

Rotavirus diarrhoea hospitalizations among children under 5 years of age in Nigeria, 2011–2016



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ABSTRACT

Background: The high burden of rotavirus acute gastroenteritis (AGE) is well documented among children under 5 years of age, with the majority of mortality occurring in developing countries. Nigeria ranked second worldwide in the number of rotavirus deaths in 2013. As Nigeria plans to introduce rotavirus vaccine soon, a pre-vaccine documentation of rotavirus disease burden is necessary to determine vaccine impact. **Methods:** Routine rotavirus surveillance was conducted during 2011–2016 in 3 sentinel sites in Nigeria using the standard WHO protocol. Children under 5 years of age hospitalized for acute gastroenteritis were enrolled and demographic, clinical and outcome data were collected. A stool sample was subsequently obtained and tested for human rotavirus antigen using the Enzyme-linked immunosorbent assay (ELISA).

Results: 2694 children with acute gastroenteritis were enrolled during January 2011 to December 2016; of these, 1242 (46%) tested positive for rotavirus. Among the rotavirus positive cases, 66% and 94% were younger than 12 months and 24 months respectively. Marked peaks in rotavirus positivity were seen in January of each year. Vomiting, and use of oral and intravenous fluids occurred more often in rotavirus positive cases as compared to rotavirus negative cases.

Conclusion: The high prevalence of rotavirus disease highlights the need for urgent introduction of rotavirus vaccine in Nigeria. Additionally, this study provides pre-vaccine introduction disease-burden data that will serve as a baseline for rotavirus vaccine impact-assessment once vaccine has been introduced in the national immunization program.

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1. Introduction

The high global burden of rotavirus AGE hospitalization and deaths are well documented. Rotavirus AGE was responsible for 30–50% of acute gastroenteritis (AGE) hospitalizations in both developing and developed countries in the pre-vaccine era [1–4].

Rotavirus mortality disproportionately affects developing countries, with about 82–95% [4,5] of mortalities among children under 5 years of age occurring in these areas. The most recent WHO annual global estimates place the number of global under 5 rotavirus related deaths at 215,000 (197,000–233,000) in 2013 [6,7]. Nigeria alone contributes 14% (30,800) of global RV deaths. It also one of the top ten countries with the highest under 5 rotavirus associated mortality rate in the world (>100/100,000) [7,8].

Following the availability of 2 rotavirus vaccines- the pentavalent human-bovine reassortant rotavirus vaccine, Rotateq (RV5 by Merck) in 2006 and the monovalent human rotavirus vaccine, Rotarix (RV1 by GSK) in 2008, over 80 countries have introduced rotavirus vaccines into their national routine immunization schedules. As of December 2016 [9] this includes 31 (66%) out of 47 countries in the WHO African Region. These efforts have resulted in significant decline in rotavirus disease burden in the countries where vaccines have been introduced [10–16].

As Nigeria is on the threshold of introducing rotavirus vaccine [17–19], this paper aims to assess and document baseline rotavirus acute gastroenteritis (AGE) hospitalizations and associated characteristics among children under 5 years of age.

2. Patients and methods

Ethical approval was obtained from the Health Research Ethics Committee of the University of Nigeria Teaching Hospital and informed consent was obtained from care-givers of enrolled children prior to enrolment (NHREC/05/01/2008B-FWA00002458-IRB0002323).

Surveillance was carried out at the Institute of Child Health, University of Nigeria Teaching Hospital, Mother of Christ Specialist Hospital and Tender Care Specialist Hospital, all in Enugu during January 2011 through December 2016. Using the WHO standardized protocol [15] children under 5 years of age who were hospitalized for the primary reason of treatment of acute gastroenteritis (AGE) were eligible for inclusion. AGE was defined as passage of 3 or more watery or looser than normal stools in a 24 h period. Exclusion criteria included (1) bloody diarrhoea; (2) AGE symptoms lasting greater than 14 days before presentation to the hospital; (3) AGE acquired during a hospitalization for another disease; and (4) children whose primary diagnosis was not AGE.

Demographic, clinical and treatment data (i.e., age, sex, presence of vomiting, receipt of oral or intravenous fluids (considered as one variable), and outcome) were obtained using the standardized case report form [20,21]. Receipt of oral or intravenous fluid was one of the variables on the case report form.

2.1. Specimen testing

Approximately 5 ml of diarrhoeal stool samples were collected from enrolled patients within 48 h of hospitalization for AGE. Samples were temporarily stored in a refrigerator at 2–8 °C and/or transferred to the lab for storage and subsequent enzyme-linked immunosorbent assay (ELISA) testing.

Rotavirus detection was carried out on 10%–20% suspensions of all the stool samples by the ELISA using the ProSpecT[®] Rotavirus Kits, Oxoid LTD, United Kingdom. A subset of sample aliquots were shipped for quality control (by retesting by ELISA) to the WHO Regional Reference Laboratories (RRLs) at Medical Research Council Diarrhoeal Pathogens Research Unit, University of Limpopo, Pretoria, South Africa and Noguchi Memorial Institute of Medical Research, University of Ghana, Accra. The concordance rate was 100%.

2.2. Analysis

The revised WHO Epi-info (v3.5) based new vaccine surveillance module, Microsoft Excel and GraphPad Prism version 7 were used for data analysis. Frequencies, proportions and means are reported for rotavirus positive and rotavirus negative cases. Contingency tables were used to determine association between variables. Chi square and Fisher's exact tests were used to compare categorical variables while the unpaired Mann-Whitney test was used to compare continuous variables. The level of significance was set at <0.05.

3. Results

A total of 2694 children under 5 years of age with AGE were enrolled during 2011–2016 and had stool samples collected and tested. Of these, 1242 (46%) were rotavirus positive by ELISA. Rotavirus percentage positivity ranged from 41 to 48% across the sites (Table 1). The number of enrolled cases of AGE increased until 2014; then began to drop from 2015 while the percentage rotavirus positive decreased to the lowest in 2013 and 2014; then rose in 2015 and declined in 2016 (Fig. 1). The rotavirus season (cold dry months when the percentage rotavirus positive is highest) lasted from December to April (Fig. 2), with seasonal peaks in rotavirus hospitalizations during January of each year. The rotavirus positivity was up to 84% during the peak seasons; and more than 90% of positive cases occurred during the months of December to March within the study period (Fig. 3).

Of the children who tested positive for rotavirus, 726 (59%) were male and 516 were female giving a male to female ratio of 1.4:1. The median age of the rotavirus positive cases was 9 months, with 66% and 94% of enrolled rotavirus positive children aged <12 months and <24 months, respectively ($p = 0.00$) (Fig. 4, Table 2).

Ninety per cent of rotavirus positive cases had vomiting as compared to 83% of rotavirus negative cases ($p = 0.00$, Table 2). Rotavirus positive cases were more likely to receive ORS/IVF compared to rotavirus negative children (73% vs 64%, respectively, $p = 0.00$). Mortality among rotavirus positive cases was 0.5% (Table 2).

4. Discussion

We found a high prevalence of rotavirus among children under 5 years of age hospitalized with AGE in our sentinel sites. The prevalence of 46% rotavirus positivity found in this study is in keeping with data from elsewhere in Africa, where the reported average for 8 sub-Saharan African countries (Cameroon, Ethiopia, Tanzania, Zimbabwe, Ghana, Kenya, Uganda, and Zambia) and others ranged from 23 to 40% [21–23] and 48–49% [24,25] in Togo and Ghana. However, it is lower than previous reported prevalence of 56%–61% in Nigeria and Democratic Republic of Congo [26,27]. The yearly variations in rotavirus positivity observed in our study could be attributed to normal fluctuations in annual disease burden or changes in enrolment practices.

There was a marked seasonal peak, with more than 90% of rotavirus detections occurring (cumulatively) during December to March of the 6 years studied. Although in some countries, like Uganda [21], rotavirus transmission does not show any distinct seasonal peaks, probably due to an all-year-round temperate climate, in this study, there is a clear seasonal pattern in the cool dry months of the year from December to April. Outside the season, prevalence dropped markedly, sometimes as low as zero. This pattern is similar to the peak activity reported in Ghana (January–February) and Zimbabwe, where the peak activity occurred in the

Table 1
Enrollment of children under five years of age with acute gastroenteritis by sentinel hospital, Nigeria 2011–2016.

	UNTH ^a	MOCOSH ^b	TCSH ^c	Total
Rotavirus positive	875	167	200	1242
Rotavirus negative	952	211	289	1452
Total	1827	378	489	2694
Rotavirus percent positive	48	44	41	46

^a University of Nigeria Teaching Hospital.

^b Mother of Christ Specialist Hospital.

^c Tender Care Specialist Hospital.

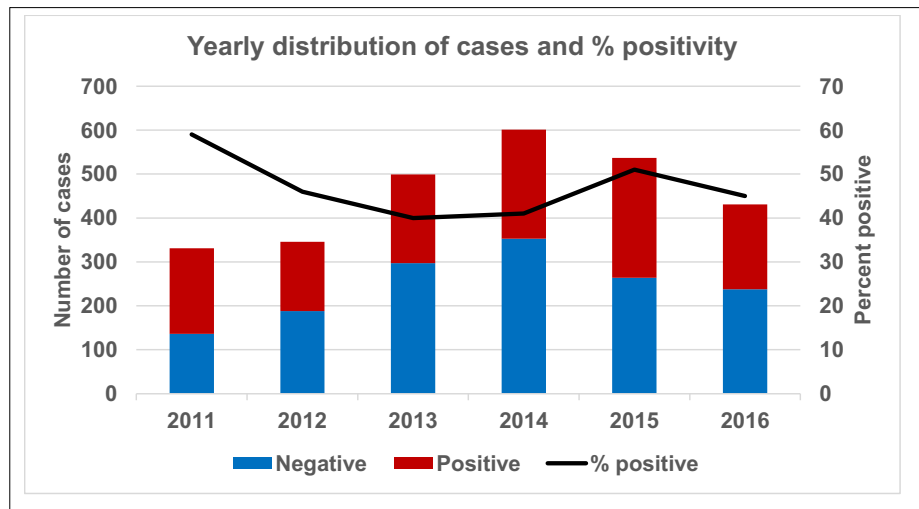


Fig. 1. Yearly distribution of total, rotavirus positive, and percent rotavirus positive acute gastroenteritis cases among children under five years of age enrolled in three sentinel hospitals in Nigeria.

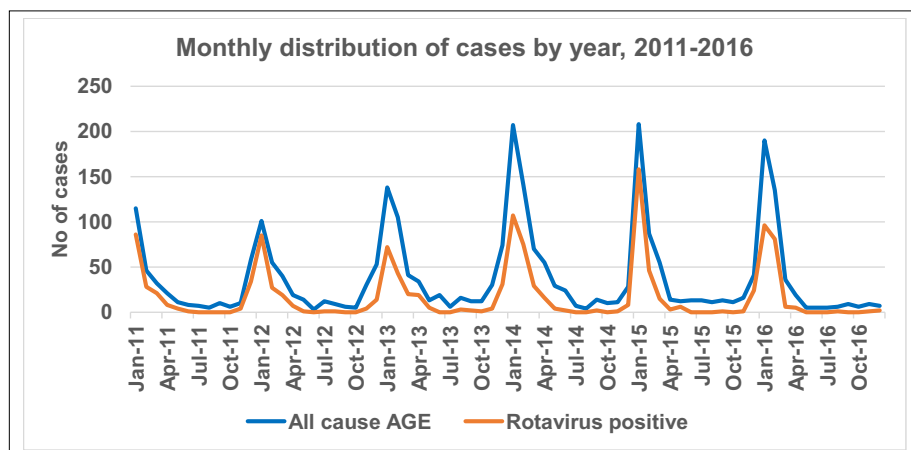


Fig. 2. Monthly distribution of all-cause and rotavirus positive acute gastroenteritis showing seasonal trends among children under five years of age enrolled in three sentinel hospitals in Nigeria, 2011–2016.

winter months (May–August), and in Ethiopia, where rotavirus transmission peaked during October to December [21].

The higher prevalence of rotavirus AGE in males has remained consistent and this has been reported by several authors [28–30]. However, there have not been clear reasons or explanations for this trend. It is suggested that this may either be due to more susceptibility in males and/or due to more likelihood of parents to take male children to hospital than females [28]. This trend is also observed in rotavirus negative cases. However, further research is

required to tease out these findings. Almost all cases of rotavirus associated AGE hospitalization in this study were less than 2 years of age with a peak age in the 6–11 month age group. This finding agrees with several reports from African countries [20] and specifies the need for Nigerian children to be protected very early in infancy. Vomiting, a prominent feature of rotavirus AGE [26], was observed in this study as more children with rotavirus associated AGE had vomiting compared with rotavirus negative AGE cases. This has been observed in previous studies [31,32]. The

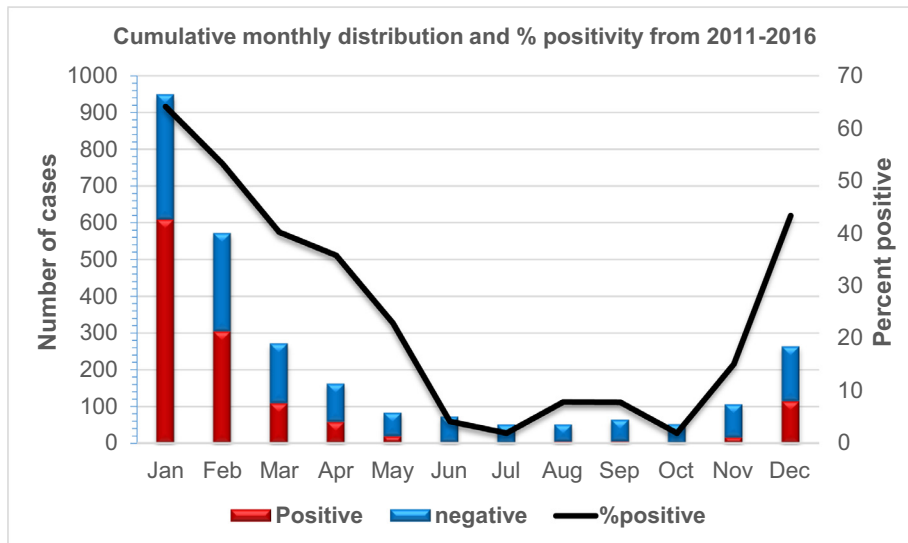


Fig. 3. Cumulative monthly distribution rotavirus positive and negative cases of acute gastroenteritis among under 5 children seen in 3 sentinel hospitals in Nigeria; as well as percentage rotavirus AGE positivity from 2011 to 2016.

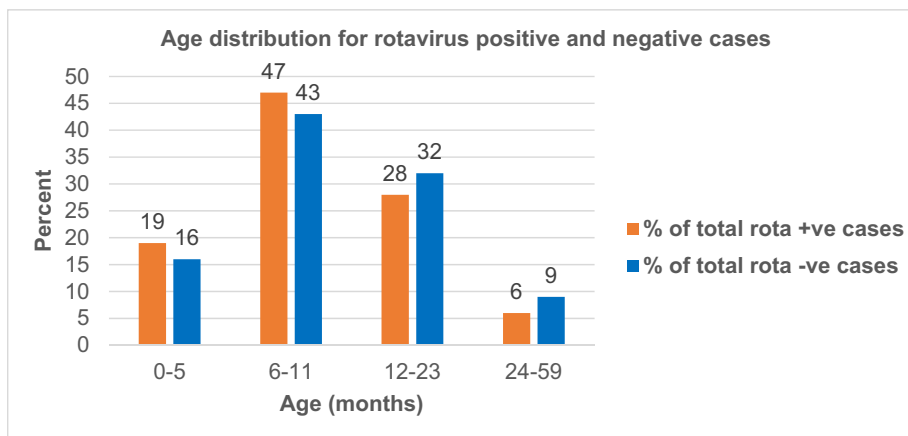


Fig. 4. Age distribution of children admitted with rotavirus positive and negative acute gastroenteritis in 3 sentinel sites in Nigeria, 2011–2016.

observation of more rotavirus positive cases receiving fluids compared to rotavirus negative cases is most likely related to the severity of illness and is probably why rotavirus is said to be the most common cause of dehydrating AGE in children under 5 years of age. Mortality from rotavirus associated AGE was very low in this study (Table 1). This may be due to the expertise of attending clinicians/paediatricians in providing prompt case management. Our main study site is a foremost teaching hospital with adequate number of paediatricians and paediatric residents in training. Most of the patients are promptly managed at the children emergency ward with good facilities. However, it is not clear why there were more deaths among rotavirus negative AGE children compared to rotavirus positive cases. Among developing countries, Nigeria is only second to India in terms of rotavirus mortality recording 38,800 deaths constituting 14% of all deaths in developing countries [7]. These deaths did not include those outside health facilities implying there could be more deaths that are not captured in hospitals. In most rural health facilities, there is inadequate capacity to manage severe dehydrating rotavirus diarrhoea. This

calls for not just establishing and equipping health facilities adequately, but also urgent rotavirus vaccine introduction to reduce severe diarrhoea hospitalizations and deaths.

This analysis is subject to several limitations. Being a hospital based study, it may not fully reflect the situation in the community as a good number of caregivers may not have access to hospital services [33]. Another limitation is that while rotavirus vaccines are not included in the national immunization program, they are available on the private market. However, it was not possible to obtain documented rotavirus vaccination status for patients. As such, we were not able to determine if any of the children had been vaccinated in the private market. Given that there are no documented estimates of rotavirus vaccination from the private market, we were also unable to estimate what proportion of the population may have received vaccine. Additionally, children whose primary diagnosis was not AGE were excluded from the study, even if AGE was present at the time of admission to the hospital. This may have resulted in missed enrolment of some cases.

Table 2

Demographic, clinical and outcome characteristics of children under five years of age with acute gastroenteritis enrolled in three sentinel hospitals, by rotavirus status, Nigeria 2011–2016.

Characteristics (n,%) unless otherwise stated	Positive(%) n = 1242	Negative(%) n = 1452	p value
Sex			
Males	726 (58.5)	910 (62.7)	0.03
Females	516 (41.5)	542 (37.3)	
Age			
Median age	9.0 (IQR 7)	10.0 (IQR 8)	0.00
0–5 m	232 (19)	242 (16)	0.00
6–11 m	592 (47)	620 (43)	
12–23 m	344 (28)	463 (32)	
24–59 m	74 (6)	127 (9)	
Clinical symptoms			
Vomiting ^a			0.00
Yes	1119 (90)	1200 (83)	
No	123 (10)	250 (17)	
Treatment			
ORS ^b /IVF ^{c,d}			0.00
Yes	775 (73)	793 (64)	
No	293 (27)	447 (36)	
Outcome			0.00
Discharged	1223 (98.5)	1401 (96)	
Died	6 (0.5)	25 (2)	
Others	13 (1)	26 (2)	

^a 2 missing from rotavirus negative cases.^b Oral rehydration solution.^c Intravenous fluid.^d 174 & 212 missing from rotavirus positive & negative cases respectively.

5. Conclusion

The burden of hospitalization in Nigerian children under 5 years of age with rotavirus AGE highlights the need for urgent introduction of rotavirus vaccine in the national routine immunization programme. This documented pre-vaccine introduction data is in preparation for the proposed vaccine introduction in the country and would serve as robust baseline data against which the impact of rotavirus vaccine could be compared after introduction. In order to achieve this, our surveillance sites require strengthening and proper positioning for vaccine impact assessment activities.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2018.03.084>.

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