FOURTEENTH INTERNATIONAL

ROTAVIRUS SYMPOSIUM

MARCH 14–16 **2023** BALI INDONESIA

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Etiology of hospitalized diarrhea in children in low- and middle-income countries: results from the Global Pediatric Diarrhea Surveillance Network, 2017-2020

14th International Rotavirus Symposium
March 14, 2023

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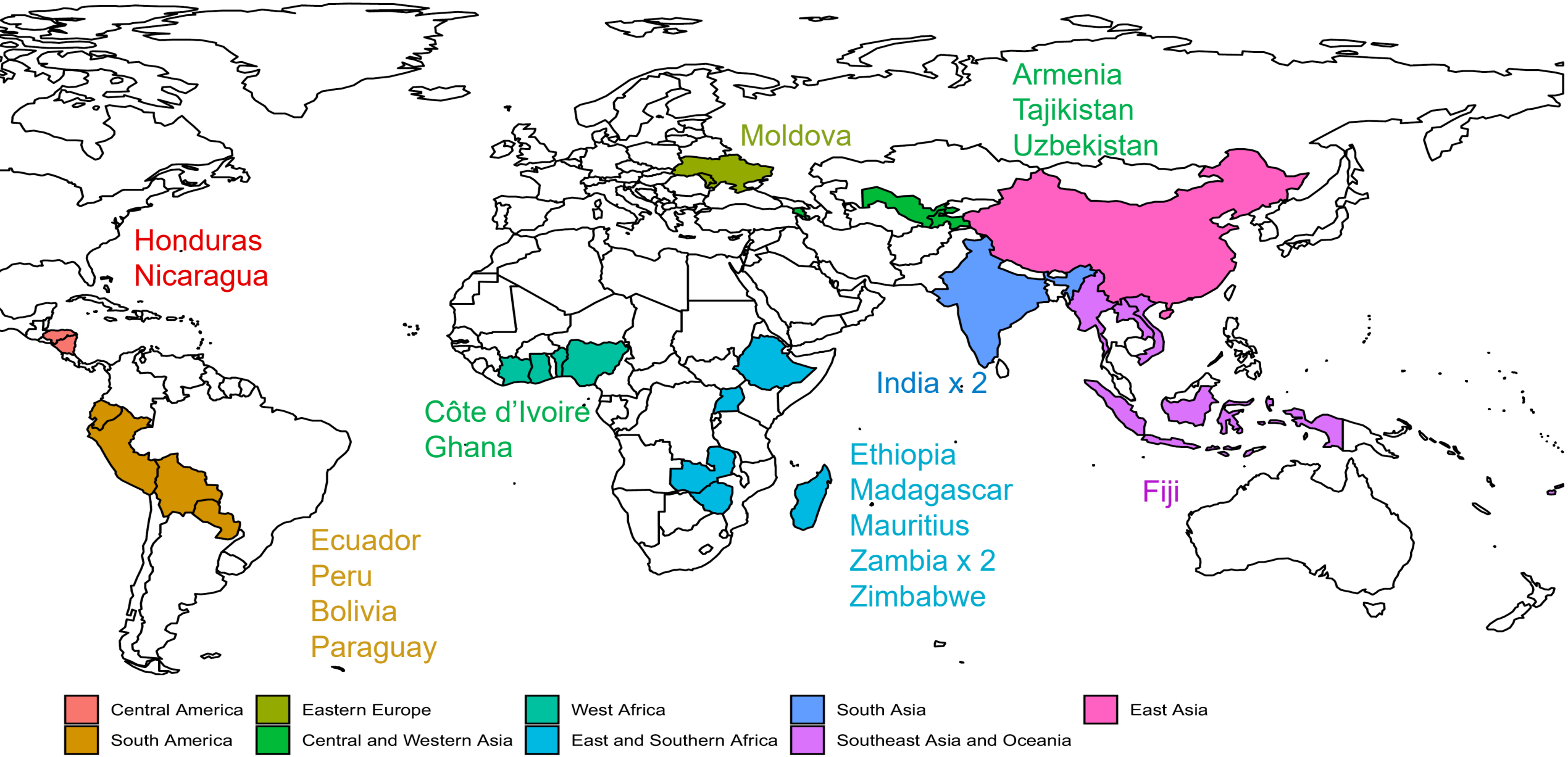
Introduction, rationale and objectives

- Outside of rotavirus, systematically collected and analyzed data on the etiology of hospitalized diarrhea in low- and middle-income countries are limited.
- Quantitative PCR testing provides high sensitivity and resolution to identify a broad range of causes of diarrhea.
- GPDS builds upon the Global Rotavirus Surveillance Network sentinel-site surveillance and regional reference laboratory system to identify the causes of hospitalized diarrhea (regardless of duration or presence of blood) in a representative set of low- and middle-income countries, using a standardized protocol to detect a broad range of etiologies of diarrhea by qPCR.
- The goal of GPDS is to estimate the burden of hospitalized diarrhea due to specific pathogens to help prioritize public health interventions.

GPDS 2017-2018: 33 surveillance sites from 28 countries



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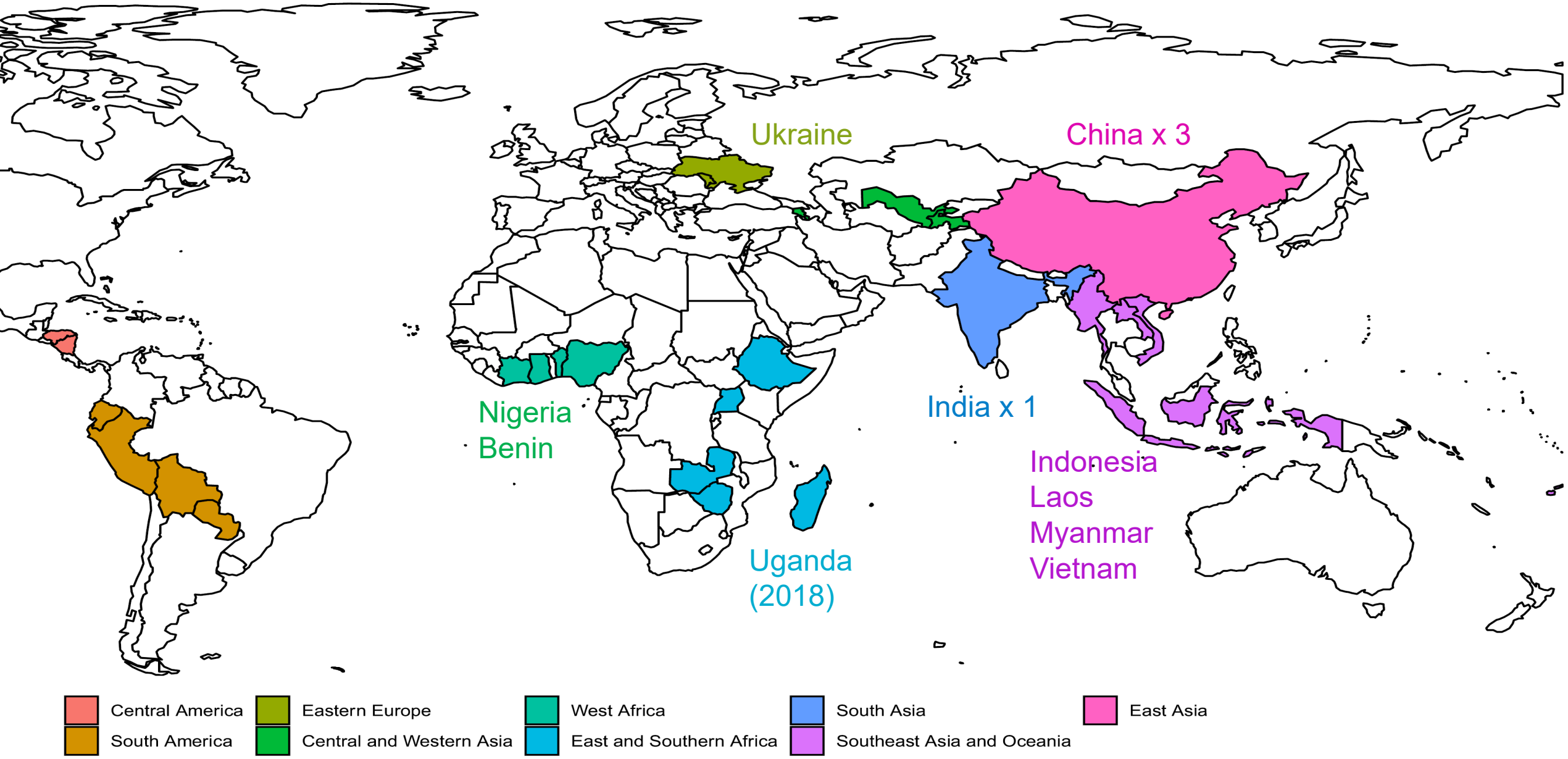


GPDS 2019-2020

WHO Region	Country	2017	2018	2019	2020
African	Benin	BEN-59 (April)	BEN-59	BEN-59	BEN-59
	Burkina Faso				BFA-64/65
	Côte d'Ivoire	CIV-8/10/14 (April)	CIV-8/10/14	CIV-8/10	
	Ethiopia	ETH-10/12 (April)	ETH-10/12	ETH-10/12/62	ETH-10/12/62
	Ghana	GHA-15 (April)	GHA-15	GHA-15	GHA-15
	Madagascar	MDG-50 (April)	MDG-50	MDG-50/51	MDG-50/51
	Mauritius	MUS-1/3	MUS-1/3	MUS-1/3/2/4	MUS-1/3/2/4
	Nigeria	NGA-25 (April)	NGA-25	NGA-25	NGA-25
	Uganda	UGA-46 (April)	UGA-46	UGA-46/48/49	UGA-46/48/49
	Zambia #1	ZMB-48 (April)	ZMB-48	ZMB-48	ZMB-48
	Zambia #2	ZMB-58 (April)	ZMB-58	ZMB-58	ZMB-73
	Zimbabwe	ZWE-1/49/69 (April)	ZWE-1/49/69	ZWE-1/49/69	ZWE-1/49/69
American	Bolivia		BOL-2	BOL-2	BOL-2
	Ecuador	ECU-40	ECU-40	ECU-40	ECU-40
	Honduras	HND-12	HND-12	HND-12	HND-12
	Nicaragua	NIC-61	NIC-61	NIC-61	NIC-61
	Peru	PER-104	PER-104	PER-104	PER-104
	Paraguay	PRY-14	PRY-14	PRY-14	PRY-14
Eastern Mediterranean	Pakistan #1			PAK-312	PAK-312
	Pakistan #2				
European	Armenia	ARM-1	ARM-1	ARM-1	ARM-1
	Moldova	MDA-6/7	MDA-6/7	MDA-6/7	MDA-6/7
	Tajikistan	TJK-8	TJK-8	TJK-8	TJK-8
	Ukraine	UKR-11	UKR-11	UKR-11	
	Uzbekistan	UZB-15	UZB-15		
South-East Asian	India #1	IND-4 (April)	IND-4	IND-4	IND-4
	India #2	IND-5 (April)	IND-5		
	India #3	IND-6 (April)	IND-6	IND-6	IND-6
	India #4			IND-7	IND-7
	Indonesia	IDN-4	IDN-4		
	Myanmar	MMR-1	MMR-1	MMR-1	
Western Pacific	China #1 (CHN-11)	CHN-11	CHN-11	CHN-11	CHN-11
	China #2 (CHN-3)	CHN-3	CHN-3	CHN-3	CHN-3
	China #3 (CHN-7)	CHN-7	CHN-7	CHN-7	CHN-7
	Fiji	FJI-11	FJI-11		FJI-11
	Lao	LAO-12 (April)	LAO-12	LAO-12	LAO-12
	Viet Nam	VNM-1 (April)	VNM-1	VNM-1*	VNM-1

Methods

Sample selection and testing: We performed stratified random selection for each 3 month interval by site in 2017-2018 and simple random selection for 2019-2020 (100 samples per site per year). We applied inverse probability of selection weighting to make the tested samples as representative as possible (in particular to accurately represent seasonal incidence of diarrhea). Samples were shipped to regional reference labs for qPCR testing using the TAC platform.

Site-level Attributable Fractions: Given the absence of non-diarrheal controls in GPDS, we combined quantitative PCR results from GPDS with the modeled association between pathogen quantity and diarrhea in two previously-published, multisite studies of diarrhea in similar settings (GEMS and MAL-ED) to determine attribution. To optimized pathogen attribution, pathogen density distributions in GPDS cases were matched to the density distributions from GEMS and MAL-ED sites.

Aggregated Attributable Fractions: Given the absence of data on population at risk or health-care seeking behavior at these sites, we used year- and age-specific estimates of the incidence of hospitalized diarrhea from the Global Burden of Disease (GBD) Study to estimate attributable fractions for geographic groupings and overall.

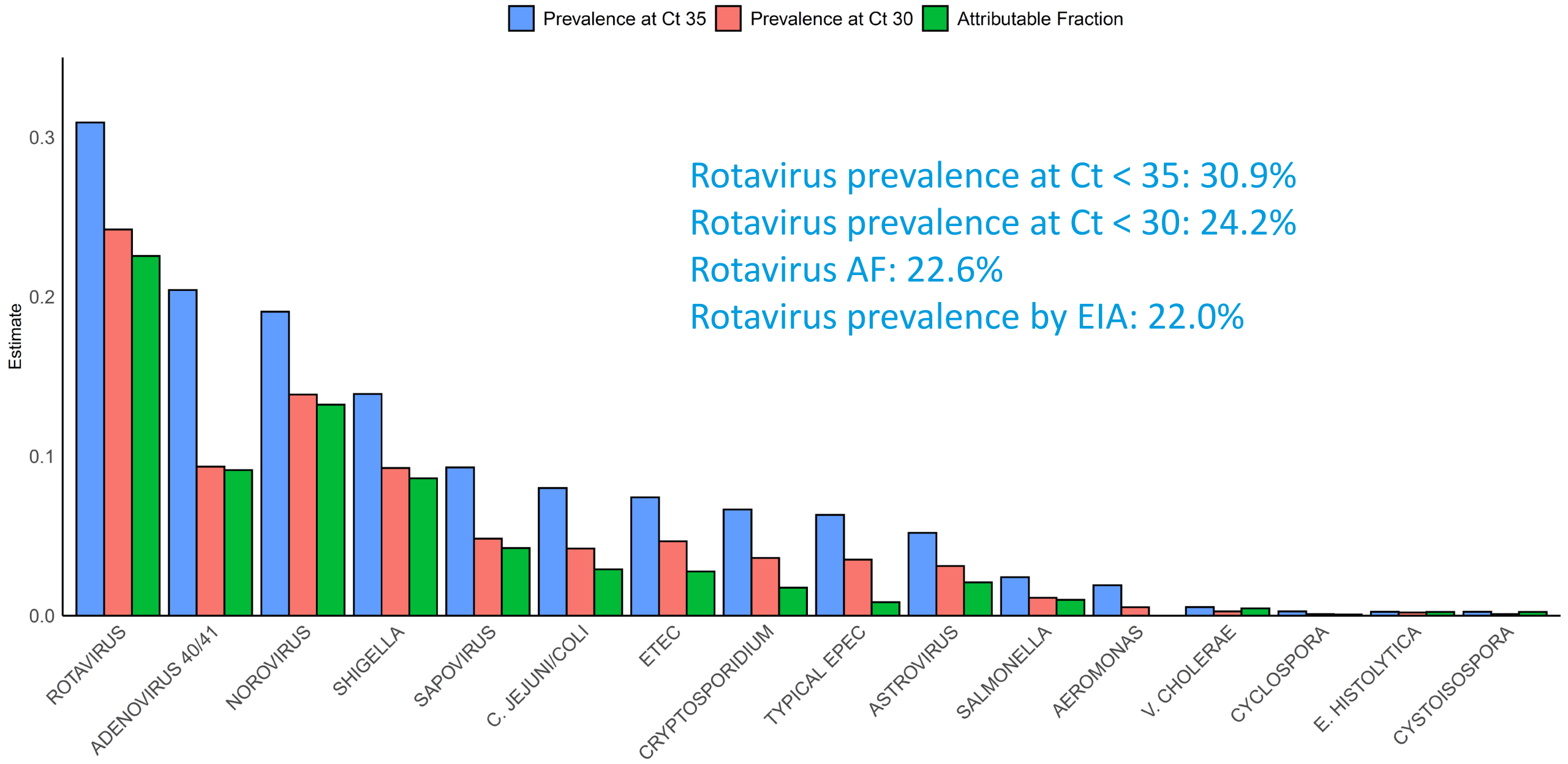
Pathogens included in etiology estimation

	Pathogen	Gene
Viruses	Adenovirus 40/41	Fiber gene
	Astrovirus	Capsid
	Norovirus GII	GII ORF1-2
	Rotavirus	NSP3
	Sapovirus	RdRp
Bacteria	Typical EPEC	bfpA
	ST-ETEC	STh and STp
	Aeromonas	Aerolysin
	Campylobacter jejuni/coli	cadF
	Salmonella	Ttr
	Shigella/EIEC	ipaH
	Vibrio cholerae	hlyA
Protozoa	*Cryptosporidium*	18S rRNA
	Cyclospora cayetanensis	18S rRNA
	Cystoisospora belli	18S rRNA
	Entamoeba histolytica	18S rRNA
Controls	MS2	MS2g1
	PhHV	gB

Demographic and clinical characteristics

	2017-2018 (N = 29502)		2019-2020 (N = 18151)	
	All enrolled cases	qPCR-tested cases (weighted)	All enrolled cases	qPCR-tested cases (weighted)
Male sex	17171 (58·3)	17217 (58·4)	10457 (57.6)	10437 (58.3)
Age				
0-11 months	12828 (43·5)	12806 (43·4)	8517 (46.9)	8585 (47.9)
12-23 months	9888 (33·5)	9785 (33·2)	5833 (32.1)	5691 (31.7)
24-59 months	6786 (23·0)	6911 (23·4)	3801 (20.9)	3662 (20.4)
World Health Organization Region				
African	7880 (26·7)	7880 (26·7)	4807 (26.5)	4678 (25.8)
Americas	5414 (18·4)	5414 (18·4)	3596 (19.8)	3596 (19.8)
Eastern Mediterranean	N/A	N/A	731 (4.0)	731 (4.0)
European	9164 (31·1)	9164 (31·1)	2978 (16.4)	2978 (16.4)
South-East Asian	3104 (10·5)	3104 (10·5)	1752 (9.7)	1752 (9.7)
Western Pacific	3940 (13·4)	3940 (13·4)	4287 (23.6)	4203 (23.2)
Acute diarrhoea (<14 days)	29055 (98·5)	29097 (98·6)	17853 (98.4)	17644 (98.4)
Bloody diarrhoea	1777 (6·6)	1614 (5·7)	1117 (6.5)	1136 (6.5)
Diarrhoeal duration (days)	2 (1-4)	2 (1-4)	3 (2-4)	3 (2-4)
Vomiting	20074 (69·6)	20176 (69·7)	11215 (65.4)	11201 (65.7)
In-hospital deaths	125 (0·5)	98 (0·4)	33 (0.2)	27 (0.2)

GPDS 2017-2020: Weighted prevalence vs Attributable Fraction (vs EIA)



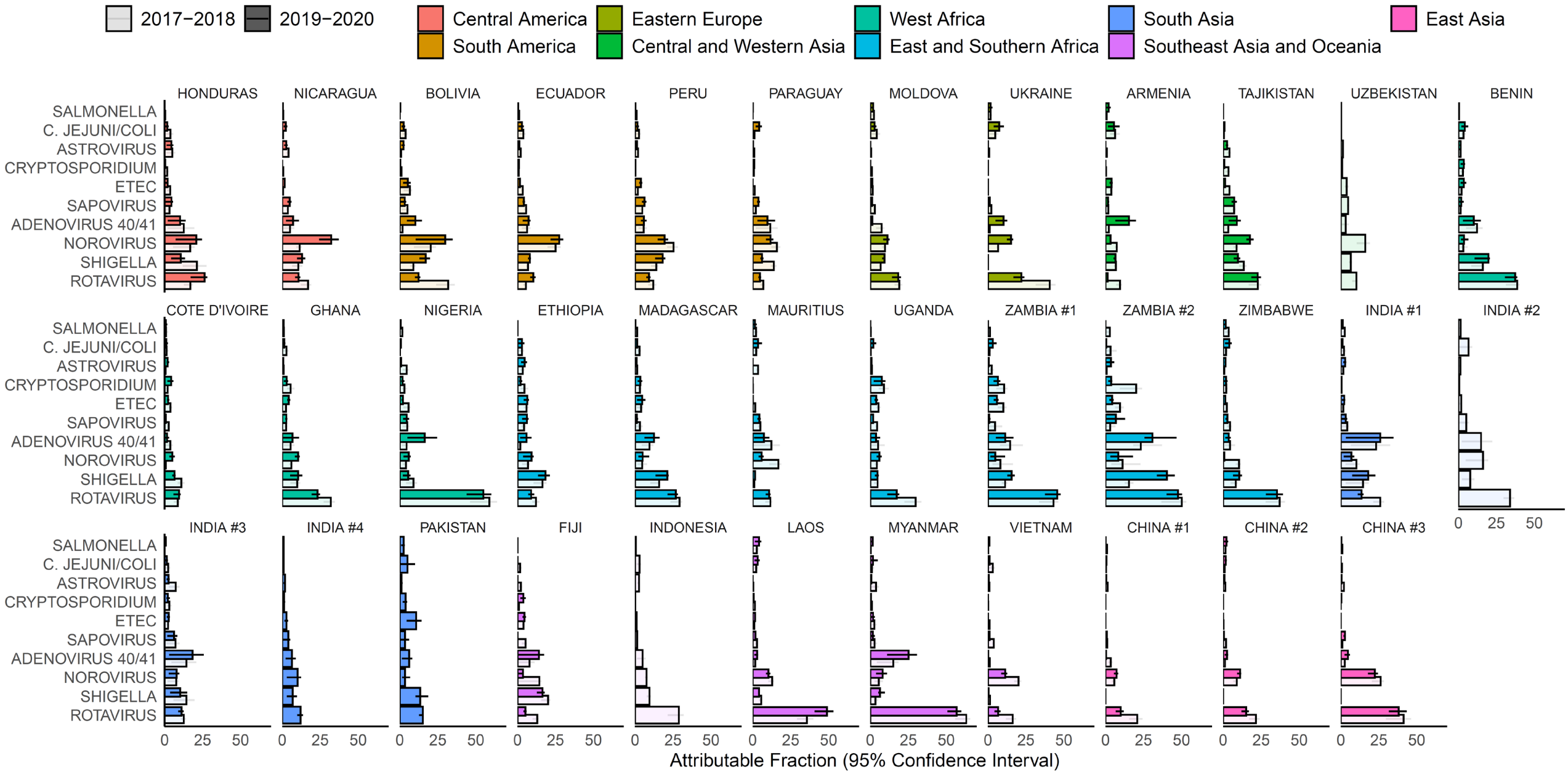
Rotavirus prevalence at Ct < 35: 30.9%

Rotavirus prevalence at Ct < 30: 24.2%

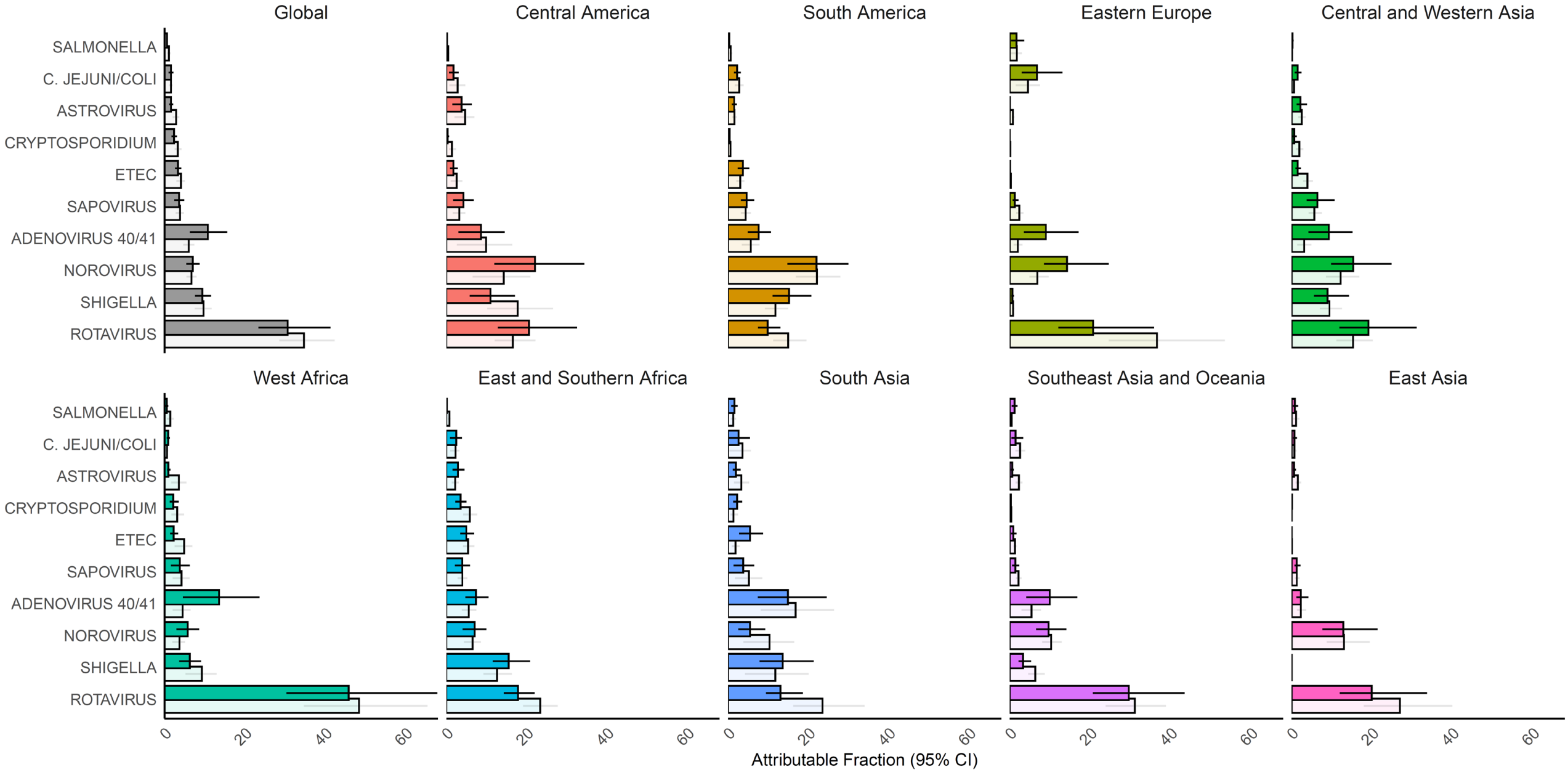
Rotavirus AF: 22.6%

Rotavirus prevalence by EIA: 22.0%

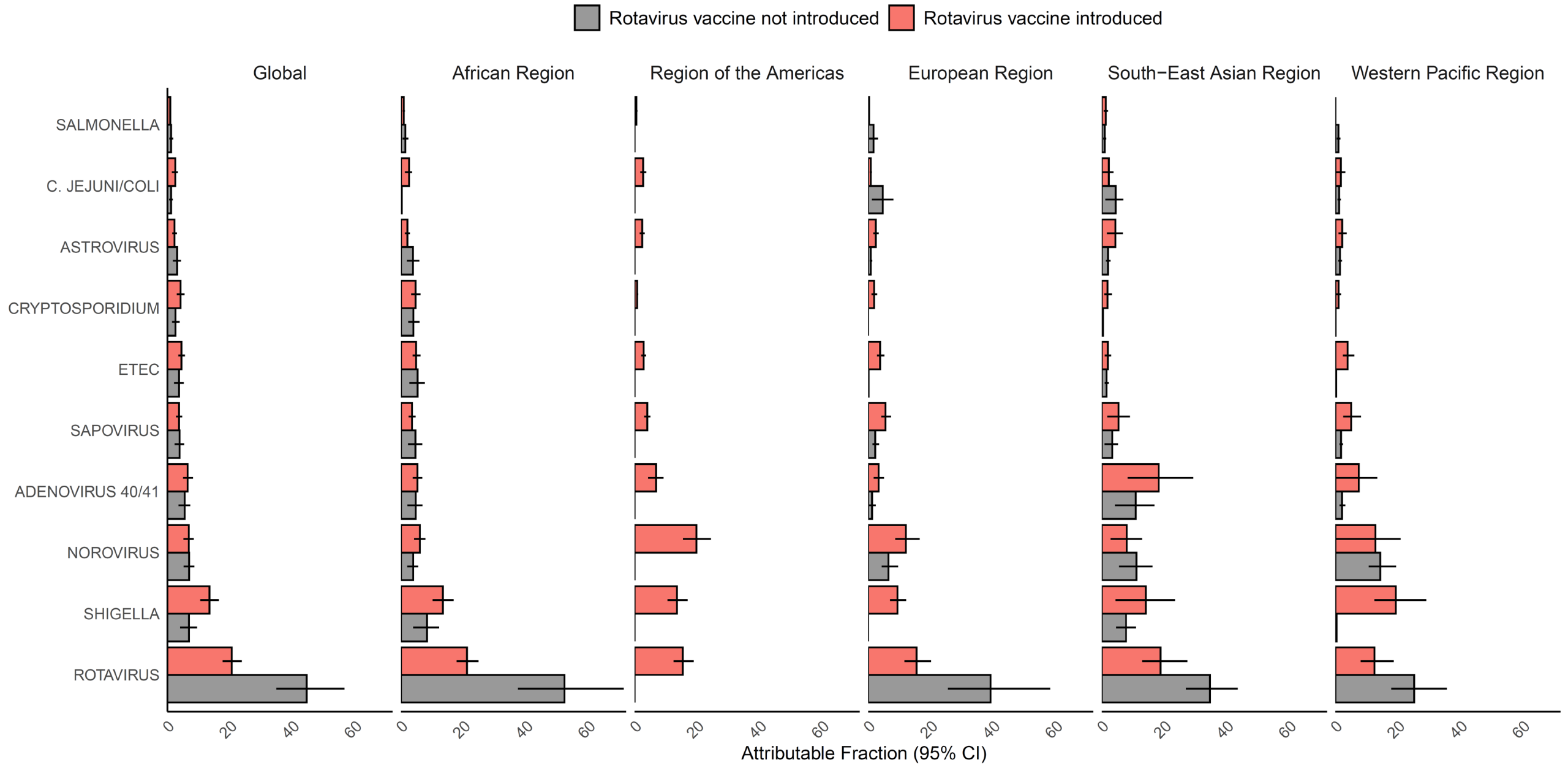
GPDS 2017-2020: Attributable fractions by site



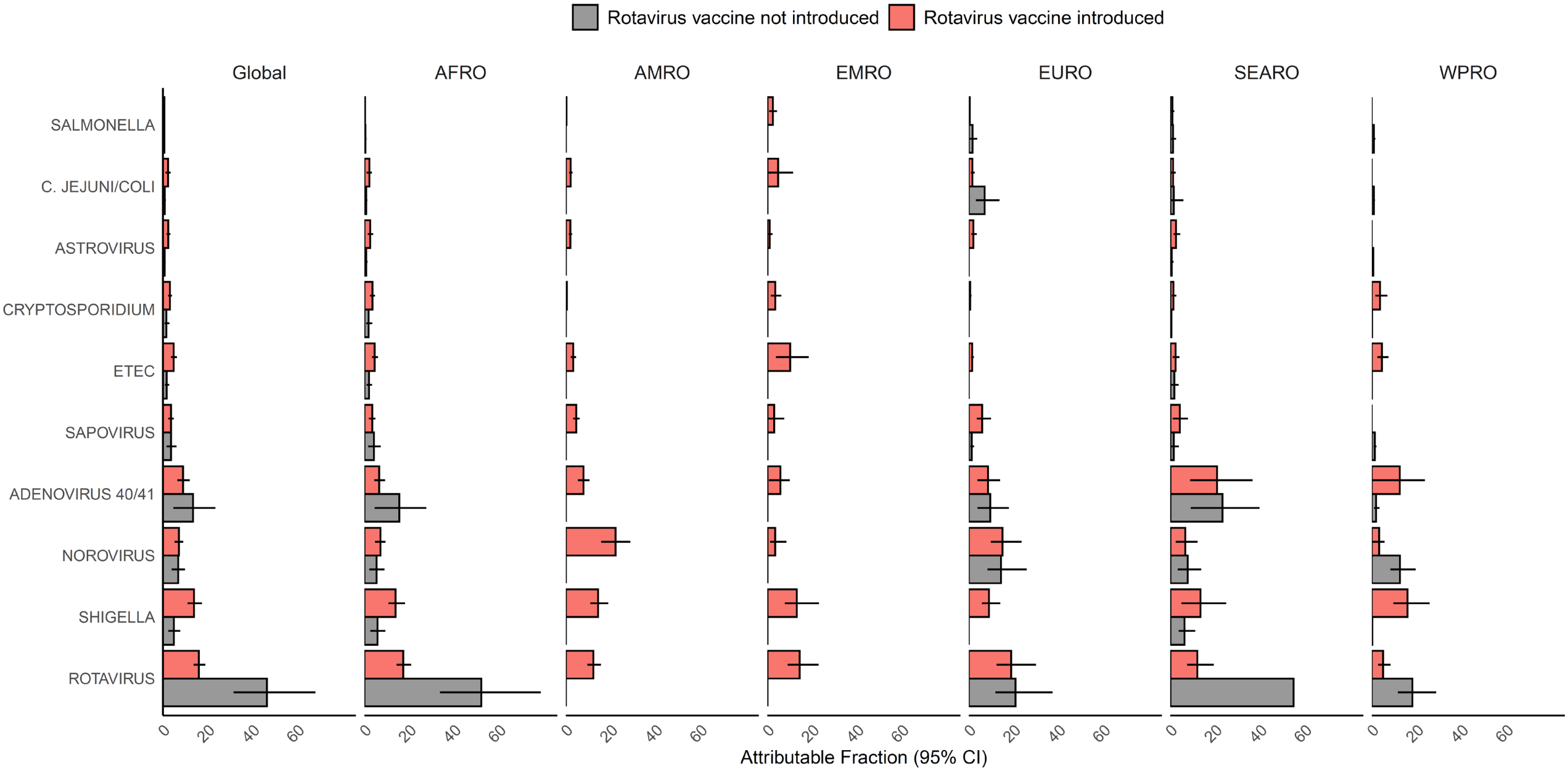
GPDS 2017-2020: Aggregated Attributable Fractions



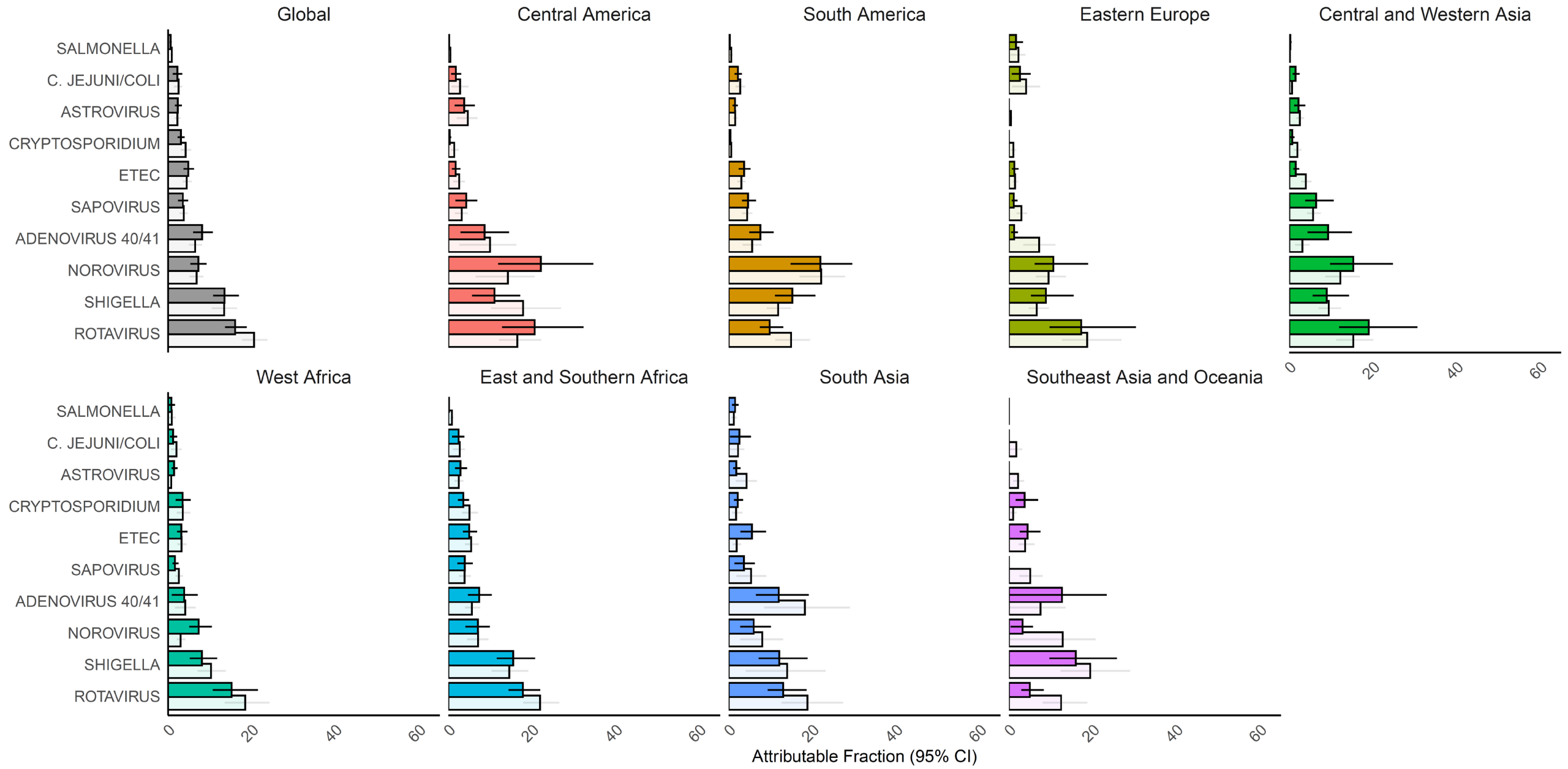
GPDS 2017-2018: Impact of rotavirus vaccine introduction



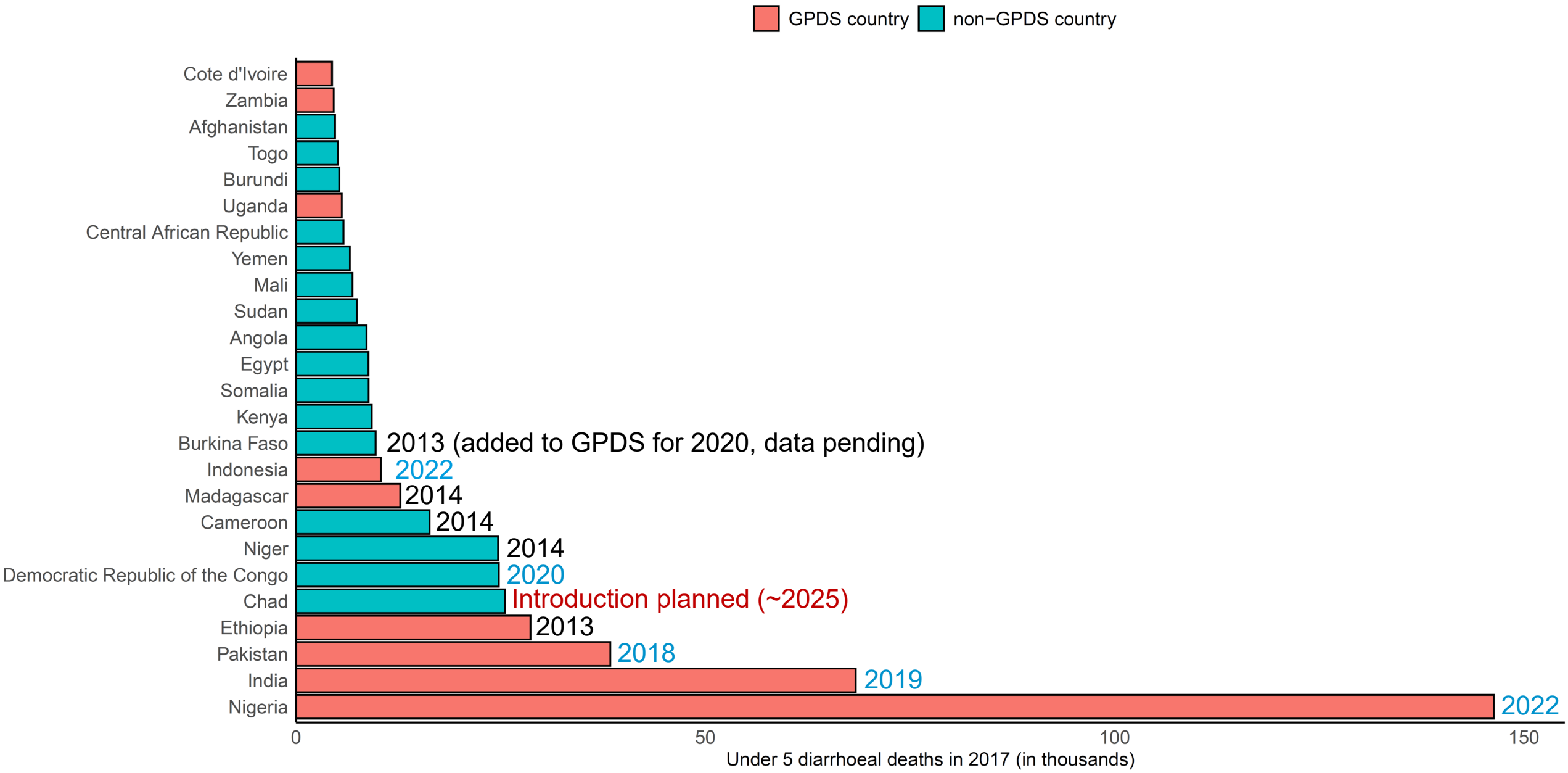
GPDS 2019-2020: Impact of rotavirus vaccine introduction



GPDS 2017-2020: Aggregated Attributable Fractions (RV introducers only)



Diarrheal deaths by country, GBD 2017



GPDS 2017-2018: Global annual etiology-specific diarrheal deaths estimates (children under 5 years of age)

	Global	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asian Region	Western Pacific Region
All-cause	582295	396459	10483	79661	1623	84565	8175
Rotavirus	208009	148931	1857	28343	342	25829	2283
Shigella	62853	43947	1570	7837	193	9164	106
Adenovirus 40/41	36922	15117	765	8182	54	12701	175
Norovirus	35914	19562	1843	5881	156	6960	1094
Sapovirus	22704	17060	396	2539	108	2302	143
ETEC	22530	18879	338	1988	63	1158	28
Cryptosporidium	19905	17121	116	1553	51	984	22
Astrovirus	17213	13208	289	1832	63	1670	110

Nigeria: 77,239 rotavirus-attributable deaths (95% CI: 55,513 – 102,917)

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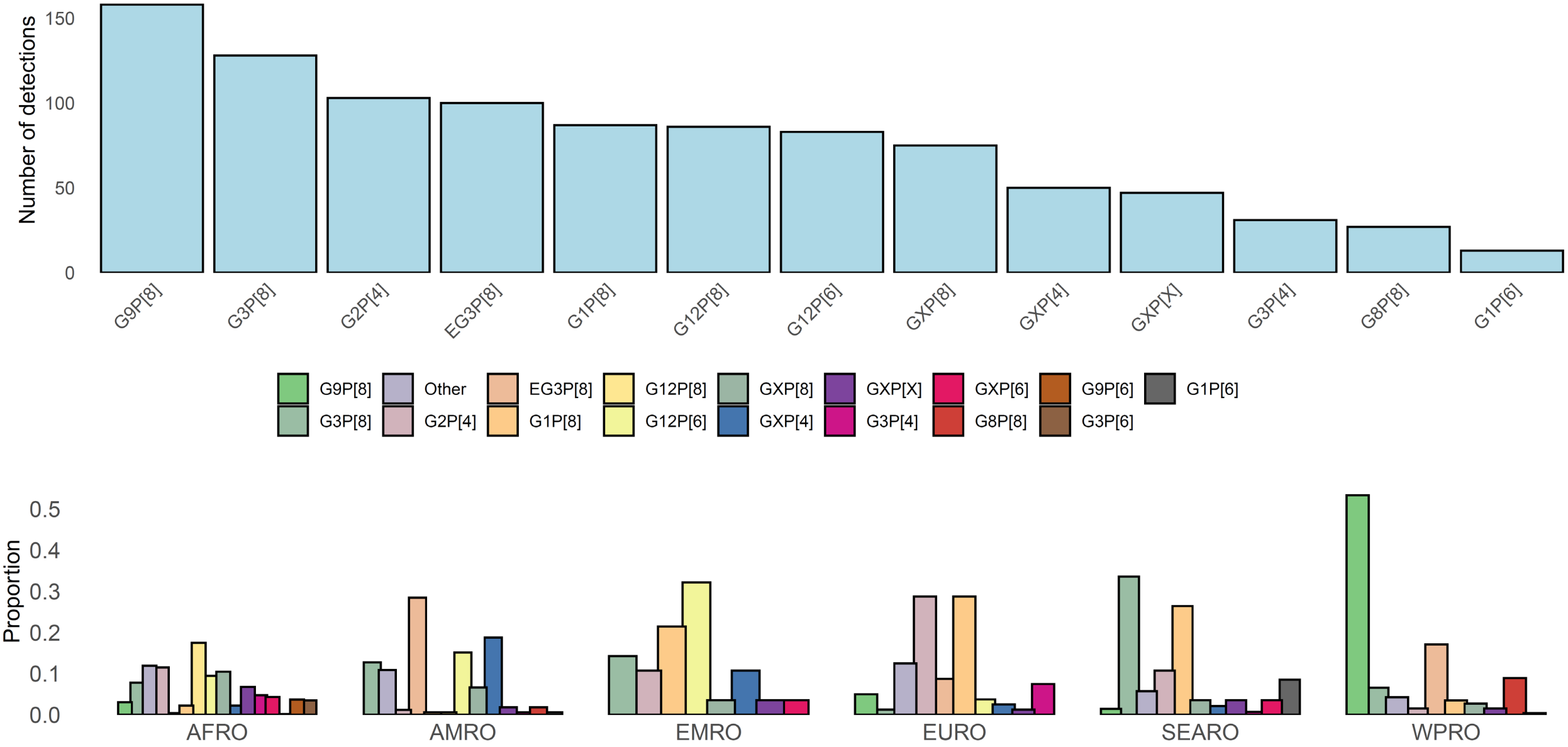
GBD 2019-2020: Rotavirus type distribution (N = 1156)



Conclusions

- Despite the substantial impact of rotavirus vaccine introduction, rotavirus remained the leading cause of pediatric diarrhea hospitalizations in both 2017-2018 and 2019-2020, but the gap to other pathogens closed substantially.
- *Shigella*, norovirus, and adenovirus were other important causes of diarrhea requiring hospitalization in these settings.
- Ongoing vaccine introductions as well as improving the efficacy and coverage of rotavirus vaccination could further reduce diarrhoea morbidity and mortality.
- Looking forward, this network can provide a platform for understanding the impact of the ongoing introduction and optimization of rotavirus vaccines, as well as provide support for future enteric vaccines.

GPDS Network

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

Global Burden of Disease Study

Institute for Health Metrics and Evaluation

Hmwe Kyu