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Impact of pentavalent rotavirus vaccine against severe rotavirus diarrhoea in The Gambia

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Abstract

Introduction: Rotavirus vaccines protect against the leading cause of severe childhood diarrhoea, and have been introduced in many low-income African countries. The Gambia introduced Rotateq® (RV5) into their national immunization program in 2013. We reviewedata from an active rotavirus sentinel surveillancesite for early evidence of vaccine impact.

Methods: We compared rotavirus prevalence in diarrhoeal stool in children< 5 years of age admittedat the Edward Francis Small Teaching Hospital sentinel surveillance site before (2013) andafterRV5 introduction (2015–2016) in the Gambia. The rotavirus-percent positive was separately compared for all diarrhoealhospitalizations and for hospitalizations with severe symptoms. Rotavirus prevalence was compared annually for the pre-vaccine year of 2013 with post-vaccine years of 2015 and 2016 using chi-square or Fisher's exact tests and the p-value to establish significant relationship was set at $p < 0.05$. All analyses were completed in SAS 9.3 (SAS Analytics, North Carolina).

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Author contributions

Maki Taal, Bakary Sanneh, SheriffoJagne, Jason M. Mwemba and JacquelineTate conceptualized and designed the rotavirus surveillance program. Mariama Sonko, ModouLaminJarjue, SheriffoJagne, Bakary Sanneh and Dawuda Sowe participated in the field work and laboratory testing of samples. Data entry, cleaning and analysis was done by Alhagie Papa Sey and Minesh Shah. The manuscript was written by Bakary Sanneh, Minesh Shah and JacquelineTate, and edited by UmeshParashar, Jason M. Mwenda, Adam Cohen, SheriffoJagne. Maki Taal and Modulamin Jarjue.

Consent

The caregiver for all the enrolled children were consented to participate in the rotavirus surveillance.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO).

Declaration of conflict of interest

Authors have no conflict of interest.

Results: Rotavirus prevalence among all diarrhoeahospitalizations decreased from 22% in 2013 to 11% in 2015 (p = 0.04), while remaining unchanged in 2016 (18%, p = 0.56). For hospitalizations that were clinically severe and/or treated with intravenous fluids (mean of 46 per year), the rotavirus prevalence decreased from 33% in 2013 to 8% in 2015 (p = 0.04), and to 15% in 2016 (p = 0.08). The children with age <1 year accounted for 45% the population infected with rotavirus in both pre and post rotavirus vaccination periods.

Conclusions: Rotavirus vaccine introduction in the Gambia could be among factors resulting in decreased diarrhea hospitalizations among children at the Edward Francis Small Teaching Hospital, particularly those with severe disease. These results support the continuation of rotavirus vaccine and additional monitoring of rotavirus hospitalization trends in the country.

Keywords

Rotavirus; Severe diarrhea; Hospitalization; Vaccine impact

1. Introduction

Rotavirus is the leading cause of severe childhood diarrhoea worldwide [1], with disproportionate mortality in sub-Saharan African countries [2]. Two, live attenuated oral rotavirus vaccines are licensed globally and recommended by the World Health Organization (WHO) for use in all countries: RV1, the human monovalent strain vaccine (Rotarix®; GlaxoSmithKline Biologics, Rixenstart, Belgium) and RV5, a pentavalent bovine-human reassortment vaccine (RotaTeq®; Merck Vaccines, Whitehouse Station, New Jersey) [3]. While clinical trials of both vaccines have shown reduced efficacy in African countries with higher childhood mortality rates [4,5], there is potential for greater reduction in numbers of rotavirus attributable hospitalizations and deaths in countries with higher disease burden [3,6].

The Gambia is a low-income country in West Africa, with an estimated population of 2 million people and a birth cohort of almost 85,000 [7]. Hospital-based surveillance studies for rotavirus in the Gambia prior to vaccine introduction found that rotavirus is the most common cause of childhood hospitalization and mortality associated with gastroenteritis, with prevalence ranging from 20% in a rural setting in southern Gambia to 24% in an urban setting in northern Gambia [8,9]. The highest prevalence of rotavirus infection was during dry seasons, and up to 18 genotypes of rotavirus with similar distribution in urban and rural settings were found. Children <2 years are at highest risk for rotavirus infection [8], and other risk factors include drinking untreated water and exposure to rodents and pets [9].

By the end of 2016, 39 countries in Africa had introduced rotavirus vaccination, with 34 countries using RV1 and 5 countries using RV5 in their current national immunization programs [10]. Gambia introduced RV5 into routine childhood immunization in August 2013, with three doses given to infants at 2, 3, and 4 months of age. Post-rotavirus vaccine introduction studies of RV1 have shown reduction of rotavirus hospitalizations in Botswana [11], Ghana [12], Malawi [13], South Africa [14], Tanzania [15], Togo [16], Zambia [17]. Rwanda is among the few countries with published data following the introduction of RV5, reporting a substantial reduction in the number of diarrhoea hospitalizations [18]. As the

Gambia has a higher child mortality rate due to rotavirus (45 per 100,000 children < 5 years of age) compared to Rwanda (38 per 100,000 children < 5 years of age) [19], the impact of RV5 vaccination on childhood diarrhoea hospitalizations would be relevant for other similar countries in Africa.

This impact evaluation study seeks to monitor the impact of rotavirus vaccine in The Gambia by assessing trends in the number of hospitalizations for diarrhoea and rotavirusprevalence before and after the introduction of RV5. As rotavirus causes more severe illness than non-rotavirus diarrhoea [20], we further looked at the impact on hospitalizations disease severity.

2. Methods

2.1. Surveillance setting and enrollment of patients

Royal Victoria Teaching Hospital (renamed Edward Francis Small Teaching Hospital in 2015), located in the capital city of Banjul, is the sentinel site for national rotavirus surveillance in the Gambia. Rotavirus surveillance followed the WHO-recommended protocol [21], and data were regularly reported to the WHO/ AFRO-coordinated Regional Rotavirus Surveillance Network [22]. Since January 2013, all children <5 years old admitted with diarrhoea (≥3 loose stools in a 24-h period) with or without vomiting and duration ≤7 days were eligible for enrollment in the surveillance program. The care givers of eligible patients provided consent for participation. A structured questionnaire was administered to collect on illness symptoms, and vaccination history.

2.2. Sample collection and laboratory testing

Approximately 10 g of stool were collected in screw cap stool collection containers within 48 h of hospitalization and stored temporarily at 2–4 °C for not more 48 h at the sentinel surveillance site. Stool samples were transported from the surveillance site to the reference laboratory (National Public Health Laboratory (NPHL)) and stored at −20 °C. Diagnosis of rotavirus infection was determined by ELISA using the rotavirus Prospect test kit. Positive samples and 10% of the negative samples were further characterized at the rotavirus Regional Reference Laboratory in Noguchi Medical Research Centre (Ghana) for confirmatory testing and rotavirus genotyping.

2.3. Analysis of diarrhoea and rotavirus hospitalizations

Monthly diarrhoea hospitalizations were recorded, and illness severity based on clinical symptoms and treatment required was assessed using a modified Vesikari scoring system [20]. Any hospitalization that resulted in the administration of intravenous fluids (IVF) was also considered severe. As changes in local practice and referral patterns during the study period could affect the overall number of diarrhoea hospitalizations, the rotavirus prevalence (percent positive) was the primary outcome analyzed. Rotavirus prevalence was compared annually for the pre-vaccine year of 2013 with post-vaccine years of 2015 and 2016 using chi-square or Fisher’s exact tests. Rotavirus vaccine was introduced in August 2013 which after the well established seasonal rotavirus period (January to May) and 97%(33/34) rotavirus confirmed cases that year were test before the vaccination. Given that there was no

catch-up campaign for rotavirus vaccine, very few children <5 years of age were eligible to receive the vaccine.2014 was considered a transitional year and thus excluded from analysis. All analyses were completed in SAS 9.3 (SAS Analytics, North Carolina).

3. Results

The Gambia introduced rotavirus vaccination (rotateq) in August 2013 in the EPI vaccination schedule through a massive vaccination campaign and had a vaccine of 90%. Moverall in the subsequent years under-review for this study (2014, 2015 and 2016) rotavirus vaccine (Rota3) coverage were 92%,97% and 95%respectively which were high

From January 2013 – November 2016, a total of 405 children were enrolled in surveillance. A distinct rotavirus season was observed from January – April of each calendar year, with rare rotavirus hospitalizations also observed during October 2013 and August 2016 (Fig. 1). Following RV5 introduction in August, the rotavirus season was slightly delayed in 2015 and 2016, with a lower percent positive during peak months compared to 2013 and 2014 (Fig. 2).

Among all diarrhoea hospitalizations, the rotavirus prevalence was 22% in 2013, decreased to 11% in 2015 ($p = 0.04$), and did not significantly change in2016 (18%; $p = 0.56$) (Table 2 and Fig. 3A). Compared to the annual fluctuations in all diarrhoea hospitalizations, the number of severe hospitalizations and/or those treated with IVF remained more stable (Table 2 and Fig. 3B).

The rotavirus prevalence for severe hospitalizations was 33% in 2013, decreased to 8% in 2015 ($p = 0.04$), and to 15% in 2016 ($p = 0.08$), although the 2016 difference was not statistically significant. In contrast, the rotavirus prevalence for non-severe hospitalizations not treated with IVF, or for those with unknown severity or treatment, did not significantly change during post-vaccine years.

During the pre and post rotavirus vaccination era under review, 80% cases about 405 associated gastroenteritis were confirmed for rotavirus infection. The children with age <1 year accounted for 45% the population infected withrotavirus. Besides children between 12 and 23 months old were also infected with the rotavirus with a percentage of 34. The same trend of rotavirus infection burden in the pre-post vaccination heavily hit the children and under 12 months of age (Table 3).

4. Discussion

Following the introduction of rotavirus vaccine in Gambia in 2013, rotavirus hospitalizations in children <5 years of age to a sentinel surveillance hospital decreased in 2015 and 2016. The annual number of clinically-severe diarrhoea hospitalizations during this time remained relatively stable, suggesting that the decrease in overall diarrhoea hospitalizations seen over time is reflective of more selective criteria for hospital hospitalization. In this category of severe diarrhoea, the rotavirusprevalence declined substantially in 2015, while a more moderate decrease was seen in 2016. Similarly, GEM study found that in the prevaccination period rotavirus account for the most prevalence aetiological agent associated with of the

gastroenteritis cases and the same virus was found to be the second most common causes of gastroenteritis in the post vaccination rural community of upper river region of the country [9,24]. These findings are consistent with other studies showing the rotavirus vaccination is more effective against severe disease than non-severe disease [23]. Although the sharp decline in the prevalence of the rotavirus between 2013 and 2015 could be associated with the numbers cases enrolled for testing of rotavirus in 2015 as compared to a similar study in rural country site.

In the pre-vaccination era of rotavirus in the Gambia seasonality of rotavirus infections have been described from January to April rural-urban country (Western Region) [24,25]. Very few cases of rotavirus infections were confirmed in May, however in GEM study it was found that the rotavirus seasonality continued to June in Rural communities (Upper river Region). This study found Similarly found similar finding with a shift of peak period of seasonality in April in the post vaccination periods of 2015 and 2016. The study was also found confirmation of rotavirus infection in October and August which were also rare as compare to the all the years underreview. The study found that children less than one year old were the most infected by rotavirus in both the pre and post rotavirus vaccinations (Table 3) despite the high rotavirus vaccine courage (Table 1). The rota-teq was found to be highly efficacious in high-income countries but reduced of impact of this vaccine have been report in developing countries [12,26]. The post GEM study in rural Gambian communities found similar findings that rotavirus infections though reduce to lesser degree is still account as the second causes of gastrienteristic in the post rotavirus vaccination era [24] which similar to other African countries [27].

5. Limitations

Rotavirus surveillance was initiated in January 2013 and rotavirus vaccine was introduced in August 2013. Thus, we did not have a full year of pre-vaccine data. However, given that there was no catch-up campaign for rotavirus vaccination in The Gambia, very few children < 5 years of age would have been eligible to receive rotavirus vaccine in 2013. Furthermore, rotavirus disease is very seasonal in The Gambia with the majority of disease occurring from January to April. Thus, rotavirus vaccine introduction in August 2013 would have had little effect on the rotavirus disease burden in 2013 and the observed impact in subsequent years will have been conservatively underestimated. The lack of statistical significance for 2016 is likely due to a low number of hospitalizations reducing statistical power. Further, the relative increase in rotavirus-positive hospitalizations from 2015 to 2016 may also be due to small sample size, and requires further monitoring in the Gambia and in the region. Continued rotavirus surveillance, and evidence of vaccine impact, would be more robust with strengthening the sentinel site to enrol more study participants. Lack of complete data set for analysis to link the relationship of had been vaccinated and contracting rotavirus infections. We could not also analyse to link the age brackets to severity in the dehydration to admission for better understanding of which age group was still at high risk.

6. Conclusions

The finding of an early impact from RV5 introduction in Gambia is similar to the findings in Rwanda, which similarly shows reductions in rotavirus hospitalizations in the first two post-vaccine years [18], and adds to the larger body of evidence showing the impact of rotavirus vaccines in countries across income and mortality strata [23]. The study also found that the burden of rotavirus infection still take tool in the children less than one year in the post vaccination era. These results also support continued use of rotavirus vaccines in the Gambian immunization schedule, and should encourage other, similar countries to consider rotavirus vaccination if not yet introduced.

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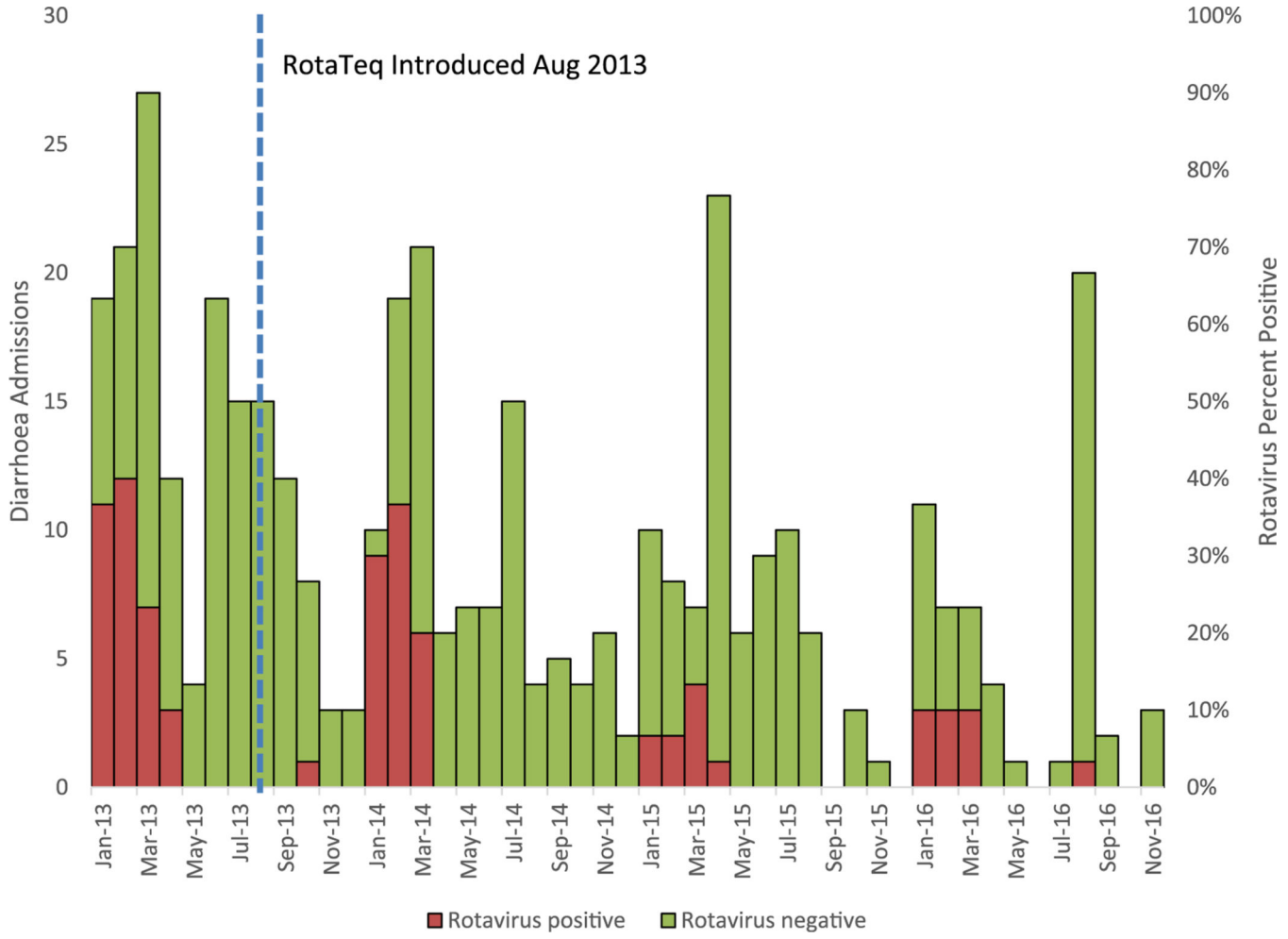

Fig. 1.

Monthly diarrhoea hospitalizations in children <5 years of age to Edward Francis Small Teaching Hospital, Banjul, Gambia; January 2013 – November 2016.

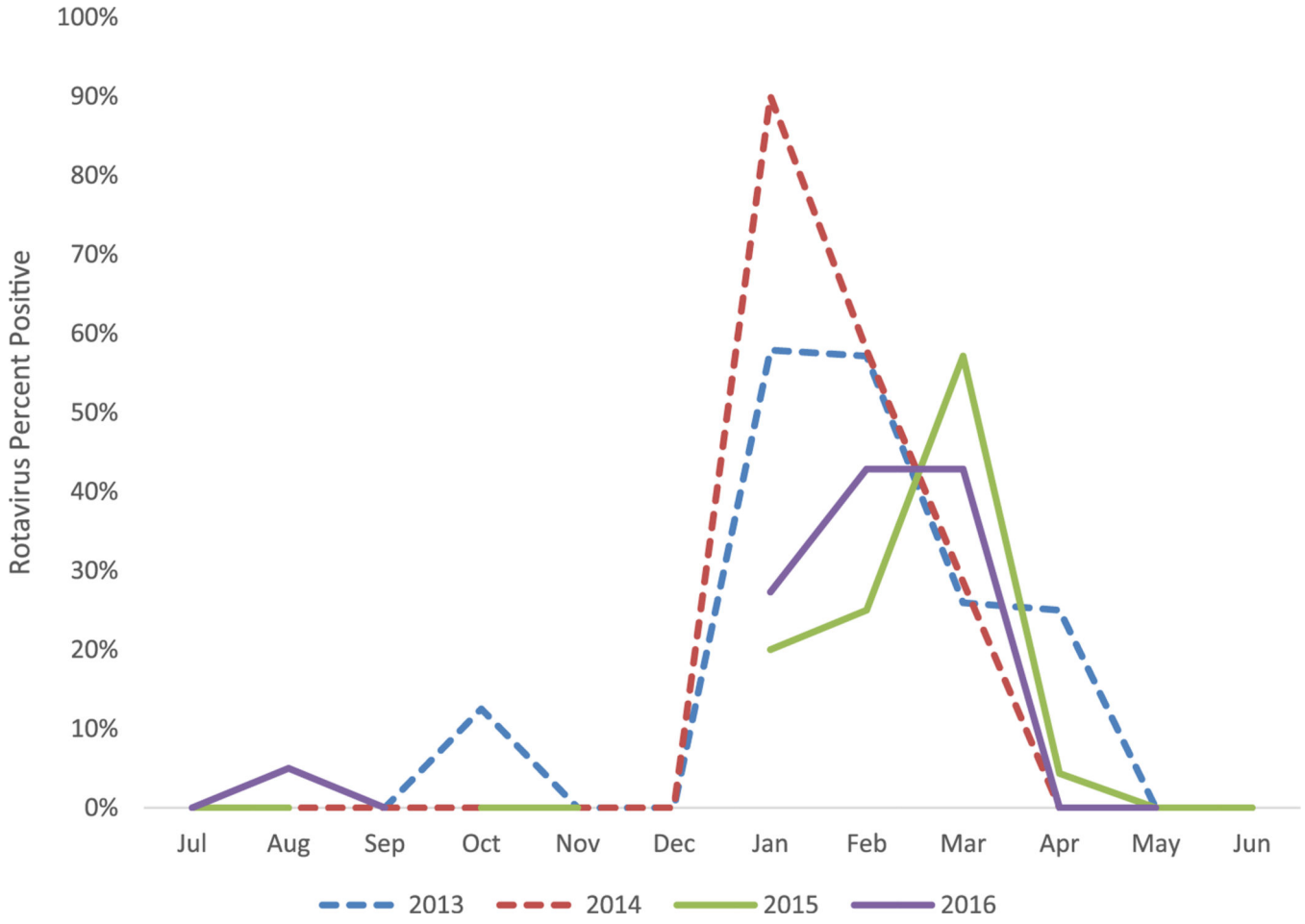

Fig. 2.

Monthly rotavirus prevalence in children <5 years of age hospitalized for diarrhoea to Edward Francis Small Teaching Hospital, Banjul, Gambia; 2013–2016.

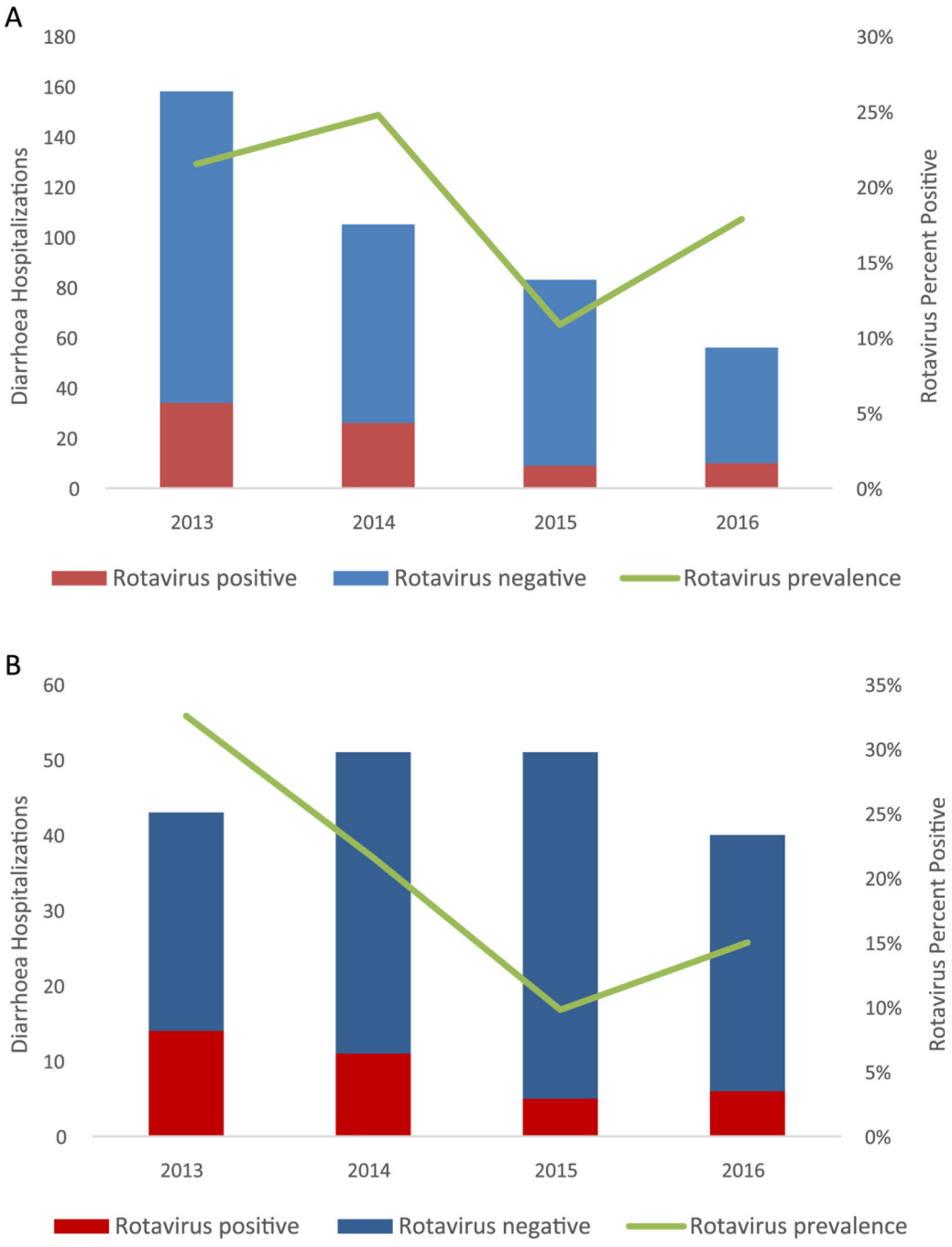

Fig. 3.

Annual diarrhoea hospitalizations (A) and severe diarrhoea hospitalizations (B) to Edward Francis Small Teaching Hospital, Banjul, Gambia; 2013–2016.

Table 1

Rotateq vaccination courage from August 2013 to December 2016 in The Gambia.

Year of vaccination	Rota3 vaccine coverage (%)
2013	90
2014	92
2015	97
2016	95

Table 2

Yearly diarrhoea admissions in children <5 years of age for rotavirus and non-rotavirus diarrhoea, stratified by clinical severity, Edward Francis Small Teaching Hospital, Banjul, Gambia; 2013–2016.

	Pre-vaccine			**Post-vaccine**									
	2013			**2014**			**2015**				**2016**			
All cases	**Rota pos (n)**	**All (n)**	**Rota pos (%)**	**Rota pos (n)**	**All (n)**	**Rota pos (%)**	**Rota pos (n)**	**All (n)**	**Rota pos (%)**	**p-value**	**Rota pos (n)**	**All (n)**	**Rota pos (%)**	**p-value**
	34	**158**	**22%**	**26**	**105**	**25%**	**9**	**83**	**11%**	**0.04**	**10**	**56**	**18%**	**0.56**
Clinical severity and treatment														
-Severe and/or IVF received	14	43	33%	11	48	23%	4	50	8%	0.04	6	39	15%	0.08
-Moderate, no IVF received	9	30	30%	6	23	26%	1	5	20%	1.0	1	7	14%	0.65
-Unknown, no/unknown IVF received	11	85	13%	9	34	26%	4	28	14%	1.0	3	10	30%	0.16

Table 3

Distribution of rotavirus positivity among children 5 year among admissions at Edward Francis Small Teaching Hospital, Banjul, Gambial,; 2013–2016.

Year tested	12 to 23 months		24 to 59 months		<12 months		Total rotavirus positive	
	No	%	No	%	No	%	No	%
2013	11	32	10	29	13	38	34	100
2014	8	31	4	15	14	45	26	100
2015	3	33	2	22	4	45	9	100
2016	5	45	0	9	5	46	10	100
Total rotavirus positive	27		16		36		79	