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Impact of rotavirus vaccine introduction on rotavirus hospitalizations among children under 5 years of age — World Health Organization African Region, 2008–2018

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Abstract

Background: Rotavirus is the leading cause of acute gastroenteritis (AGE) among children worldwide. Prior to rotavirus vaccine introduction, over one third of AGE hospitalizations in Africa were due to rotavirus. We describe the impact of rotavirus vaccines using data from the African Rotavirus Surveillance Network (ARSN).

Methods: For descriptive analysis, we included all sites reporting to ARSN for any length of time between 2008–2018. For vaccine impact analysis, continuous surveillance throughout the year was required to minimize potential bias due to enrollment of partial seasons and sites had to report a minimum of 100 AGE cases per year. We report the proportion of rotavirus AGE cases by year relative to vaccine introduction, and the relative reduction in the proportion of rotavirus AGE cases reported following vaccine introduction.

Results: From 2008–2018, 97,366 prospectively enrolled hospitalized children <5 years of age met the case definition for AGE, and 34.1% tested positive for rotavirus. Among countries that had introduced rotavirus vaccine, the proportion of hospitalized AGE cases positive for rotavirus declined from 39.2% in the pre-vaccine period to 25.3% in the post-vaccine period, a 35.5% (95% CI: 33.7–37.3) decline. No declines were observed among countries that had not introduced the vaccine over the 11-year period.

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DISCLAIMER

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

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Conclusion: Rotavirus vaccine introduction led to large and consistent declines in the proportion of hospitalized AGE cases that are positive for rotavirus. To maximize the public health benefit of these vaccines, efforts to introduce rotavirus vaccines to the remaining countries in the region and improve coverage should continue.

Keywords

rotavirus; Africa; vaccine; surveillance; acute gastroenteritis; AGE; diarrhea; hospitalization

Background

Rotavirus is the leading cause of severe gastroenteritis among children worldwide and is estimated to cause over 215,000 deaths every year among children <5, with over half (121,000) occurring in Sub-Saharan Africa [1]. Prior to vaccine introduction, 38.2% of all hospitalized acute gastroenteritis cases among children <5 were attributed to rotavirus in the African region [2]. After completion of clinical trials, including two trials in African countries, in 2009 the World Health Organization (WHO) recommended rotavirus vaccine for all infants [3–5]. Introduction of rotavirus vaccines in the WHO African region (WHO/AFRO) started in 2009 and as of 2018, 35 of the 47 AFRO countries had introduced rotavirus vaccine. To assess the burden of rotavirus disease in WHO/AFRO, the African Rotavirus Surveillance Network (ARSN) was established in 2006 [6]. ARSN expanded from 4 countries participating in 2006, to 28 countries in 2018 (with a total of 33 countries reporting data between 2008–2018). By 2018, 27 countries that reported data to the ARSN had introduced rotavirus vaccine and these countries achieved a median coverage of 89% [11]. In this analysis, we used data from the ARSN to evaluate the impact of rotavirus vaccines on hospitalizations for rotavirus among children <5 years of age in WHO/AFRO countries.

Methods

Sentinel sites, case enrollment, and testing

Pediatric hospitals in each country were selected as a sentinel surveillance site for ARSN based on existing infrastructure and capacity to recruit at least 100 diarrheal cases per year and that had access to laboratory facilities [2]. At these hospitals, children <5 years of age were eligible for enrollment if they were admitted to the hospital or emergency room with acute gastroenteritis (AGE) and had 3 or more loose, non-bloody stools in a 24-hour period and had a symptom duration of ≤7 days. Children who developed AGE during a hospitalization for other health conditions (hospital-acquired AGE cases) were excluded. Demographic information and clinical symptoms of enrolled children were recorded, and stool specimens were collected within 48 hours of admission. Stool specimens were tested for rotavirus using an enzyme-linked immunosorbent assay (ELISA) at the hospital's laboratory facilities or national reference laboratory and a proportion of samples were sent to a regional reference laboratory for quality control.

Analyses

For descriptive analysis, we included all sites reporting to ARSN for any length of time between 2008–2018. All AGE cases that were reported as bloody, chronic, fell outside of the age range (>5 years of age), or had no ELISA test result were excluded from the analysis. We report the number of reporting countries, sites, and site-years (defined as one year of data from one site) as well as the number of AGE cases, number of rotavirus AGE cases, and the proportion of AGE cases that are rotavirus positive.

For vaccine impact analysis, continuous surveillance throughout the year is necessary to minimize potential bias due to enrollment of partial seasons given the seasonal nature of rotavirus disease. Data for this analysis were analyzed using site-years. For a site to be included for a particular year, that site had to report AGE cases in all 12 months and report a minimum of 100 AGE cases that year. Surveillance sites could drop in and out of the analysis over the eleven-year surveillance period based on their ability to meet inclusion criteria. Data on vaccine introduction status, the year of vaccine introduction and coverage were obtained from WHO website and were used to classify site-years as pre- or post-vaccine periods. As vaccine coverage is low in the under 5 population during the year of vaccine introduction, the year of vaccine introduction was excluded from the analysis as a transitional year. In the vaccine impact analysis, “year” is in reference to the year of vaccine introduction (which was year “0”), with each pre-vaccine year categorized as “−1”, “−2”, etc. and each post-vaccine year as “1”, “2”, etc. Among included sites we report the proportion of rotavirus AGE cases by year, and the proportion of rotavirus AGE cases by year relative to vaccine introduction. In addition, we report the number of AGE cases, rotavirus positive AGE cases, proportion of rotavirus positive AGE cases, and the relative reduction in the proportion of rotavirus AGE cases reported overall and by region.

We preformed three sensitivity analyses comparing the proportions of rotavirus AGE cases in the pre-and post-vaccine periods for different subgroups. The first subgroup analysis accounted for any potential biases that could have occurred with countries only providing data in the pre- or post-vaccine period, with a lack of data in both periods. This analysis was limited to sites that provided at least one year of data in both periods. The second subgroup analysis accounted for the fact that the impact of rotavirus vaccine may have been impacted by low coverage in some regions. For this analysis, data from the post-vaccine period was only included among site-years in which full dose rotavirus vaccine coverage was >=80%. The third subgroup analysis accounted for sites that would have been excluded due to lower enrollment or those with incomplete reporting. For this analysis sites were included if they reported AGE cases in at least 11 months of the calendar year and reported a minimum of 80 cases a year.

Results

In the AFRO region, 111,986 children from 33 countries and 87 sites were enrolled in ARSN during 2008–2018. Of these, 97,366 (86.9%) children from 32 countries and 86 sites met the case definition for AGE and were included in the descriptive analysis (Supplement Table 1). A majority of children (68.7%) were enrolled from the Eastern and Southern sub-region, with 20.1% and 11.2% enrolled in the West and Central sub-regions, respectively.

Overall, 33,241 (34.1%) children with AGE tested positive for rotavirus, with some variation by sub-region; 37.6% West Africa, 42.6% Central Africa, and 31.5% Eastern and Southern Africa.

In the absence of rotavirus vaccine introduction, the proportion of AGE cases positive for rotavirus were relatively stable over the eleven-year study period (Figure 1a). Utilizing data from countries prior to vaccine introduction and those who have not introduced the vaccine, the average proportion of AGE cases positive for rotavirus was 39.2%, with some variation by sub region; 43.2% in West Africa, 47.6% in Central Africa, and 35.3% in Eastern & Southern Africa (Table 1).

Of the children with AGE, 65,609 (67.4%) met the inclusion criteria for the main vaccine impact analysis. Among countries that had introduced rotavirus vaccine into their national immunization program, the proportion of AGE cases positive for rotavirus declined from 39.2% in the pre-vaccine period to 25.3% in the post-vaccine period, a 35.5% (95% CI 33.7–37.3) decline. Similar reductions were observed in the West, Central, and Eastern and Southern Africa sub-regions, with declines of 39.8% (95% CI 35.9–43.8), 53.1% (95% CI: 48.5–57.7), and 27.9% (95% CI: 25.5–30.3) observed, respectively. These reductions are closely aligned with the year of vaccine introduction and began to show a decline the year the vaccine was introduced (Figure 1b).

In sensitivity analyses limited to sites that reported data from both the pre- and post-vaccine introduction periods, a similar reduction in the proportion of AGE cases positive for rotavirus was observed, with a 36.3% (95% CI: 33.9–38.6) decline overall, and a 43.8% decline in the West sub-region, 48.6% in the Central sub-region, and 32.8% in the Eastern and Southern sub-region (Supplemental Table 2). When limiting data in the post-vaccine period to countries who had full-dose rotavirus vaccine coverage >=80% for that year, similar findings were observed to the overall analysis, with a 34.9% (95% CI: 33.0–36.8) reduction in the proportion of AGE cases positive for rotavirus overall, and a 39.9%, 55.3%, and 27.0% reduction in the West, Central, and Eastern and Southern sub-regions, respectively. Finally, when relaxing inclusion criteria and including sites who only reported data for a minimum of 11 months and enrolled 80 or more children per year, a 36.3% (95% CI: 34.6–38.0) overall reduction in rotavirus AGE was observed, with a 40.5% (95% CI: 36.8–44.2) in the West sub-region, 55.1% (95% CI: 50.8–59.3) in the Central sub-region, and 28.2% (95% CI: 25.9–30.5) in the Eastern and Southern sub-regions.

Discussion

The introduction of rotavirus vaccines led to large and consistent declines in the proportion of hospitalized AGE cases that are positive for rotavirus in the countries of WHO/AFRO overall and in each sub-region. These declines were not observed in countries who had not introduced the vaccine, supporting that these are specific to vaccine introduction and not just overall secular declines. Furthermore, the observed 35.5% decline in the proportion of AGE cases positive for rotavirus in this study are consistent with those expected, based on ~90% vaccine coverage with 50% vaccine efficacy [3, 7] and with declines seen globally and regionally following rotavirus vaccine introduction [2, 8, 9]. As rotavirus vaccine

implementation and coverage continues to improve in AFRO, it is likely that the impact of vaccination will continue to grow. Shah et al. estimated that in 2016 rotavirus vaccine prevented 130,000 rotavirus hospitalizations, and 21,000 rotavirus-related deaths among children <5 years in Africa, and if all countries in the region had introduced rotavirus vaccine, an additional 139,000 hospitalizations and 27,000 deaths could have been prevented [10]. These findings highlight the significant impact that rotavirus vaccine has had in WHO/AFRO, and the need to further improve vaccine coverage and accelerate introductions in this region for the countries yet to introduce the vaccine.

This analysis has several limitations. First, sites were able to drop in and out of the analysis and may have only contributed data to the pre-vaccine or post vaccine period. However, a sensitivity analysis was performed limited to sites that provided data during both time periods and results were similar. Second, we were unable to determine the vaccination status of the individual children enrolled in the ARSN network. As such, we cannot account for children who may have been partially vaccinated during introduction periods or who were vaccinated at private hospital facilities before national introduction. Due to these factors, and by excluding the year of rotavirus vaccine introduction from analyses (as opposed to including it in the post-vaccine period), we may be underestimating the impact of the rotavirus vaccine. Third, we may have underestimated the impact of rotavirus vaccine due to low vaccine coverage in some countries. However, in our second sensitivity analysis we limited the post-vaccine period to countries with >=80% rotavirus vaccine coverage and found a similar reduction in the proportion of rotavirus AGE cases. Finally, although sites from all the countries in the WHO/AFRO regions are enrolled in ARSN, due to the low number of sites reporting consistently in the Central and Western sub-regions, their findings may not be applicable to all countries who introduce rotavirus vaccine in these regions. Despite these limitations, we were able to show reductions in the proportion of AGE cases admitted to hospitals attributed to rotavirus in the post-vaccine period. These results were generated from over 65,000 children who were enrolled in the ARSN and provide strong evidence for the impact of rotavirus vaccine in this region.

Rotavirus vaccine introduction has resulted in a significant decline in the proportion of hospitalized AGE cases caused by rotavirus among children <5 years of age. This analysis highlights the importance of surveillance platforms, such as ARSN, to monitor disease burden and the impact of rotavirus vaccine in WHO/AFRO. To continue to maximize the public health benefit of available rotavirus vaccines, efforts to introduce rotavirus vaccines to the remaining countries in the region and improve vaccine coverage should continue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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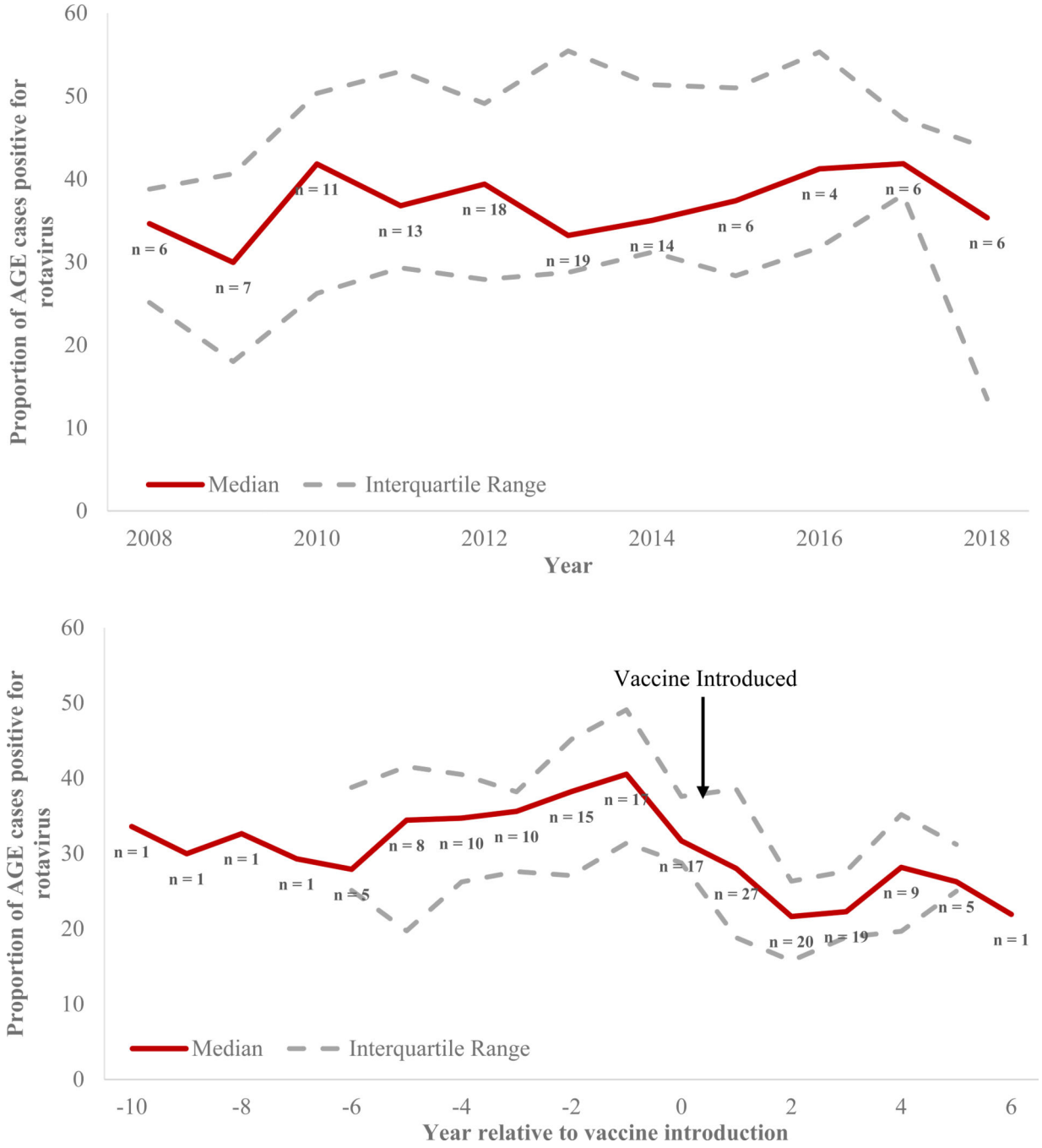

Figure 1.

Rotavirus positivity over time among countries (a) who have not (or not yet) introduced rotavirus vaccine and among those (b) who have introduced rotavirus vaccine — World Health Organization African Region, 2008–2018.

*n: number of sites contributing data for the specified year.

Table 1.

Rotavirus ELISA testing and positivity by region and rotavirus vaccine introduction status among children in sites meeting inclusion criteria — World Health Organization African Region, 2008–2018.[1]

WHO Region	RVV intro. status	No. countries	No. sites	No. site-years	No. tested	No. rotavirus positive	% rotavirus positive	% Reduction in % rotavirus positive (95%CI)
Overall	Pre	19	31	93	37041	14516	39.2%	-
	Post	17	32	81	28568	7224	25.3%	**35.5% (33.7–37.3)**
West Africa	Pre	7	10	28	9202	3976	43.2%	-
	Post	6	8	21	3998	1039	26.0%	**39.8% (35.9–43.8)**
Central Africa	Pre	3	4	15	5797	2760	47.6%	-
	Post	2	2	5	2115	472	22.3%	**53.1% (48.5–57.7)**
Eastern & Southern Africa	Pre	9	17	50	22042	7780	35.3%	-
	Post	9	22	55	22455	5713	25.4%	**27.9% (25.5–30.3)**

[1]Year of vaccine introduction year excluded from the analysis.

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