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Comparison of Rotavirus and Norovirus Post-Rotavirus vaccine introduction in 3 sub-Saharan African countries, 2015-2018: Findings from the Vaccine Impact on Diarrhea in Africa (VIDA) Study

Richard Omore[1], Helen Powell[2,3,a], Samba O. Sow[3], M. Jahangir Hossain[4], Billy Ogwel[1], Sanogo Doh[3], John B. Ochieng[1], Joquina Chiquita M. Jones[4], Syed M.A. Zaman[4], Alex O. Awuor[1], Jane Juma[1], Irene N. Kasumba[5], Anna Roose[2,b], Leslie P. Jamka[5], Dilruba Nasrin[5], Jie Liu[6], Adama Mamby Keita[3], Awa Traoré[3], Uma Onwuchekwa[3], Henry Badji[4], Golam Sarwar[4], Martin Antonio[4], Ciara E. Sugerman[7], Eric D. Mintz[7,c], Eric R. Houpt[6], Jennifer R. Verani[8], Marc-Alain Widdowson[8,d], Sharon M. Tennant[5], James A. Platts-Mills[6], Jacqueline E.Tate[9], Umesh D. Parashar[9], and Karen L. Kotloff[2,5]

[1]Kenya Medical Research Institute, Center for Global Health Research (KEMRI-CGHR), Kisumu, Kenya
[2]Department of Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[3]Centre pour le Développement des Vaccins du Mali (CVD-Mali), Bamako, Mali
[4]Medical Research Council Unit, The Gambia at the London School of Hygiene & Tropical Medicine, Banjul, The Gambia
[5]Department of Medicine, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[6]Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, Charlottesville, VA, USA
[7]Division of Foodborne, Waterborne, and Environmental Diseases, US Centers for Disease Control and Prevention, Atlanta, GA, USA
[8]Division of Global Health Protection, US Centers for Disease Control and Prevention, Nairobi, Kenya
[9]Division of Viral Diseases, US Centers for Disease Control and Prevention, Atlanta, GA, USA
[a]Current affiliation: Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore USA
[b]Current affiliation: Indiana University School of Medicine, Indianapolis, Indiana, USA
[c]Current affiliation: Retired
[d]Current affiliation: Institute of Tropical Medicine Antwerp, Brussels, Belgium

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Vaccine **I**mpact on **D**iarrhea in **A**frica ◆ CVD ◆ CVD-Mali ◆ MRC/The Gambia ◆ KEMRI-CGHR

Background

- Although increasing number of viruses have been associated with diarrheal disease in humans during the past four decades, rotavirus and norovirus remain the two most common globally

- As rotavirus vaccine are introduced in sub-Saharan African countries, it`s important to:
  - Understand the relative contribution of norovirus
  - Monitor if norovirus will subsequently fill the environmental niche of rotavirus in these settings

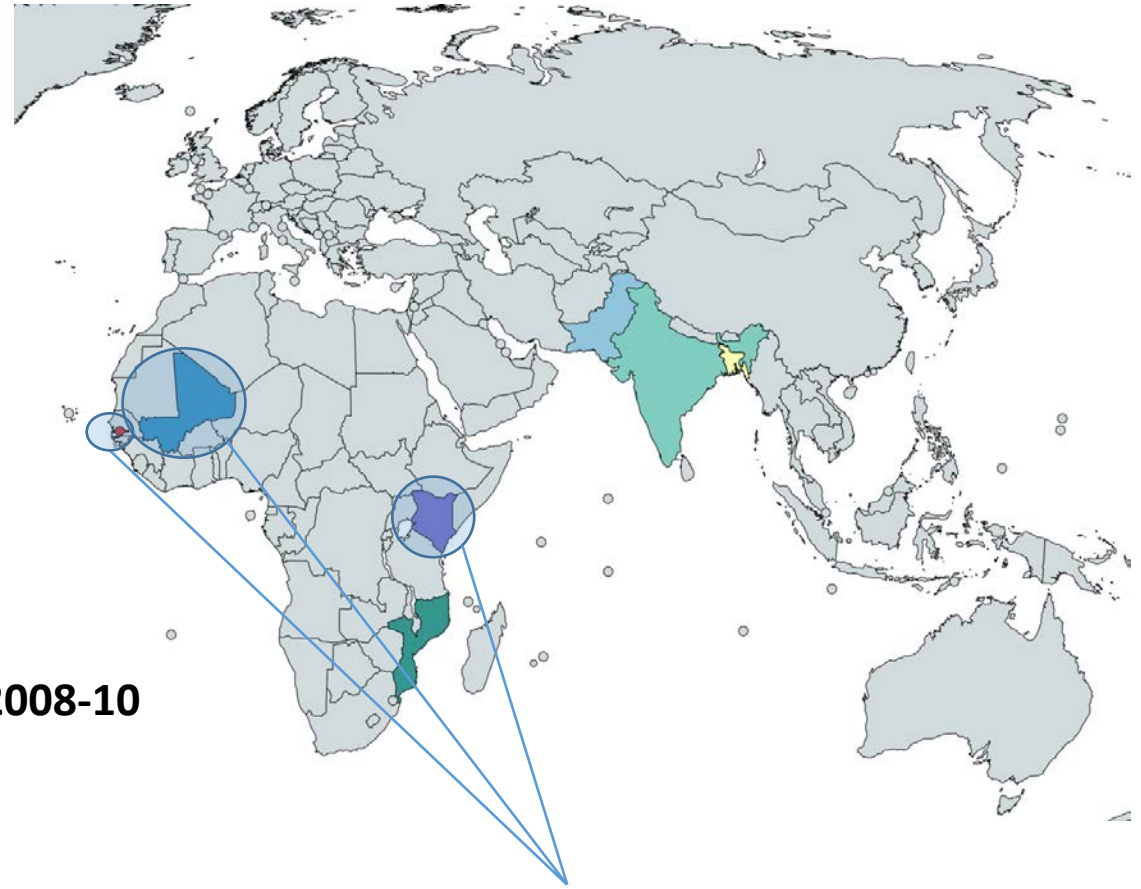
- While such data are readily available for developed countries, similar data are sparse and remain insufficient to guide interventions in sub-Saharan Africa.

- Computational simulation models suggest that the burden in Africa is large, with children <5 years old
  - Accounting for ~15% (approximately 70 million) and 40% (~38,000) of annual global norovirus cases and deaths (Bartsch Lopman, et al 2016).

- To address this issue, the Vaccine Impact on Diarrhea in Africa (VIDA) study was conducted at three sites located in sub-Saharan after rotavirus vaccine introduction.

Vaccine Impact on Diarrhea in Africa (VIDA)

- VIDA = a continuation of GEMS methods at three African sites after rotavirus vaccine had been introduced: The Gambia (2013), Mali and Kenya (2014)
- VIDA objectives:
  - To investigate the landscape of diarrheal pathogens after rotavirus vaccine introduction to inform future interventions needed in the post-rotavirus vaccine era
- VIDA started 9-18 months after rotavirus vaccine introduction
  - Rotavirus accounted for 12.6% of etiologic MSD cases regardless of co-infections or age



Objectives

- Estimate prevalence and burden
- Describe epidemiology
- Assess severity of norovirus in comparison to rotavirus illness among children <5 years old Post-Rotavirus Vaccine Introduction from the three VIDA sites in sub-Saharan African

Methods

- Population: Children < 5 years residing in demographic surveillance system (DSS) at each study site

- A Moderate-to-severe (MSD) case enrolled in VIDA was defined as;
  - A child aged 0-59 months with diarrhea (≥3 looser than normal stools within 24 hours) with onset within the past 7 days, after ≥7 diarrhea-free days, and ≥1 of the following:
    - Sunken eyes (more than normal), decreased skin turgor, dysentery (bloody stool), intravenous rehydration, or hospitalization.
- Controls: 1-3 diarrhea-free controls matched for gender, age, time, and community were enrolled at home within 14 days of the index case enrolment

Statistical methods

- Pathogen detection:
  - Norovirus was detected by “conventional methods” using RT-PCR
  - In addition, rotavirus and norovirus were detected by TaqMan Array Card quantitative PCR
  - TAC Ct-values <35 were considered positive.

- Attribution of an episode to a pathogen:
  - For each episode, pathogen-specific odds ratios (ORe) were calculated by an adjusted conditional logistic regression
  - The episode-specific attributable fraction $(AFe) = 1 - (\frac{1}{ORe})$.
  - Pathogens with AFe ≥ 0.5 were considered “etiologic” for that episode. The proportion of episodes in which the AFe ≥ 0.5 was the attributable prevalence of the pathogen.

- After finding a low attributable burden of NVI, we limited additional analyses of attributable cases to children infected with NVII.

- We also examined the proportion of MSD cases in which NVII was the sole attributable fraction versus a co-infection with any one of the more than 20 potential enteropathogens identifiable by the TAC qPCR.

Statistical methods

- We made the following comparisons between cases in which norovirus GII vs rotavirus were the sole attributable pathogen:
  - Clinical features and illness severity using the modified Vesikari score
  - Age distribution

- Chi-squared tests used for categorical variables

- Wilcoxon rank sum tests used for continuous non-normal variables

Proportion of children **at all sites** who were positive for norovirus GI (NVI) by conventional reverse transcriptase (RT)-PCR or TAC qPCR (where positivity is defined as a pathogen-specific cycle threshold (Ct) < 35), and the proportion who had an attributable detection of norovirus (AFe ≥ 0.5) by qPCR in the VIDA study, 2015-2018

	NVI	
	All sites	
Enrolled	Cases (N = 4,840)	Controls (N = 6,213)
No. (%) positive by RT-PCR†	1.4%	1.6%
No. (%) positive (Ct< 35) by qPCR†	4.7%	4.9%
No. (%) attributable (AFe ≥ 0.5)	<0.1%	

NVI denotes norovirus genogroup I. RT-PCR denotes reverse transcriptase PCR. †All cases and controls were tested by RT-PCR whereas all cases but only the first matched control were tested by qPCR. The denominators are the total number for whom the laboratory test was successfully conducted.

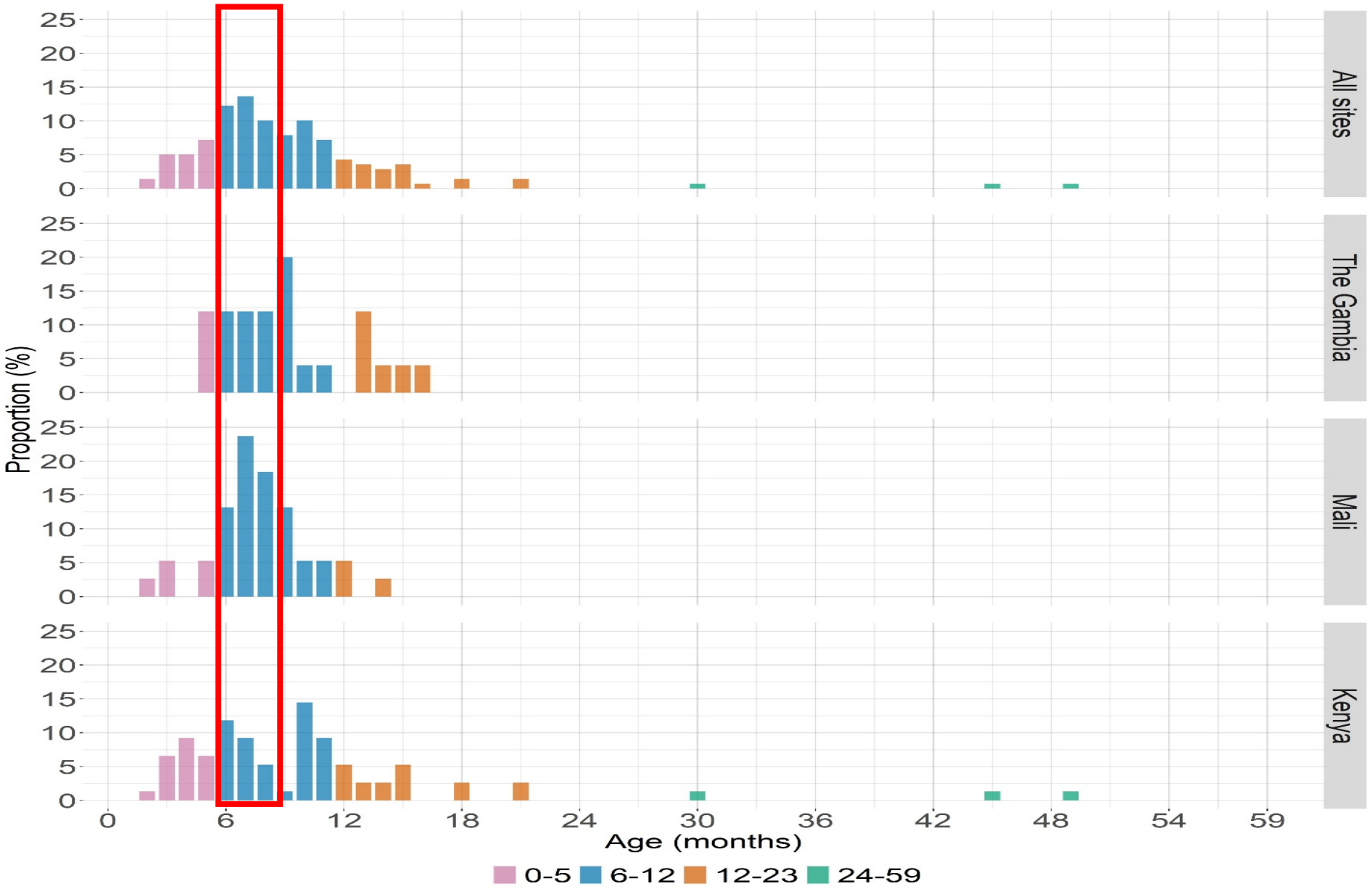
Proportion of children **at each site** who were positive for norovirus GII (NVII) by conventional reverse transcriptase (RT)-PCR or TAC qPCR (where positivity is defined as a pathogen-specific cycle threshold (Ct) < 35), and the proportion who had an attributable detection of norovirus (AFe ≥ 0.5) by qPCR in the VIDA study, 2015-2018

	NVII							
	All sites		The Gambia		Mali		Kenya	
Enrolled	Cases (N = 4,840)	Controls (N = 6,213)	Cases (N = 1,678)	Controls (N = 2,138)	Cases (N = 1,608)	Controls (N = 1,980)	Cases (N = 1,554)	Controls (N = 2,095)
No. (%) positive by RT-PCR†	4.5%	3.5%	4.6%	4.3%	2.9%	2.6%	6.1%	3.7%
No. (%) positive (Ct< 35) by qPCR†	11.5%	10.8%	10.8%	10.9%	11.0%	11.6%	12.8%	9.9%
No. (%) attributable (AFe ≥ 0.5)	3.8%		2.3%		2.8%		6.6%	

NVII denotes norovirus genogroup II. RT-PCR denotes reverse transcriptase PCR. †All cases and controls were tested by RT-PCR whereas all cases but only the first matched control were tested by qPCR. The denominators are the total number for whom the laboratory test was successfully conducted.

In total, 139 (3%) and 483 (10%) of the MSD cases were included in further analysis as they were attributable to NVII and rotavirus as a single agent , respectively.

Frequency distribution of 139 cases of moderate-to-severe diarrhea where NVII was the single attributed pathogen (AFe ≥ 0.5) by age group and study site in the Vaccine Impact on Diarrhea in Africa (VIDA) study (2015-2018).



Measures of disease severity amongst Norovirus GII vs. Rotavirus single etiologic cases (AFe ≥ 0.5)

Characteristics		NVII (N=139)	Rotavirus (N=483)	P[3]
Duration of diarrhea (days)	Median (Q1-Q3)	3 (2, 4)	3 (2, 3)	0.2182
Max # loose stools in 24 hours	1-3	29 (20.9%)	77 (15.9%)	0.4671
	4-5	85 (61.2%)	301 (62.3%)	
	6-10	25 (18.0%)	103 (21.3%)	
	>10	0	2 (0.4%)	
Experienced vomiting	Yes	93 (66.9%)	378 (78.3%)	**0.0083**
Max # vomiting episodes on worst day[1]	1	13 (14.0%)	36 (9.5%)	0.3479
	2-4	65 (69.9%)	265 (70.1%)	
	≥5	15 (16.1%)	77 (20.4%)	
Duration of vomiting (days)[2]	Median (Q1-Q3)	2 (1, 2)	2 (2, 3)	**0.0216**
Axillary temperature (°C)	37.2 – 38.4	41 (29.5%)	170 (35.2%)	0.4364
	38.5 – 38.9	3 (2.2%)	18 (3.7%)	
	≥39	2 (1.4%)	9 (1.9%)	
	Median (Q1-Q3)	36.7 (36.4, 37.3)	36.9 (36.5, 37.5)	**0.0147**

Measures of disease severity amongst Norovirus GII vs. Rotavirus single etiologic cases (AFe ≥ 0.5)

Characteristics		NVII (N=139)	Rotavirus (N=483)	P[3]
Dehydration (%)	No dehydration	5 (3.6%)	29 (6.0%)	0.4053
	Some dehydration	109 (78.4%)	382 (79.1%)	
	Severe dehydration	25 (18.0%)	72 (14.9%)	
Treatment	None	0 (0.0%)	10 (2.1%)	**0.0001**
	Oral rehydration only	133 (95.7%)	398 (82.4%)	
	IV rehydration or hospitalization	6 (4.3%)	75 (15.5%)	
mVS (integer)	Median (Q1-Q3)	9 (7, 11)	11 (8, 12)	**0.0003**
mVS severity category	Mild	24 (17.3%)	65 (13.5%)	**<0.0001**
	Moderate	73 (52.5%)	172 (35.6%)	
	Severe	42 (30.2%)	246 (50.9%)	

[1]Includes parameters that comprise the modified Vesikari Score (mVS)

[2]Among children with vomiting,

[3]Two-tailed p-values generated by chi-squared test for categorical variables (except when the expected count was

Summary and Conclusions

- NVII accounted for
  - ~4% of all MSD etiologic cases in VIDA regardless of co-infection
    - 2%, 3% and 7% of MSD in The Gambia, Mali and Kenya
- NVII accounted for ~3% of all MSD as a single pathogen vs. ~10% of rotavirus
- The highest disease burden of NVII was observed in infants aged 6-11 months
  - Suggest potential benefit of early infant norovirus vaccination schedule
- MSD due to NVII was observed to be slightly less severe than that due to rotavirus
- Use of a highly sensitive qPCR increased pathogen identification in both cases and controls without increasing the attributable burden of NV II in MSD, corroborating findings from other case control and birth cohort studies.
  - Further understanding of the role of high rates of asymptomatic infection in enteric function and illness may provide additional insight into the burden of this infection.

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VIDA Team

Thank you!

Distribution of NVII and Rotavirus Etiologic Cases (regardless of co-infection) by age group and study site in VIDA, 2015-2018

	GII Etiologic Cases				Rotavirus Etiologic Cases			
	The Gambia	Mali	Kenya	Overall	The Gambia	Mali	Kenya	Overall
Age group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0-11	25 (65.8)	43 (91.5)	74 (71.2)	**142 (75.1)**	91 (39.1)	90 (46.9)	81 (43.3)	**262 (42.8)**
12-23	12 (31.6)	4 (8.5)	26 (25.0)	**42 (22.2)**	96 (41.2)	75 (39.1)	64 (34.2)	**235 (38.4)**
24-59	1 (2.6)	0 (0)	4 (3.8)	**5 (2.7)**	46 (19.7)	27 (14.0)	42 (22.5)	**115 (18.8)**
Total	**38**	**47**	**104**	**189**	**233**	**192**	**187**	**612**