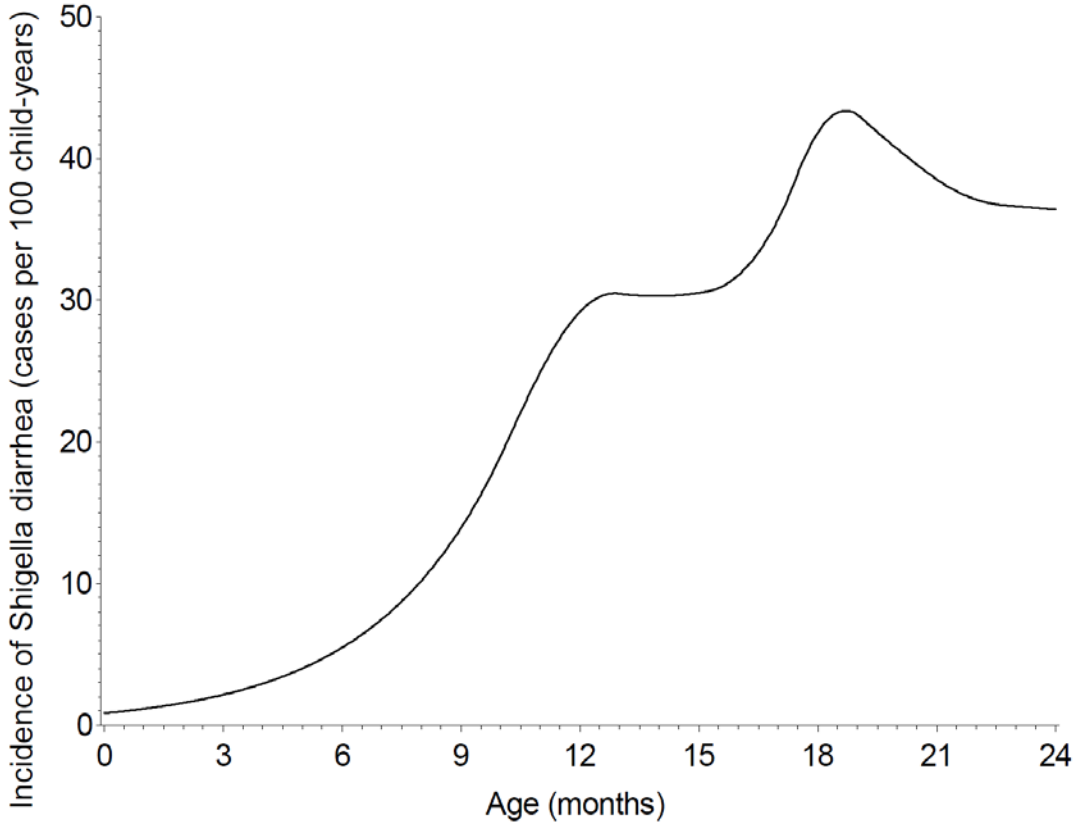
Shigella was the leading etiology of community diarrhea using qPCR (MAL-ED)

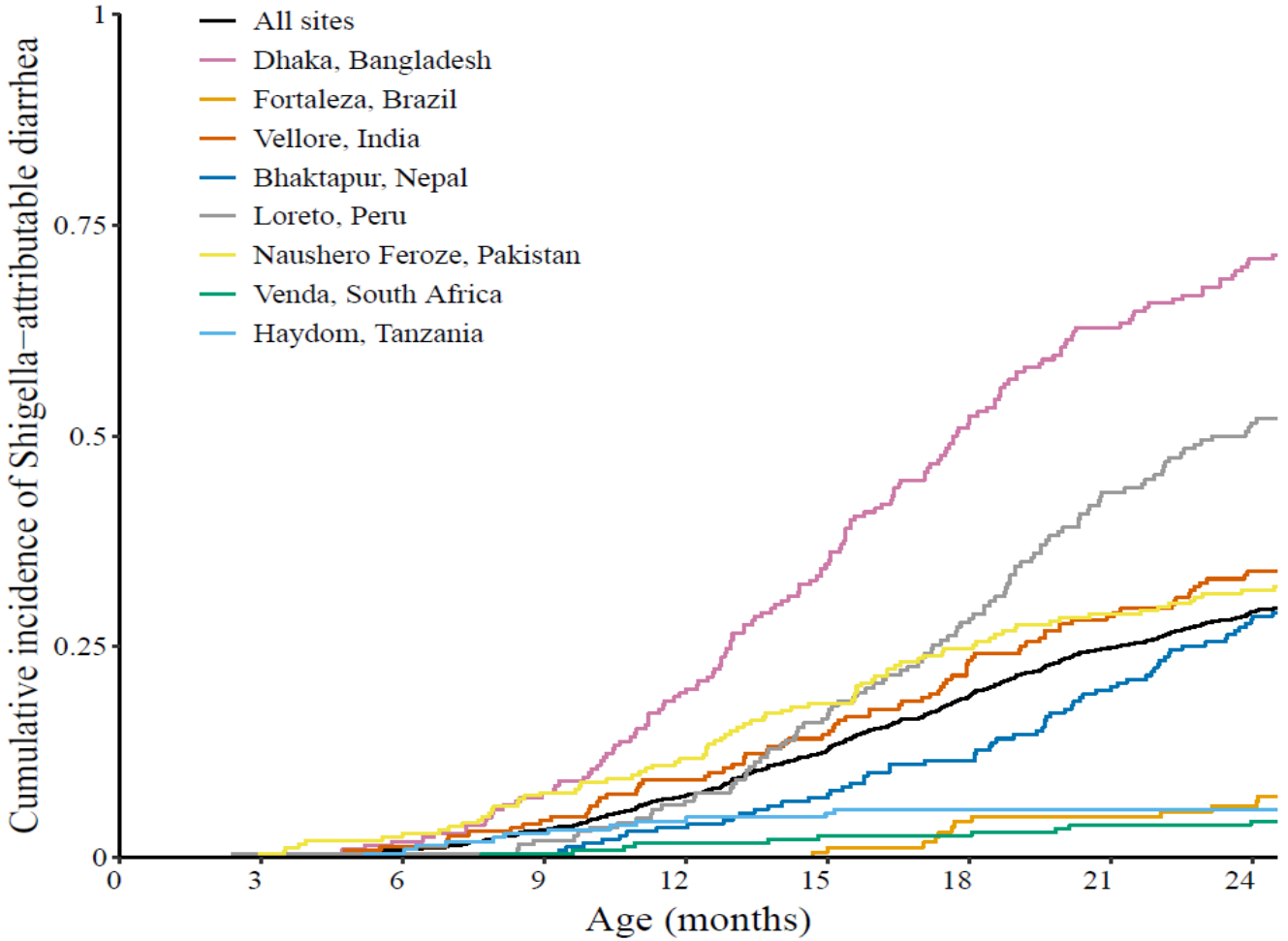


Platts-Mills JA, et al. Lancet Glob Health 2015

Platts-Mills JA and Liu J, et al. Lancet Global Health 2018

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.

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

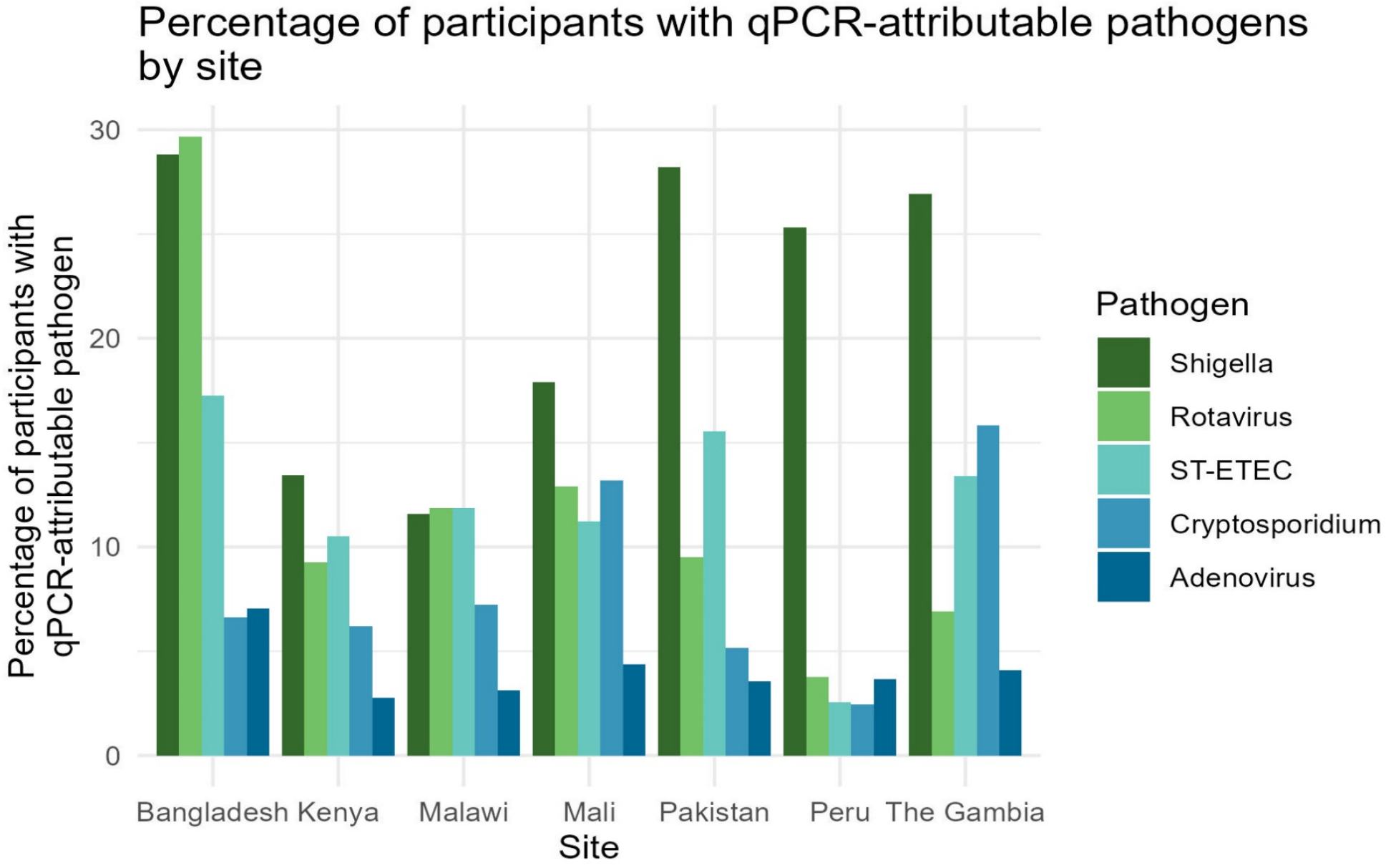
- We tested samples from 1729 episodes of diarrhea with Vesikari score >=7 (moderate to severe) from a phase 3 efficacy trial of Rotasiil in Niger, the country with the third highest diarrhea mortality in 2016 (IHME).
- *Shigella* was the leading etiology of diarrhea and the majority of shigellosis occurred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

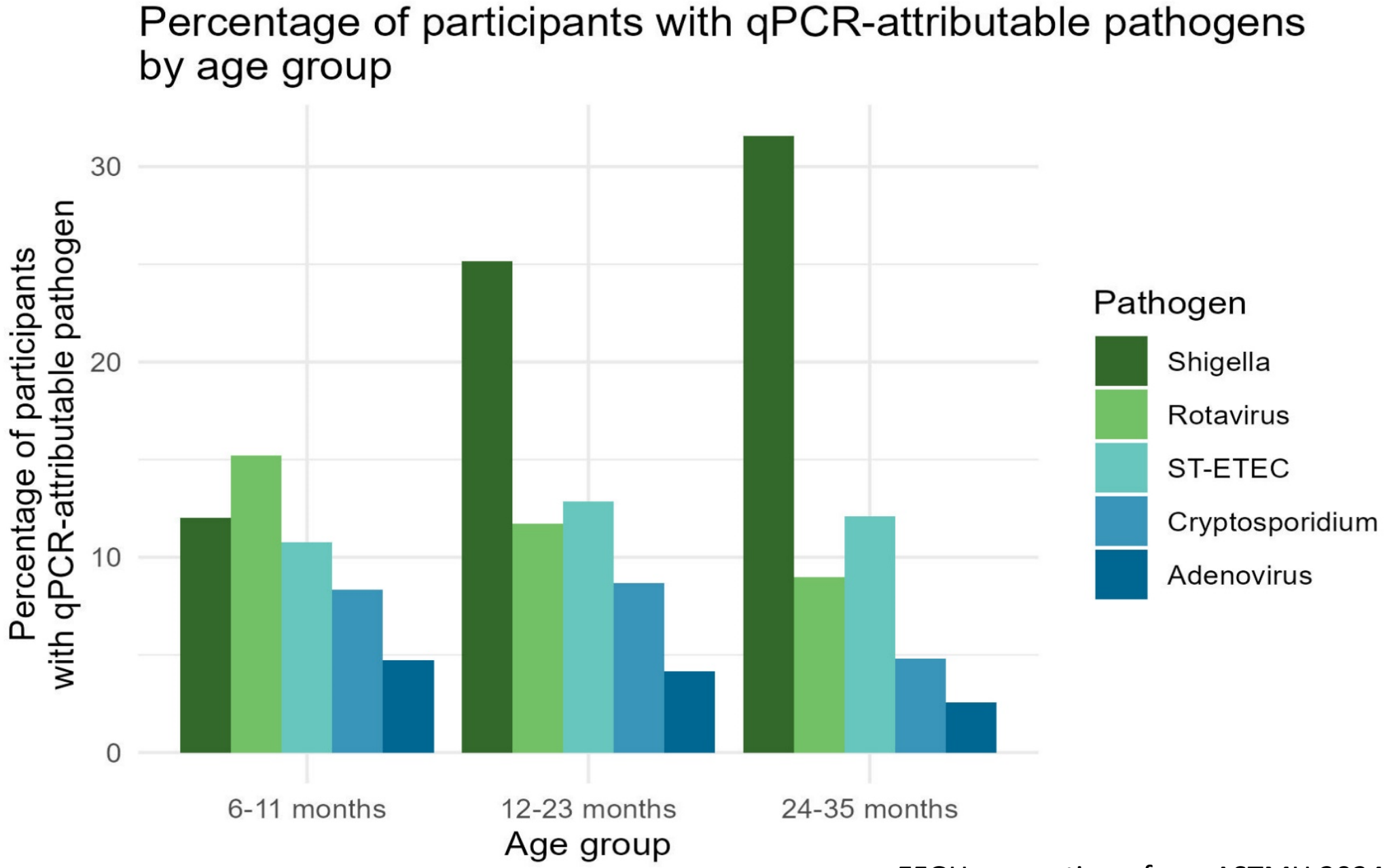
Platts-Mills JA et al. *J Pediatr Infect Dis Soc* 2021

Shigella top cause of medically-attended diarrhea (EFGH)



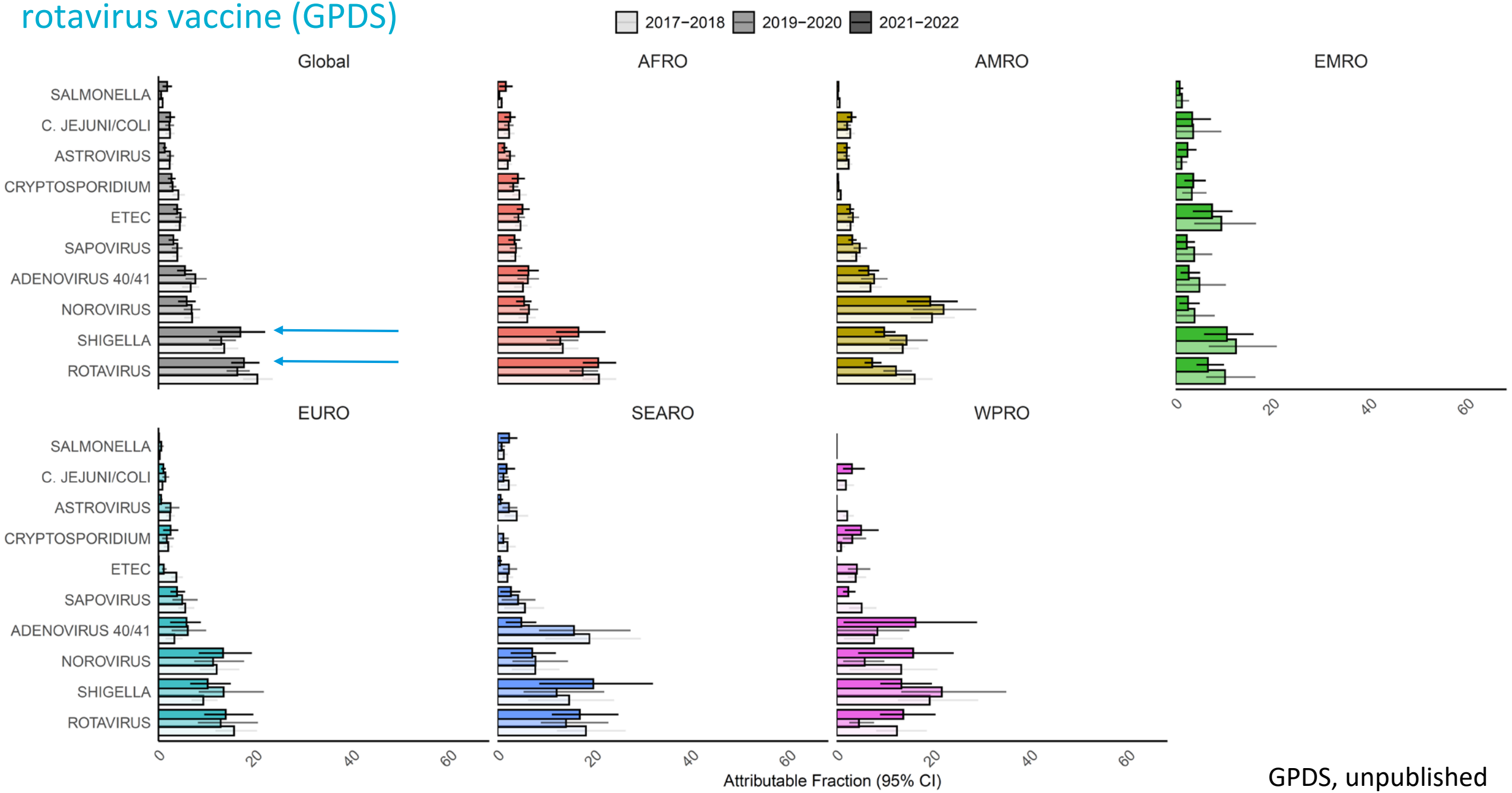
EFGH consortium, from ASTMH 2024 symposium

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



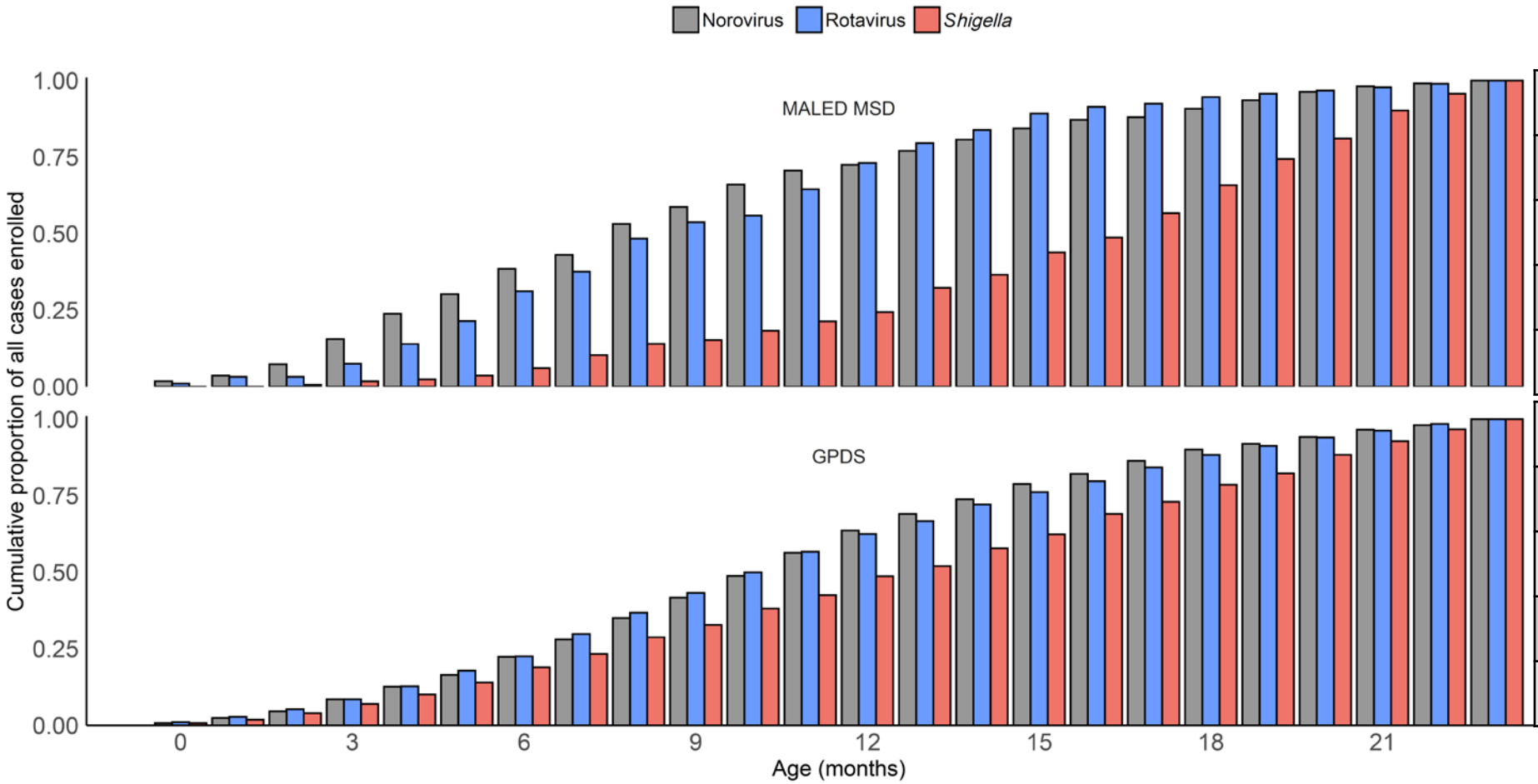
EFGH consortium, from ASTMH 2024 symposium

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



GPDS, unpublished

Age distribution (for children 0-23 months of age) for norovirus, rotavirus, and *Shigella* in MAL-ED (MSD only) vs. GPDS



	Age		
Pathogen	6mo	9mo	12mo
Shigella	6%	15%	24%
Rotavirus	31%	54%	73%
Norovirus	39%	59%	73%

	Age		
Pathogen	6mo	9mo	12mo
Shigella	19%	33%	49%
Rotavirus	23%	43%	63%
Norovirus	22%	42%	64%

MAL-ED/GPDS, unpublished

Shigella diarrhea mortality may be underestimated without application of CFRs: sensitivity analysis using GEMS CFRs and GPDS AFRO 2017-2018

Pathogen	GEMS CFR (per 1,000)*
tEPEC	81.08
Salmonella	50.00
Cryptosporidium	45.75
ST-ETEC	42.86
Shigella	39.44
Astrovirus	35.78**
Isospora	35.78**
Aeromonas	35.78**
Cyclospora	35.78**
E. histolytica	35.78**
Adenovirus 40/41	32.97
C. jejuni/coli	26.74
V. cholera	24.39
Rotavirus	20.90
Sapovirus	15.15
Norovirus GII	14.29

*proportion of hospitalized children in GEMS who had each pathogen detected with Ct < 30 who died in the subsequent 14 days (unpublished);
**CFR estimate is the average across all other pathogens (there were no deaths within 14 days for these pathogens in GEMS)

	Base case	25% presenting to care	50% presenting to care
All-cause	395711 (324958 to 484982)	395452 (331813 to 471033)	393852 (335062 to 470010)
Rotavirus	150603 (114296 to 191685)	147189 (117311 to 182022)	145092 (118544 to 176732)
Shigella	43670 (31664 to 56131)	53992 (41801 to 66772)	63844 (51165 to 79868)
Norovirus GII	19622 (13849 to 25734)	17866 (13143 to 22410)	16229 (12794 to 20361)
ST-ETEC	18953 (14427 to 24499)	23772 (19762 to 29240)	28581 (23350 to 34909)
Sapovirus	16983 (12250 to 22430)	15960 (12087 to 20138)	14623 (11549 to 18175)
Cryptosporidium	16722 (11376 to 22555)	21768 (16757 to 27413)	26572 (20333 to 33598)
Adenovirus 40/41	15364 (9690 to 21016)	16778 (12107 to 21618)	18626 (13623 to 23736)
Astrovirus	13201 (8842 to 18039)	15427 (11675 to 19970)	17481 (13027 to 22338)
C.jejuni/C.coli	4245 (2258 to 6875)	4542 (2867 to 6712)	4892 (3249 to 6954)
Salmonella	3673 (1271 to 5668)	4761 (2797 to 6948)	5749 (3075 to 8653)
tEPEC	3213 (1459 to 5135)	5604 (3394 to 8181)	8045 (4538 to 12117)
Isospora	656 (122 to 1319)	785 (287 to 1311)	908 (306 to 1575)
E. histolytica	587 (50 to 1537)	758 (103 to 1645)	876 (103 to 2213)
V. cholerae	149 (38 to 1066)	308 (64 to 949)	413 (63 to 1022)
Aeromonas	102 (0 to 263)	118 (29 to 268)	121 (34 to 256)
Cyclospora	69 (0 to 826)	156 (3 to 747)	179 (5 to 865)

Base case (no CFR weighting) uses the GPDS etiology distribution (see Cohen AL and Platts-Mills JA, BMJ Global Health 2022;7:e009548). For the sensitivity analyses (25% and 50% presenting to care), the GPDS etiology distribution is used for diarrheal deaths in children that did NOT present to care, and a CFR-weighted etiology distribution is used for diarrheal deaths in children that DID present to care. CFRs incorporated by calculating a weighted AF, namely $wAF_i = AF_i * CFR_i * \sum_1^n AF_n * CFR_n$ where AF_n and CFR_n are the AF and CFR for each pathogen included in the analysis.

GPDS, unpublished

Key points

- *Shigella* is consistently a leading etiology of diarrhea in a broad range of settings
- *Shigella* is likely to become THE leading etiology of diarrhea, including diarrhea requiring hospitalization, with the ongoing introduction of rotavirus vaccine.
- Current estimates of etiology-specific diarrhea mortality likely underestimate *Shigella* mortality.
- The relative burden of *Shigella* diarrhea in infants may have been previously underappreciated, especially for subsets of more severe disease. It is critical to evaluate recent data to fully inform and optimize the timing of vaccination.

Thank you

UVA Division of Infectious Diseases & International Health

Eric Houpt, Jie Liu, Timothy McMurry, Sarah Elwood, Stephanie Brennhofer, Ryan Dodd, Suzanne Stroup, Jixian Zhang

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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 and Regional offices
National, Regional, and Global Reference Laboratories
Partners (University of Virginia, U.S. CDC)

EFGH

University of Washington, University of Maryland, University of Virginia, Emory University
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Duncan Steele, Carl Kirkwood, Calman Maclennan, Kirsten Vannice

Shigella Vaccine Update and Potential Shigella Combination Vaccines

Calman A. MacLennan

WHO PDVAC, Geneva

December 11, 2024

Disclosure

- On December 2, 2024, I became an employee of Pfizer
- Pfizer is not developing a vaccine against Shigella (as far as I am aware)

Shigella – largest burden of diarrhea deaths without a vaccine

GBD 2019 Burden Estimates

	Deaths						DALYs					
Pathogen	All Ages	Lower CI	Upper CI	<5	Lower CI	Upper CI	All Ages	Lower CI	Upper CI	<5	Lower CI	Upper CI
Rotavirus	235,331	110,221	415,457	151,514	70,588	266,416	17,071,346	8,567,481	29,151,299	13,568,166	6,391,731	23,612,454
Shigella	148,202	61,975	284,541	93,831	35,860	185,931	10,602,910	4,538,791	20,242,702	8,402,887	3,274,243	16,542,456
Adenovirus	107,065	63,519	172,993	83,492	43,914	143,867	8,321,445	4,701,161	14,131,064	7,415,744	3,914,145	12,770,032
Cryptosporidium	133,423	26,424	360,303	77,523	15,962	190,426	8,170,908	1,797,798	20,226,898	6,862,766	1,463,118	16,773,435
Typhoid fever	110,029	52,810	191,206	18,934	7,228	38,033	8,053,346	3,864,905	13,925,252	1,635,423	625,745	3,279,949
Campylobacter	139,080	47,005	304,635	58,911	24,006	116,236	7,307,840	3,204,436	14,174,900	5,324,624	2,230,951	10,387,448
Cholera	117,241	71,090	177,806	55,701	28,044	93,931	7,134,552	4,032,717	11,139,174	4,837,150	2,438,859	8,153,152
Norovirus	135,798	25,103	303,735	43,481	11,754	99,172	6,879,357	2,085,136	14,198,132	3,962,128	1,192,131	8,842,284
Invasive Non-typhoidal Salmonella (iNTS)	79,046	43,013	124,207	49,869	27,161	80,009	6,114,292	3,323,425	9,705,739	4,318,828	2,355,108	6,931,248
Non-typhoidal Salmonella Diarrhea	61,647	4,376	190,566	39,493	4,376	107,810	4,269,216	475,319	12,056,915	3,500,124	426,309	9,395,645
Entamoeba	33,409	10,529	82,410	19,049	4,952	50,300	2,539,799	850,865	6,186,972	1,706,349	448,942	4,485,968
Aeromonas	28,019	12,945	50,322	19,651	7,871	39,046	2,073,448	932,430	3,883,407	1,744,504	709,751	3,449,201
Enterotoxigenic E coli	39,802	18,039	76,964	12,399	4,983	26,372	1,695,355	828,589	3,252,268	1,133,338	466,320	2,389,033
Enteropathogenic E coli	20,613	10,118	37,221	15,844	7,447	29,987	1,679,423	858,148	3,045,518	1,412,061	667,888	2,658,679
Paratyphoid fever	23,337	9,801	45,680	2,727	844	6,588	1,638,424	682,263	3,206,062	235,120	72,825	567,486
Clostridium difficile	32,134	28,131	36,549	2,102	1,306	3,218	870,814	722,988	1,052,360	182,179	113,038	278,999

(Data from Global Burden of Disease 2019, Institute for Health Metrics and Evaluation)

Most *Shigella* Vaccines are combination vaccines

Vaccine serotypes:

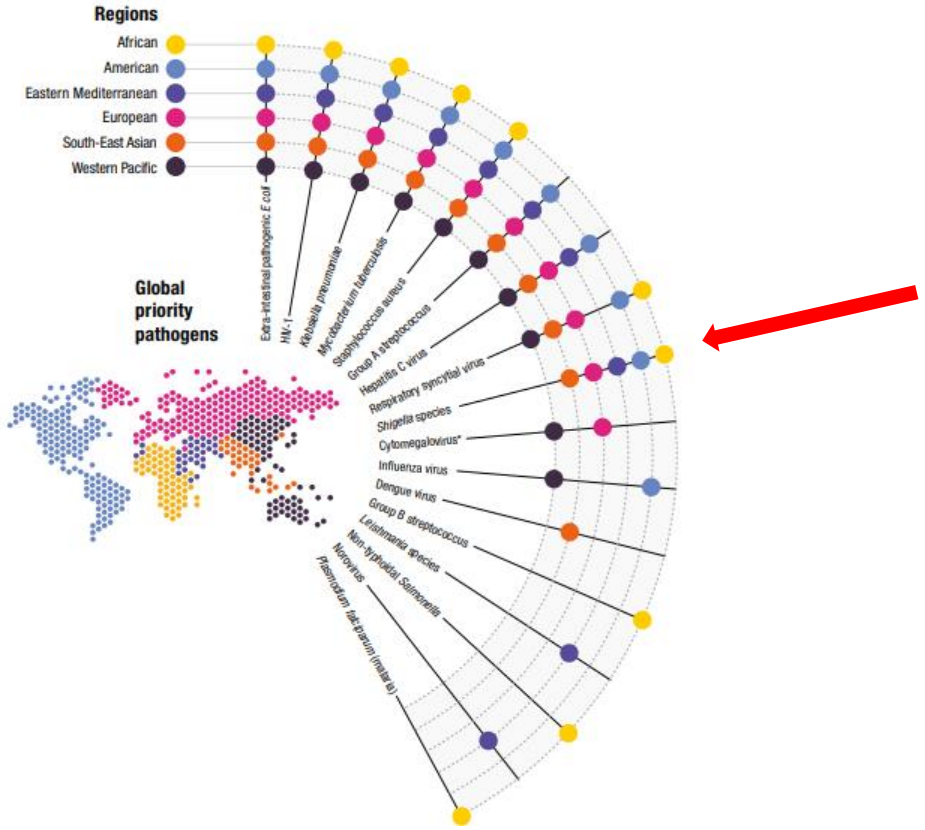
Shigella sonnei

Shigella flexneri, serotypes:

- ***Shigella flexneri* 2a**
- *Shigella flexneri* 3a
- *Shigella flexneri* 6
- *Shigella flexneri* 1b

Gavi VIS 2024 shortlist

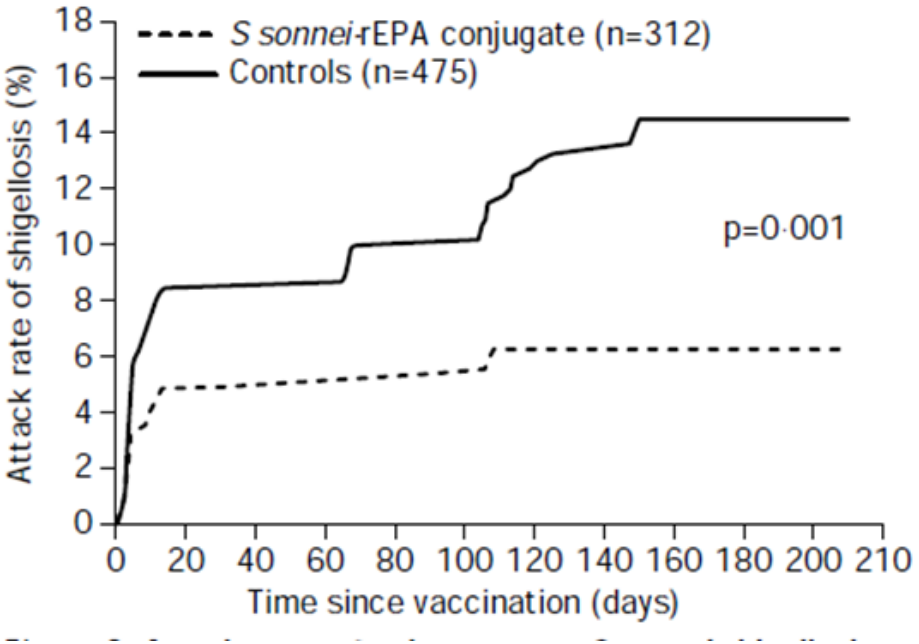
Learning agenda support



(Hasso-Agopsowicz M EBioMedicine 2024 Nov 4:105424.)

Proof of concept that *Shigella* conjugate vaccines are efficacious

- **25 years ago** a 1st generation NIH *S. sonnei* conjugate vaccine gave 74% efficacy among Israeli military.
- Protection strongly associated with serum IgG antibody response to LPS O-antigen, supporting this modality as a correlate of protection…
- **Issue:** many years later, the vaccine failed to protect children <3 years. Loss of protection closely associated with decreased induction of LPS O-antigen IgG



(Cohen D et al, Lancet 1997)
(Passwell JH et al Vaccine 2010)

PDVAC Dec 2023 Summary & Question

- Multiple O-antigen-based subunit vaccines in clinical trials with different technological approaches
- Evaluation for immunogenicity in descending-age/dose-finding studies LMIC children
- Quadrivalent format appears necessary for sufficient serotype coverage
- Preparations for Phase 3 field efficacy studies
- Advanced assay harmonisation & standardisation work
- Correlate of protection established for *Shigella sonnei* O-antigen serum IgG in adults
- Subsequent vaccines could potentially be licensed on basis of immune non-inferiority
- Opportunity for combination vaccines

- **If correlate of protection status can be established in the pediatric global health target population (LMIC infants) from a Phase 3 efficacy study of a first *Shigella* vaccine, could PDVAC opine on the broad concept of an accelerated pathway to licensure for subsequent *Shigella* vaccines based on immunobridging and safety?**

Shigella multivalent vaccines clinical trials & updates 2024

LimmaTech S4V (Ss, Sf2a, Sf3a, Sf6 – bioconjugate)

- June 2024 Results of Phase 2 descending-age dose-finding study in Kenya with S4V (4V) *Shigella* vaccine candidate presented at ASM Microbe (previously presented at BactiVac 2023) Wellcome funding
- August 2024 Exclusive worldwide license granted to Valneva for S4V *Shigella* vaccine candidate
- LimmaTech to conduct a Phase 2 Controlled Human Infection Model (CHIM)
- LimmaTech to conduct a Phase 2 pediatric study in LMICs in 2H2024 BMGF funding
- Valneva to assume all further development, including CMC and regulatory activities, and be responsible for worldwide commercialization

GVGH altSonflex1-2-3 (Ss, Sf2a, Sf3a, Sf1b – OMV/GMMA)

- June 2024 Results of Phase 1 adult study in Belgium with altSonflex1-2-3 (4V) *Shigella* vaccine candidate presented at ASM Microbe BMGF/Wellcome funding
- Phase 2 descending-age dose-finding study in Kenya with altSonflex1-2-3 (4V) *Shigella* vaccine candidate currently in progress BMGF/Wellcome funding

Shigella multivalent vaccines clinical trials & updates 2024

Institut Pasteur IP-QSV (Ss, Sf2a, Sf3a, Sf6 – synthetic O-antigen TT conjugate)

- June 2024 Results of Phase 2 descending-age dose-finding study Kenya with Sf2a-TT15 (1V) Shigella vaccine candidate presented at ASM Microbe Wellcome/BMGF funding
- IP-QSV (4V) GMP DS/DP manufactured BMGF funding

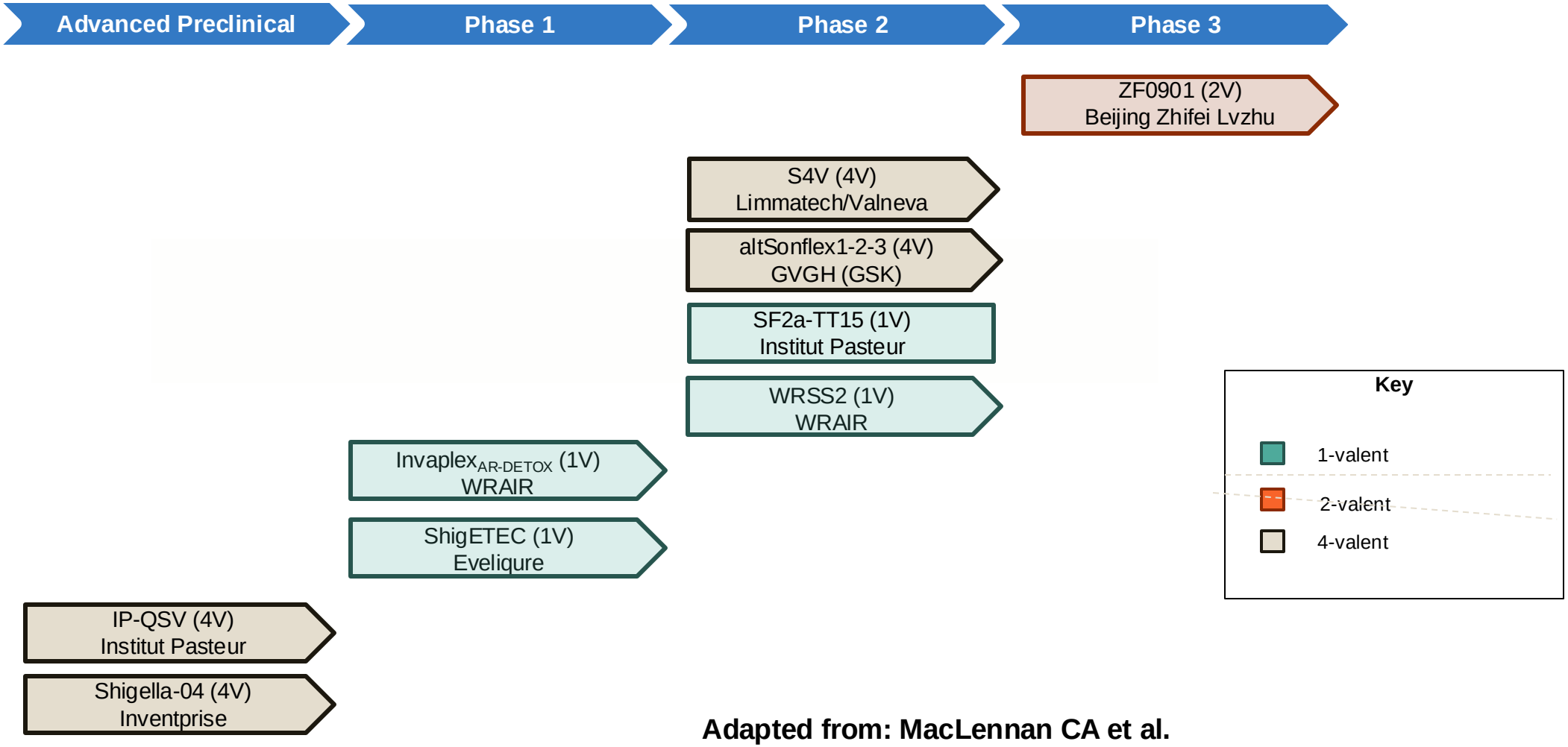
Inventprise Shigella-4 (Ss, Sf2a, Sf3a, Sf6 – O-antigen IpaB conjugate)

- Shigella-4 (4V) GMP DS/DP (**IpaB** carrier protein) manufactured BMGF funding

Zhifei ZF0901 (Ss, Sf2a – O-antigen TT conjugate)

- ZF0901 (2V) in Phase 3 clinical trials

Shigella Subunit vaccine pipeline – updated December 2024



Adapted from: MacLennan CA et al. Vaccines 2022, 10, 1376,

Zhifei Phase 3 Correlate of Protection substudy

- ZF0901 Phase 3 study in infants and young children at icddr,b Bangladesh
- BMGF funding to icddr,b for Correlates of Protection substudy
- **Aim to confirm serum IgG to O-antigen of *S. sonnei* & *S. flexneri* 2a as the correlate of protection against shigellosis in LMIC children/infants**
- …thereby facilitating the accelerated licensure of O-antigen-based *Shigella* vaccines.

Qualification of *Shigella* Immunoassays

- Paul Rhyne, Gates MRI
- Vismederi, Siena, Italy

- Multiplexed bead array assay
- Developed at Luminex with input from Johns Hopkins University
- Able to measure IgG/IgA to
  - O-antigens from Shigella sonnei, Shigella flexneri 1b, 2a, 3 and 6
  - Carrier proteins: TT, rEPA, IpaB

- Serum bactericidal assay
- Luminescence based
- Tech transferred from GVGH

Qualification of *Shigella* Immunoassays

Paul Rhyne, Gates MRI

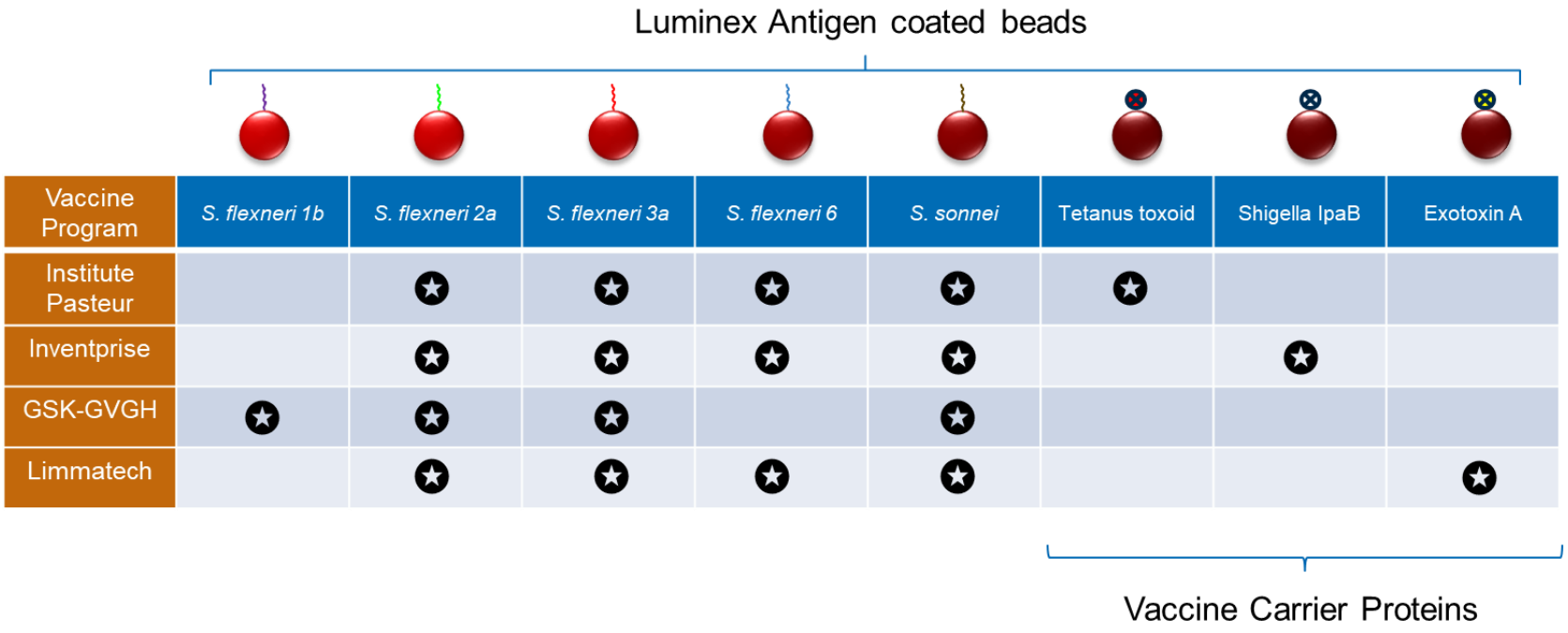
Vismederi, Siena, Italy

Serum bactericidal assay

- Luminescence based
- Tech transferred from GVGH

Multiplexed bead array assay

- Developed at Luminex with input from Johns Hopkins University
- Able to measure IgG/IgA to vaccine O-antigens & carrier proteins
- Currently undergoing validation



Shigella combination vaccines workshop – PATH Washington DC 2022

Conference report

Challenges and opportunities in developing a *Shigella*-containing combination vaccine for children in low- and middle-income countries: Report of an expert convening

Mark S. Riddle [a,*], A. Louis Bourgeois [b], Allison Clifford [b], Suhi Jeon [c], Birgitte K. Giersing [d], Mark Jit [e], Marta Tufet Bayona [f], Jared Ovitt [a], William P. Hausdorff [b,g]

(Vaccine 2023; 41:2634-2644)

Combinations considered

- Measles + Shigella +/- adjuvant
- Meningococcal A + Shigella
- TCV + Shigella

Shigella combination vaccines workshop – BMGF London 2024

- *Desire to prioritize combination opportunities that align with both epidemiology/public health need, as well as pathogens with existing or near-term vaccines*
- *Based on these criteria, TCV identified as the most promising option for combination*
- *With more recent data on the earlier age-distribution of more severe shigellosis as well as duration of protection of TCV, suggesting a potential booster dose or shifted schedule to later in the EPI, combination with TCV is a less clear-cut option.*
- *The London workshop interrogated TCV in great detail and offered high level overviews of potential alternative pathogens with combination potential*

Key criteria to evaluate pathogens for a potential *Shigella* combo vx include measures across burden, geography, and vaccine characteristics

Pathogen-centric → Product-centric

Starting point

- Pathogens with an **applicable burden in <5** populations
- **Licensed vaccines for U5** based on WHO guidance to take advantage of programmatic efficiencies

Clinical development

- At least **one** candidate in clinical development

Schedule compatibility

Shigella burden peaks in the second year of life

- Vaccine schedule should occur **before 12 months of age**

Extent of geographic overlap

# of additional doses

Administration Route

Most Shigella vx in the pipeline are administered parenterally

- Combo vaccine should be **parenteral**

Platform Compatibility

Some platforms are too difficult to combine with other platforms without negative interactions

- Not on an mRNA platform
- Not live attenuated

Chemistry "sandbox"

Certain antigens do not work together

- Similar chemistries
- Not whole protozoa
- No combos with hexavalent vx

Extent of formulation change

Valency

3 – 5 Priority Combinations

Product Development Timeline

PTRS

Stakeholder interest

On foundation strategy

Key

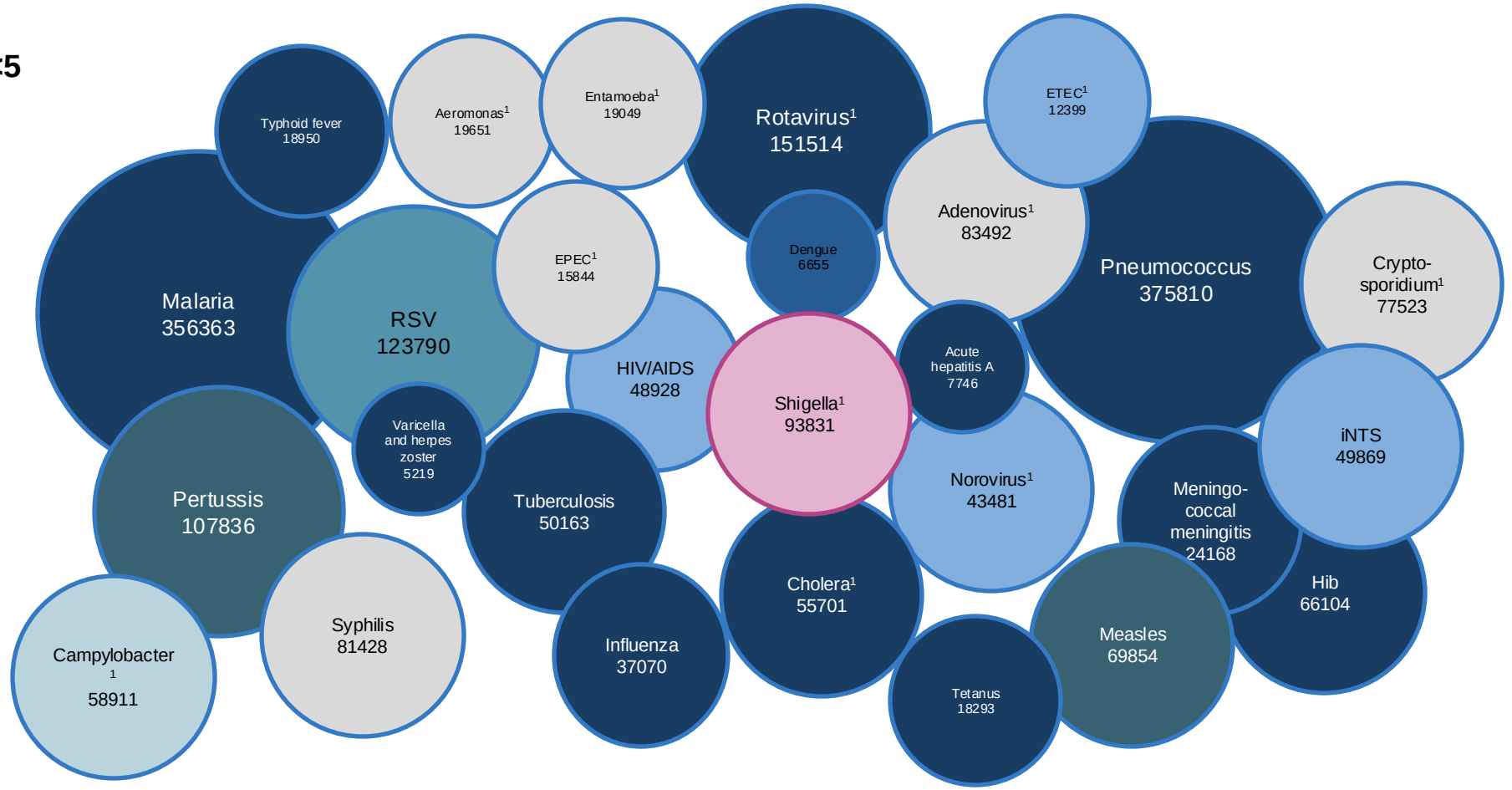
Must-have criteria

***Considerations** for prioritization*

26 possible partner pathogens with a vaccine in clinical development

Top pathogens by burden in <5 age group

- Disease or pathogen # of deaths in <5 population, per GBD 2019
- Vaccines in preclinical development or N/A
- At least one vaccine in clinical development
- A nationally approved vaccine with an indication for an over 5 age group
- A nationally approved vaccine with an indication for an under 5 age group

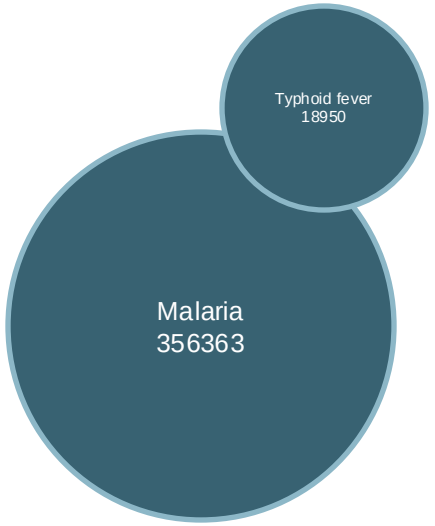


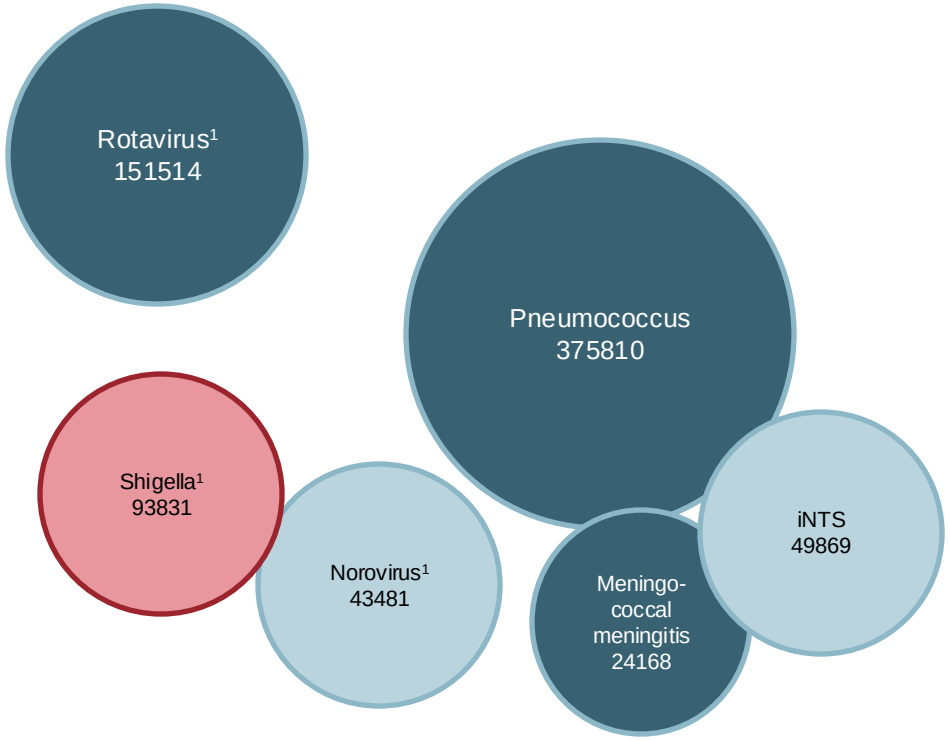
SOURCES, NOTES: Data from GBD 2019, retrieved May 24, 2023; excepting for diarrheal deaths, level 3 or 4 cause of death was used. Searches within ClinicalTrials.gov used to determine if a vaccine in clinical development exists. Etiology used for diarrheal deaths. 1. Attribution of deaths due to diarrheal burden

Last updated: December 17, 2024

Final 7 pathogens for consideration

- **Malaria**
- **Typhoid**
- **Rotavirus**
- **Norovirus**
- **Pneumococcus**
- **Meningococcal meningitis**
- **iNTS**





TCV/Shigella Summary Scorecard

Domain		Score
Disease attributes	Age distribution / target schedule	
	Geographic range	
Existing Guidance	E.g. supportive / compatible WHO guidance	
Vaccine attributes	Clinical development pipeline	
	Platform compatibility	
	Number of doses	
	Extent of formulation change & valency	
	Product development timelines	
	PTRS (licensed, CoP, CHIM, etc.)	
Political will	Stakeholder interest	

Opportunities	Challenges
• Licensed vaccine • Efficient licensure pathways (immunogenicity) • Conjugate vaccine with likely platform compatibility	• SAGE recommendations may change TCV schedule • Uncertainty about optimal TCV vaccine schedule to impact disease in high FOI settings • Younger schedule preferred for Shigella, older schedule may be preferred for TCV • Shigella vaccines may be 2-dose vaccines, TCV recommended as 1-dose • Potential for combo & standalone booster of TCV (which could be 3 total doses) • Complicated to have different products for TCV catch-up campaign • 6-month visit may come online with Africa malaria but requires new touchpoint in SEARO • Significant changes to TCV schedule/ formulation could require redoing efficacy • Other TCV combination options: bivalent, NTS etc.

 Promising, no major barriers

 May represent have important limitations or too soon to tell

 May be prohibitive, lowers likelihood of success

PCV/Shigella Summary Scorecard

Domain		Score
Disease attributes	Age distribution / target schedule	🟡
	Geographic range	🟢
Existing Guidance	E.g. supportive / compatible WHO guidance	?
Vaccine attributes	Clinical development pipeline	🟢
	Platform compatibility	🟢
	Number of doses	🟡
	Extent of formulation change & valency	🟢
	Product development timelines	🟡
	PTRS (licensed, CoP, CHIM, etc.)	🟡
Political will	Stakeholder interest	?

Opportunities	Challenges
• Licensed vaccine • Potential licensure pathways may emerge for 2v Shigella vaccine from ongoing Zhifei studies and prior work with S. sonnei • Conjugate vaccine with likely platform compatibility • Simplified PCV licensure pathway by immuno	• WHO SAGE initiating process to review durability data, to inform any potential update to schedule recommendations • Uncertainty about optimal vaccine schedule to impact disease in high FOI settings • Younger schedule preferred for PCV than for Shigella • Will likely require 3 doses unless PCV migrates to a 1+1 schedule

🟢 Promising, no major barriers

🟡 May represent have important limitations or too soon to tell

🔴 May be prohibitive, lowers likelihood of success

Summary Scorecard (rotavirus)

Domain		Score
Disease attributes	Age distribution / target schedule	
	Geographic range	
Vaccine attributes	Clinical development pipeline	
	Platform compatibility	
	Number of doses	
	Extent of formulation change & valency	
	Product development timelines	
	PTRS (licensed, CoP, CHIM, etc.)	
Political will	Stakeholder interest	

Opportunities	Challenges
• Diarrhea vaccine is a coherent concept • Burden case for rotavirus is clear	• No licensed parenteral vaccine • Role of IM rotavirus vaccine TBD – and may have geographic heterogeneity? • Rotavirus vaccine must be given in early infancy (~2, 3, +/- 4 months) -- though perhaps *Shigella* should be too!

Promising, no major barriers

May represent have important limitations or too soon to tell

May be prohibitive, lowers likelihood of success

Summary Scorecard (norovirus)

Domain		Score
Disease attributes	Age distribution / target schedule	🟢
	Geographic range	🟢
Vaccine attributes	Clinical development pipeline	🟡
	Platform compatibility	🟡
	Number of doses	🟢
	Extent of formulation change & valency	🟡
	Product development timelines	🟡
	PTRS (licensed, CoP, CHIM, etc.)	🔴
Political will	Stakeholder interest	🟡

Opportunities	Challenges
• Diarrhea vaccine is a coherent concept • Vaccination schedule (~2 doses at ~6 months of age) is compatible	• No licensed vaccine • Concerns about platform compatibility for HIL-214 • Norovirus burden case will be hard to make

🟢 Promising, no major barriers

🟡 May represent have important limitations or too soon to tell

🔴 May be prohibitive, lowers likelihood of success

Key Workshop Takeaways

- **No perfect combination vaccine option for Shigella emerged**, and there was no full consensus among the group on the best combination option.
- **Any combination requires trade-offs in terms of avertable disease burden, schedule/doses, product development timelines and/or PTRS**.
- However, there were both pragmatic and blue-sky opportunities that the group felt warranted further exploration.
- PTRS was seen to be highest with **TCV**, but from a public health perspective, **PCV** and **injectable rotavirus vaccine** were of highest interest due to the global reach and maximal impact on disease/death with early EPI schedule.
- Decisions moving forward would be informed by the emergence of new data, not least on the longevity of protection from TCV and development progress with other candidate vaccines.
- **Development of Shigella vaccines should not be delayed by the absence of a clear decision in relation to combinations**
- Discussions with potential combination asset owners, further 'feasibility and acceptability' (F & A) work around specific combinations and formulation work though to Phase 1 continue to move ahead, with readiness to immunobridge post-Phase 3 if efficacy ends up being achieved by a standalone vaccine before a combination vaccine.

Update:

WHO Regulatory Science Workshop on Clinical Pathways for Shigella vaccines

Robert Kaminski, Ph.D.
WHO Consultant

WHO Regulatory Science Workshop on Clinical Pathways for Shigella vaccines intended for use in children in LMICs

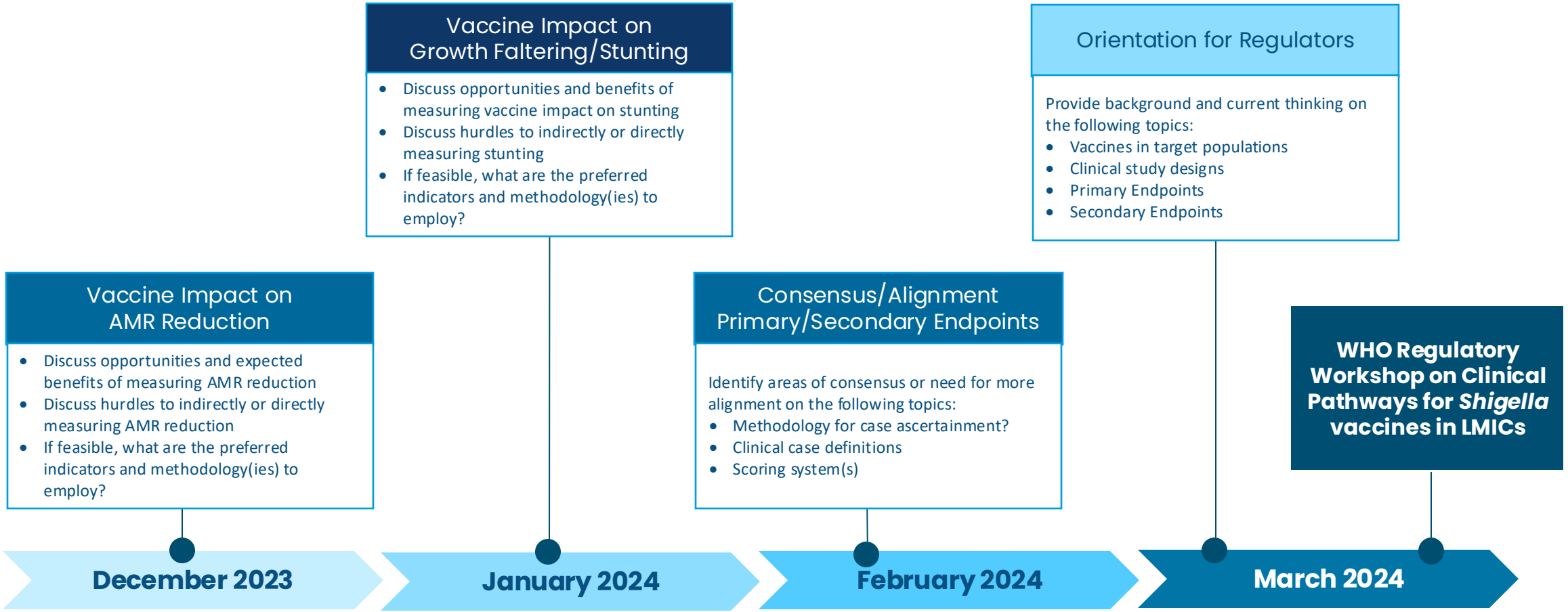
WHO: Regulators, Clinicians, Policy makers, Laboratory SMEs, Donors, Vaccine manufacturers

WHAT: Two-day WHO Regulatory Workshop focused on clinical pathways for Shigella vaccines

WHERE: Nairobi, Kenya

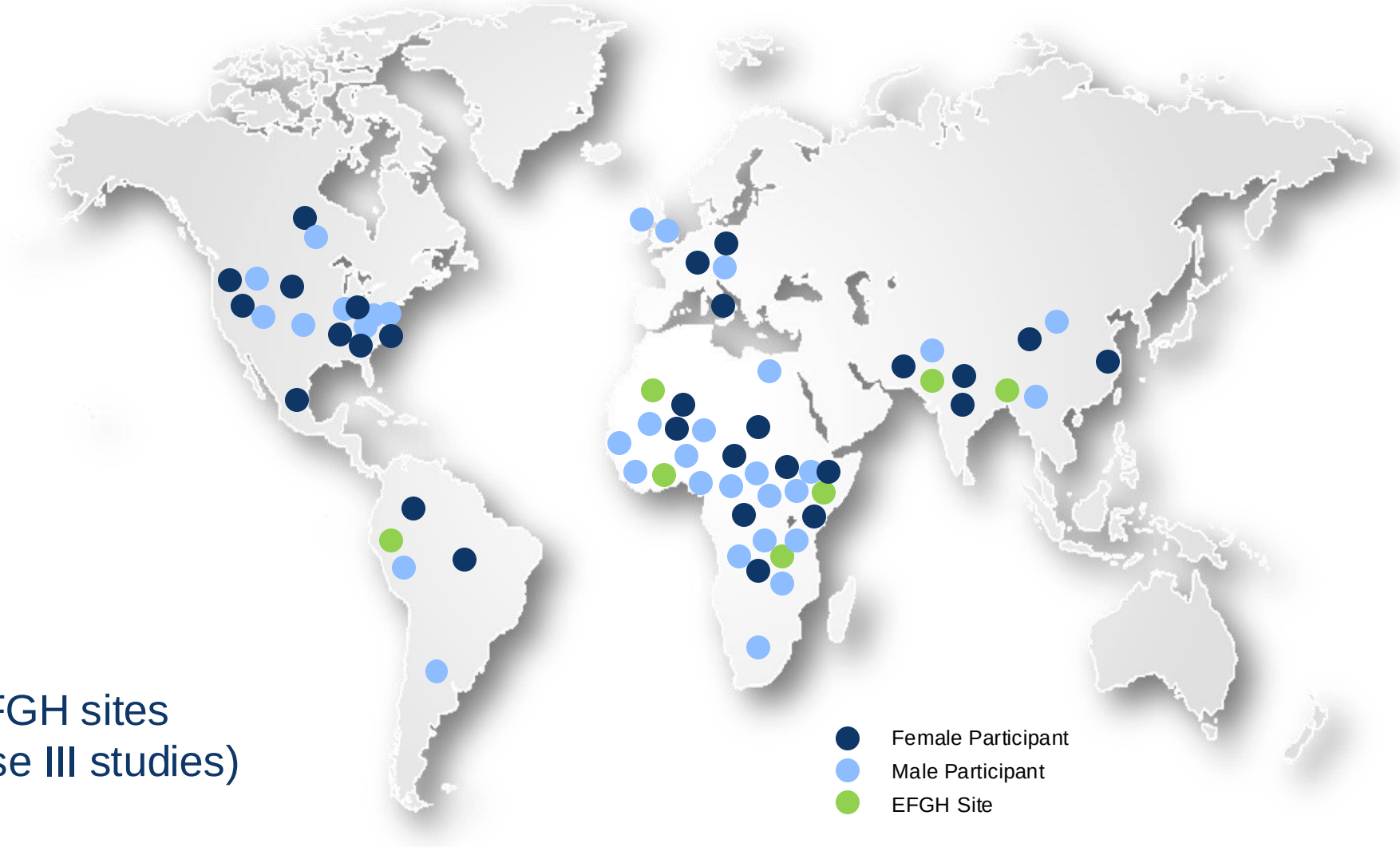
WHEN: 20-21 March 2024

Preparation for Regulatory Meeting: Virtual Engagements



Global Distribution of Participants

Over 35 regulators from **AFRO, AMRO, EMRO, EURO** and **SEARO** WHO regions participated in the workshop



Representation from EFGH sites (likely locations for phase III studies)

Workshop Objectives

- **Raise awareness** of Shigella burden and vaccine development status with regulators, particularly those from countries in which the phase III study is expected to be conducted

- Review the current thinking, **study design considerations** and preparations for **phase III** field efficacy studies in **high burden countries**, and discuss with **regulators** through a series of round tables

- **Identify** aspects of **consensus** and areas that require **additional discussion/alignment** to inform phase III study design in line with regulatory expectations.

Regulatory Science Discussion Domains

SEVEN Domains

- ❖ Safety Considerations
- ❖ Primary Endpoint
- ❖ Secondary Endpoints
- ❖ Clinical case definitions
- ❖ Laboratory Confirmation of *Shigella* Infection
- ❖ Vaccine Impact on antibiotic usage/AMR reduction
- ❖ Vaccine Impact on Growth Faltering/Stunting

Domain	Issues/Complexities	Input/Next Steps
Laboratory Confirmation of Shigella Infection	• Culture and qPCR considered for Shigella case detection • Culture allows AST and investigations into vaccine impact on AMR • qPCR is more sensitive facilitating lower phase III study sample sizes • qPCR capable of serotyping but limited to *S. sonnei* and *S. flexneri* serotypes	• Regulators open to either culture or PCR as case detection methodology • PCR will require submission of data package to support phase III usage • Efforts underway to develop data package; comparisons in the context of EFGH study • Both should be done in a trial regardless of what is used for the primary endpoint.

Key Workshop Outcomes

- Convene an **expert consultation** to finalize recommendations regarding **case definition/scoring system**
- Pursue **qPCR methodology qualification and validation** to support Phase III studies
- Convene a **WHO Policy workshop** with LMIC stakeholders to discuss how outcomes from a phase III Shigella vaccine study (such as **reductions in stunting/growth faltering** and **AMR/antimicrobial usage**) can further support vaccine implementation and uptake in LMICs
- Potential refinement to WHO Preferred Product Characteristics (PPC)

PDVAC Questions

Would PDVAC endorse, based on the investment case and recent outcomes from Gavi VIS 6.0, expanding the initial Shigella combination vaccine discussions by broadening engagement with LMIC stakeholders on Shigella combination vaccines?

Would PDVAC endorse beginning the development of an Evidence Considerations for Vaccine Policy (ECVP) to provide early information on the data and evidence that is likely to be required to support WHO policy recommendations for Shigella containing vaccines?

Many thanks