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ROTAVIRUS SYMPOSIUM

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Epidemiology of enteric viruses in children under 5 years before and after rotavirus vaccine introduction in Manhiça district, southern Mozambique, 2008-2019

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BACKGROUND (I)

- Diarrhoea is the third leading cause of morbidity and mortality in children under 5 years old worldwide

  -Responsible for 1.7 billion cases and 370,000 deaths;

  - Most deaths occur in Sub-Saharan Africa and South Asia.

- >75% of acute infectious diarrhoea is due to enteric viruses

  - Rotavirus A (RVA) is the most important;

  - Norovirus, Astrovirus, Sapovirus and enteric Adenovirus (40/41) are also important.

(Vos *et al*. 2020; WHO, 2017, 2019; Nasab *et al*. 2020)

BACKGROUND (II)

Diarrheal Disease in Rural Mozambique: Burden, Risk Factors and Etiology of Diarrheal Disease among Children Aged 0–59 Months Seeking Care at Health Facilities

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Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Early impact of rotavirus vaccination in children less than five years of age in Mozambique

Nilsa de Deus [a,*], Jorfélia José Chilaúle [a], Marta Cassocera [a], Miguel Bambo [a], Jerónimo Sozinho Langa [a], Ezequias Sitoe [b], Assucênio Chissaque [c], Elda Anapakala [a], Júlia Sambo [a], Esperança Lourenço Guimarães [a], Diocreciano Matias Bero [a], Eva Dora João [a,d], Idalécia Cossa-Moiane [a], Jason M. Mwenda [e], Goitom G. Weldegebriel [f], Umesh D. Parashar [g], Jacqueline E. Tate [g]

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Vaccine

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Impact of rotavirus vaccination on diarrheal hospitalizations in children younger than 5 years of age in a rural southern Mozambique

Filomena Manjate [a,b], Llorenç Quintó [a,c], Percina Chirinda [a], Sozinho Acácio [a,d], Marcelino Garrine [a,b], Delfino Vubil [a], Tacilta Nhampossa [a,d], Eva D. João [a], Arsénio Nhacolo [a], Anelsio Cossa [a], Sérgio Massora [a], Gizela Bambo [a], Quique Bassat [a,e,f,g], Karen Kotloff [h], Myron Levine [h], Pedro L. Alonso [a,e,i], Jacqueline E. Tate [j], Umesh Parashar [j], Jason M. Mwenda [k], Inácio Mandomando [a,d,*]

- Pre-vaccine: 35% of MSD in infants attributable to RVA;
- Vaccine introduction: September 2015.

RVA positivity in MSD

- Pre-vaccine: 40.2%
- Post-vaccine: 13.5%

Acute gastroenteritis prevalence

- Pre-vaccine: 19%
- Post-vaccine: 10%

- Data on contribution of other enteric viruses in Mozambique is scarce specially after RVA vaccine introduction.

OBJECTIVES

Determine the frequency of enteric viral pathogens (Rotavirus, Norovirus, Adenovirus 40/41, Astrovirus and Sapovirus) detected in children under 5 years old, with and without diarrhoea before and after rotavirus vaccine introduction in rural Mozambique.

METHODOLOGY: STUDY DESIGN (I)

Pre-vaccine: The Global Enteric Multicenter study (GEMS)

- 2007- 2012 in Africa (**Manhiça-Mozambique**, Kenya, The Gambia and Mali) and Asia (Bangladesh, India and Pakistan);
- Aim: identify the aetiology and burden of paediatric diarrhoea;
- Children aged 0-59 months old with MSD, LSD and 1-3 community controls matched by age, sex and neighborhood with the index case.
- MSD and controls enrollment: December 2007- October 2011; inclusion of LSD cases and their controls in November 2011.

Kotloff *et al*, 2013; Nhampossa *et al*, 2015

METHODOLOGY: STUDY DESIGN (II)

Post-vaccine: Diarrhoeal diseases surveillance platform

- 2015- 2019 in Manhiça, Mozambique;

- Aim: Evaluate the impact of Rotavirus vaccine;

- Children aged 0-59 months old with **MSD**, **LSD** and 1-3 community **Controls** matched by age, sex and neighborhood with the index case;

- MSD data enrollment: September 2015- March 2017; inclusion of LSD cases and controls (MSD and LSD).

Manjate *et al* (2022)

METHODOLOGY: STUDY DESIGN (III)

Sub-analysis inclusion criteria:

- Stool samples from MSD, LSD and Controls with laboratory results complete to all viruses of interest;

- Pre-vaccine: January 2008-December 2012;

- Post-vaccine: January 2016- December 2019.

METHODOLOGY: LABORATORY TESTING

Commercial ELISA kits

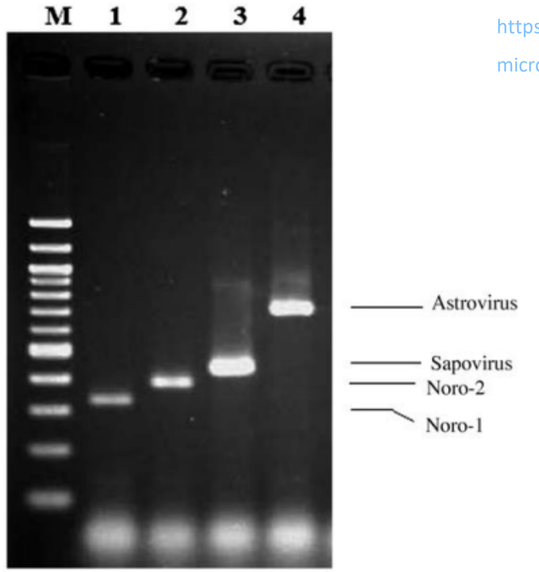
- Rotavirus and Adenovirus 40/41

https://www.fishersci.co.uk/shop/products/prospect-rotavirus-microplate-assay/11993132

Conventional multiplex RT-PCR

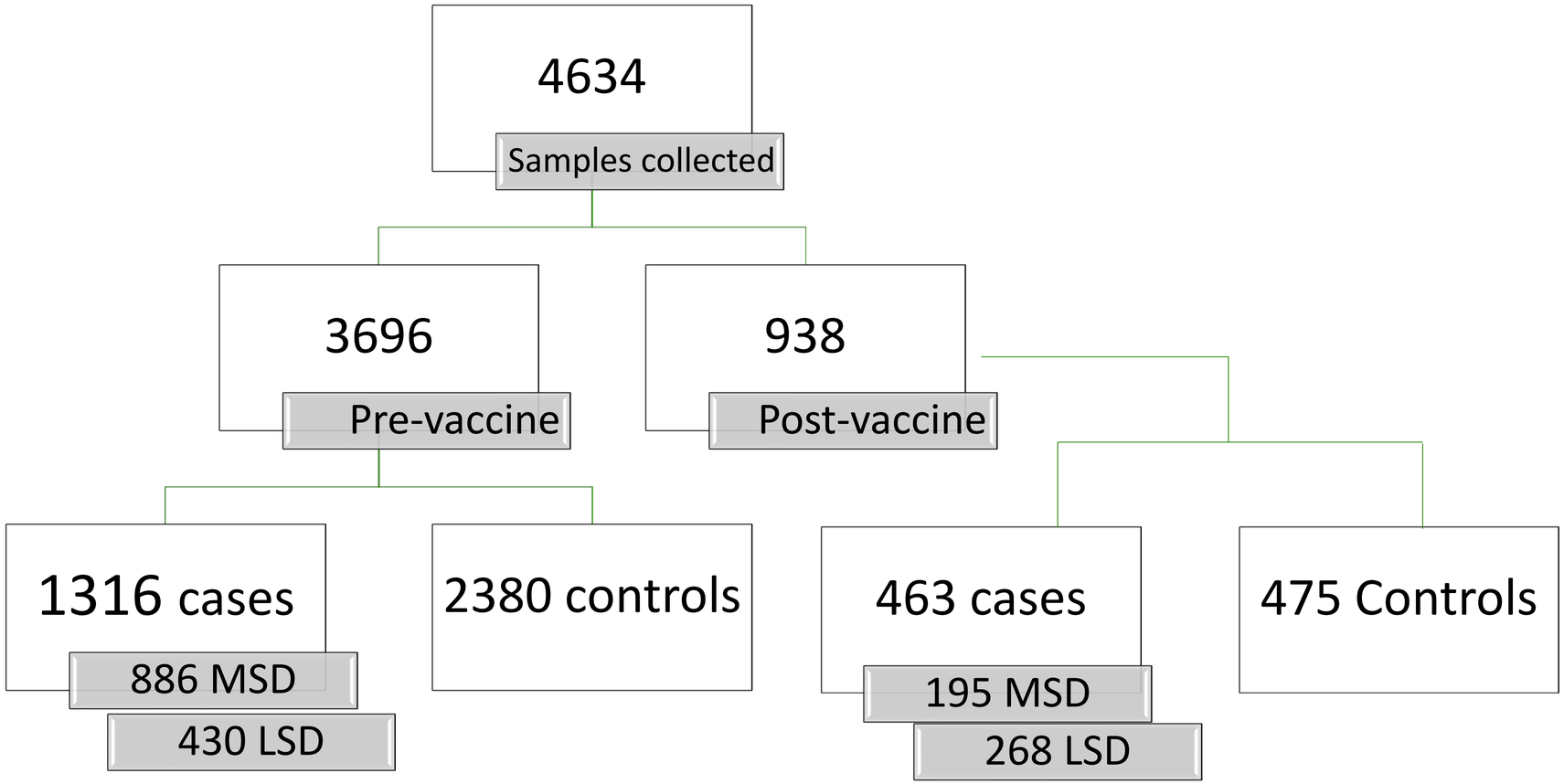
- Norovirus GI and GII, astrovirus and sapovirus.

Virus	Primer	Amplicon bp
Norovirus GI	G1SKR	330
	G1SKF	
Noroviru GII	G2SKR	387
	COG2F	
Sapovirus	SLV5749	434
	SLV5317	
Astrovirus	82b	719
	PreCAP1	



Panchalingam *et al* (2012)

RESULTS: TRIAL PROFILE



DEMOGRAPHIC CHARACTERISTICS OF DIARRHOEAL CASES AND COMMUNITY CONTROLS ENROLLED IN MANHIÇA DISTRICT: 2008 TO 2019

	Cases N=1,779				Controls N=2855	
	MSD N=1081		LSD N=698			
Characteristic	**Pre-vaccine**	**Post-vaccine**	**Pre-vaccine**	**Post-vaccine**	**Pre-vaccine**	**Post-vaccine**
	n (%) [N=886]	**n (%) [N=195]**	**n (%) [N=430]**	**n (%) [N=268]**	**n (%) [N=2380]**	**n (%) [N=475]**
Age strata						
0-11 months	480 (54.2)	101 (51.8)	155 (30.0)	132 (49.3)	1184 (49.7)	195 (41.0)
12-23 months	266 (30.0)	67 (34.4)	175 (40.7)	89 (33.2)	797 (33.5)	208 (43.8)
24-59 months	140 (15.8)	27 (13.8)	100 (23.3)	47 (17.5)	399 (16.8)	72 (15.2)
Sex						
Male	527 (59.5)	115 (59.0)	236 (54.9)	147 (54.9)	1427 (60.0)	256 (53.9)
Female	359 (40.5)	80 (41.0)	194 (45.1)	121 (45.1)	953 (40.0)	219 (46.1)
Rotavirus vaccination status		N=186		N=258		N=459
Vaccinated (fully/partially)	NA	137 (73.7)	NA	222 (86.0)	NA	365 (79.5)
Unvaccinated	NA	49 (26.3)	NA	36 (14.0)	NA	94 (20.5)

ENTERIC VIRUS DETECTION AMONG DIARRHOEA CASES AND CONTROLS IN MANHIÇA DISTRICT, MOZAMBIQUE, 2008-2019.

Virus	Total N=4643	Cases n (%) [N=1779]	Controls n (%) [N=2855]	p value
Rotavirus	886 (19.1)	500 (28.1)	386 (13.5)	**<0.001**
Norovirus GI	65 (1.4)	17 (0.9)	48 (1.7)	**0.041**
Norovirus GII	137 (3.0)	71 (4.0)	66 (2.3)	**0.001**
Adenovirus 40/41	84 (1.8)	59 (3.3)	25 (0.9)	**<0.001**
Astrovirus	88 (1.9)	46 (2.6)	42 (1.5)	**0.007**
Sapovirus	129 (2.8)	57 (3.2)	72 (2.5)	0.170

ENTERIC VIRUS DETECTION AMONG CHILDREN WITH MSD, LSD AND CONTROLS IN THE PRE (2008-2012) AND POST (2016-2019) ROTAVIRUS VACCINE INTRODUCTION PERIODS IN MANHIÇA DISTRICT, MOZAMBIQUE.

	Cases						Controls		
	MSD			LSD					
Virus	Pre-vaccine n (%) [N=886]	Post-vaccine n (%) [N=195]	p value	Pre-vaccine n (%) [N=430]	Post-vaccine n (%) [N=268]	p value	Pre-vaccine n (%) [N=2380]	Post-vaccine n (%) [N=475]	p value
Rotavirus	**291 (32.8)**	**48 (24.6)**	**0.025**	97 (22.6)	64 (23.9)	0.687	**349 (14.7)**	**37 (7.8)**	**<0.001**
Norovirus GI	11 (1.2)	1 (0.5)	0.379	4 (0.9)	1 (0.4)	0.396	40 (1.7)	8 (1.7)	0.996
Norovirus GII	**24 (2.7)**	**13 (6.7)**	**0.006**	**9 (2.1)**	**25 (9.3)**	**<0.001**	51 (2.1)	15 (3.2)	0.179
Adenovirus 40/41	**16 (1.8)**	**14 (7.2)**	**<0.001**	20 (4.7)	9 (3.4)	0.405	22 (0.9)	3 (0.6)	0.532
Astrovirus	12 (1.4)	3 (1.5)	0.842	**11 (2.6)**	**20 (7.5)**	**0.002**	33 (1.4)	9 (1.9)	0.401
Sapovirus	**12 (1.4)**	**10 (5.1)**	**0.001**	**16 (3.7)**	**19 (7.1)**	**0.047**	**51 (2.1)**	**21 (4.4)**	**0.004**

Decrease

- Rotavirus in MSD cases and controls

Increase

- Norovirus GII in MSD and LSD
- Adenovirus 40/41 in MSD
- Astrovirus in LSD
- Sapovirus in cases and controls

ENTERIC VIRUS DETECTION AMONG MSD AND LSD CASES AND CONTROLS IN THE (2008-2012) AND POST (2016-2019) VACCINE INTRODUCTION PERIODS, ACCORDING TO THE AGE STRATA IN MANHIÇA DISTRICT, MOZAMBIQUE.

	Cases						Controls		
	MSD			LSD					
	Pre-vaccine n (%)	Post-vaccine n (%)	p value	Pre-vaccine n (%)	Post-vaccine n (%)	p value	Pre-vaccine n (%)	Post-vaccine n (%)	p value
0-11 months	**N=480**	**N=101**		**N=155**	**N=132**		**N=1184**	**N=195**	
Rotavirus	**214 (44.6)**	**26 (25.7)**	**<0.001**	46 (29.7)	33 (25.0)	0.377	**180 (15.2)**	**15 (7.7)**	**0.005**
Norovirus GI	5 (1.0)	1 (1.0)	0.963	0 (0)	1 (0.8)	0.278	10 (0.8)	3 (1.5)	0.353
Norovirus GII	**16 (3.3)**	**9 (8.9)**	**0.012**	**3 (1.9)**	**16 (12.1)**	**0.001**	30 (2.5)	7 (3.6)	0.398
Adenovirus 40/41	11 (2.3)	3 (2.9)	0.686	8 (5.2)	3 (2.3)	0.204	13 (1.1)	0 (0)	0.142
Astrovirus	6 (1.3)	2 (2.0)	0.567	**1 (0.7)**	**11 (8.3)**	**0.001**	14 (1.2)	3 (1.5)	0.676
Sapovirus	9 (1.9)	5 (5.0)	0.067	6 (3.9)	7 (5.3)	0.561	33 (2.8)	5 (2.6)	0.860
12-23 months	N=266	N=67		N=175	N=89		N=797	N=208	
Rotavirus	61 (22.9)	15 (22.4)	0.924	35 (20.0)	18 (20.0)	0.966	**123 (15.4)**	**15 (7.2)**	**0.002**
Norovirus GI	4 (1.5)	0 (0)	0.313	3 (1.7)	0 (0)	0.214	20 (2.5)	5 (2.4)	0.931
Norovirus GII	6 (2.3)	4 (6.0)	0.111	4 (2.3)	3 (3.4)	0.604	14 (1.8)	8 (3.9)	0.067
Adenovirus 40/41	**5 (1.9)**	**11 (16.4)**	**<0.001**	11 (6.3)	4 (4.5)	0.552	8 (1.0)	3 (1.4)	0.588
Astrovirus	6 (2.3)	1 (1.5)	0.697	10 (5.7)	5 (5.6)	0.975	15 (1.9)	6 (2.9)	0.368
Sapovirus	3 (1.1)	2 (3.0)	0.264	9 (5.1)	8 (9.0)	0.229	**14 (1.8)**	**14 (6.7)**	**<0.001**
24-59 months	N=140	N=27		N=100	N=47		N=399	N=72	
Rotavirus	**16 (11.4)**	**7 (25.9)**	**0.045**	16 (16.0)	13 (27.7)	0.098	46 (11.5)	7 (9.6)	0.655
Norovirus GI	2 (1.4)	0 (0)	0.532	1 (1.0)	0 (0)	0.492	10 (2.5)	0 (0)	0.175
Norovirus GII	2 (1.4)	0 (0)	0.532	**2 (2.0)**	**6 (12.8)**	**0.007**	7 (1.8)	0 (0)	0.257
Adenovirus 40/41	0 (0)	0 (0)	-	1 (1.0)	2 (4.3)	0.193	1 (0.3)	0 (0)	0.671
Astrovirus	0 (0)	0 (0)	-	**0 (0)**	**4 (8.5)**	**0.003**	4 (1.0)	0 (0)	0.394
Sapovirus	**0 (0)**	**3 (11.1)**	**<0.001**	**1 (1.0)**	**4 (8.5)**	**0.019**	4 (1.0)	2 (2.7)	0.216

MSD

Decrease

- Rotavirus in 0-11 months

Increase

- Norovirus in 0-11 months
- Adenovirus 40/41 in 12-23 months
- Rotavirus in 24-59 months
- Sapovirus in 24-59 months

LSD

Increase:

- Norovirus GII and Astrovirus in 0-11 and 24-59 months;
- Sapovirus in 24-59 months;

Controls

Decrease:

- Rotavirus 0-11 and 12-23 months

Increase:

- Sapovirus in 12-23 months;

CONCLUSION

- Higher frequencies of enteric viruses in cases than in controls, except Norovirus GI;
- Significant decrease in Rotavirus frequencies in MSD cases and controls <2 years after vaccine introduction.
- Significant increase of Norovirus GII (MSD and LSD), Adenovirus 40/41 (MSD), Astrovirus (LSD) and Sapovirus (MSD, LSD and controls) in different age strata, after vaccine introduction;

NEXT STEPS

Molecular characterization of Norovirus, Adenovirus 40/41, Astrovirus and Sapovirus circulating in Manhiça district, Mozambique for better understanding of their epidemiology;

Thank you

Special thanks

- Participants of the surveillance and all collaborators
- Diarrheal diseases surveillance team

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