Effect of pentavalent rotavirus vaccine introduction on hospital admissions for diarrhoea and rotavirus in children in Rwanda: a time-series analysis

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Summary

Background In May, 2012, Rwanda became the first low-income African country to introduce pentavalent rotavirus vaccine into its routine national immunisation programme. Although the potential health benefits of rotavirus vaccination are huge in low-income African countries that account for more than half the global deaths from rotavirus, concerns remain about the performance of oral rotavirus vaccines in these challenging settings.

Methods We conducted a time-series analysis to examine trends in admissions to hospital for non-bloody diarrhoea in children younger than 5 years in Rwanda between Jan 1, 2009, and Dec 31, 2014, using monthly discharge data from the Health Management Information System. Additionally, we reviewed the registries in the paediatric wards at six hospitals from 2009 to 2014 and abstracted the number of total admissions and admissions for diarrhoea in children younger than 5 years by admission month and age group. We studied trends in admissions specific to rotavirus at one hospital that had undertaken active rotavirus surveillance from 2011 to 2014. We assessed changes in rotavirus epidemiology by use of data from eight active surveillance hospitals.

Findings Compared with the 2009–11 prevaccine baseline, hospital admissions for non-bloody diarrhoea captured by the Health Management Information System fell by 17–29% from a pre-vaccine median of 4051 to 2881 in 2013 and 3371 in 2014, admissions for acute gastroenteritis captured in paediatric ward registries decreased by 48–49%, and admissions specific to rotavirus captured by active surveillance fell by 61–70%. The greatest effect was recorded in children age-eligible to be vaccinated, but we noted a decrease in the proportion of children with diarrhoea testing positive for rotavirus in almost every age group.

Interpretation The number of admissions to hospital for diarrhoea and rotavirus in Rwanda fell substantially after rotavirus vaccine implementation, including among older children age-ineligible for vaccination, suggesting indirect protection through reduced transmission of rotavirus. These data highlight the benefits of routine vaccination against rotavirus in low-income settings.

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Introduction

Rotavirus accounts for more than a third of diarrhoea deaths in children younger than 5 years worldwide, with more than half of these deaths happening in sub-Saharan Africa.[1] In response to this large disease burden, two live attenuated, orally taken rotavirus vaccines (RotaTeq [RV5], Merck Vaccines, Whitehouse Station, NJ, USA, and Rotarix [RV1], GSK Biologicals, Rixensart, Belgium)[2] are recommended by WHO for use in all countries and especially in those with high mortality caused by diarrhoea.[2] By September, 2015, 79 countries had introduced one or other of these rotavirus vaccines.[3] Most countries that introduced the vaccine early were high-income and middle-income countries in the Americas and Europe, and these countries have provided much of the early evidence of the substantial effect of rotavirus vaccination. In Mexico, where rotavirus vaccine was introduced nationally in 2007, all-cause diarrhoea deaths in children younger than 5 years of age fell by 35–50% during 2008–11.[4–6] Similar decreases of 17–39% in Brazil and 50% in Panama were documented after rotavirus vaccine introduction.[7–9] Additionally, many other countries have noted a substantial reduction in the number of hospital admissions for all-cause diarrhoea and rotavirus after the rotavirus vaccine introduction.[7,10–30]

Live oral vaccines, including those for rotavirus, have had poor performance in developing country settings.[31–40] Although the reasons for this lower performance are

Research in context

Evidence before this study

We searched PubMed for articles published since 2000 in any language using the terms "rotavirus" and "vaccine" and "sub-Saharan Africa" and "impact OR effectiveness". Of the 42 articles identified, two articles examined the effectiveness of rotavirus vaccine in routine use in South Africa and Malawi and one study assessed the effect of rotavirus vaccine on disease burden in South Africa. We found no reports of the effect or effectiveness of rotavirus vaccine in Rwanda or of the effect or effectiveness of pentavalent rotavirus vaccine in sub-Saharan Africa.

Added value of this study

This study provides the first evidence of the effect of pentavalent rotavirus vaccine on the severe all-cause and rotavirus diarrhoea disease burden in sub-Saharan Africa after introduction of the vaccine into the routine childhood immunisation programme. Diarrhoea and rotavirus-specific hospital admissions in Rwanda fell substantially after rotavirus vaccine implementation, including among older children age-ineligible for vaccination, suggesting indirect protection through reduced transmission of rotavirus.

Implications of all the available evidence

Our findings support the continued use of rotavirus vaccine in Rwanda and highlight the benefits of routine vaccination against rotavirus in low-income settings.

unknown and probably complex, possible explanations could be interference by maternal antibodies, concurrent oral polio vaccine administration, prevalent viral and bacterial gut infections, and malnutrition.[41] Clinical trials for both the available rotavirus vaccines done in Africa and Asia showed modest efficacy (50–70%) compared with the high efficacy (85–98%) that was recorded in trials in Latin America, the USA, and Europe.[42–46] In view of the substantial disease burden in Africa and Asia, the absolute burden of severe diarrhoea disease prevented in these settings is expected to be substantial even with moderately efficacious vaccines, but concerns remain about vaccine performance in these high burden settings.[44]

In May, 2012, Rwanda became the first low-income country in Africa to introduce RV5 into its routine expanded programme on immunisation, with three doses given to infants at 6, 10, and 14 weeks of age. Rotavirus vaccine coverage in children younger than 1 year of age increased quickly to 50% in 2012, 99% in 2013, and 98% in 2014.[47] To monitor the effect of rotavirus vaccine in Rwanda, we studied trends in the number of hospital admissions for diarrhoea and rotavirus before and after the introduction of the rotavirus vaccine.

Methods

Trends in hospital admissions for diarrhoea

To assess trends in hospital admissions for diarrhoea nationally, we reviewed data from the Health Management Information System, which electronically captures monthly data for discharges from heath facilities in Rwanda.[48] Data are reported to the national level using predefined discharge categories. We restricted our analysis to district hospitals that reported the number of hospital admissions for diarrhoea with or without dehydration in children younger than 5 years of age for every month from Jan 1, 2009, to Dec 31, 2014. We excluded children admitted with bloody diarrhoea and diarrhoea caused by chronic opportunistic infections as reported by the hospital.

To supplement Health Management Information System data, at four district hospitals (Kabgayi District Hospital, Muhima District Hospital, Musanze District Hospital, and Rwamagana District Hospital) and two teaching hospitals (University Teaching Hospital Kigali, University Teaching Hospital Butare), we reviewed the registries in the paediatric wards from Jan 1, 2009, to Dec 31, 2014, and abstracted the total number of admissions to hospital and the number of admissions to hospital for diarrhoea in children younger than 5 years by month of admission and age group (age <1 year *vs* 1–4 years).

Trends in rotavirus-specific hospital admissions and changes in rotavirus epidemiology

Active, sentinel surveillance for rotavirus diarrhoea following the standard WHO protocol[49] started in September, 2010, at one large urban referral hospital in Kigali, Rwanda, and was subsequently expanded to four additional hospitals (Kibagabaga District Hospital, Musanze District Hospital, Rwamagana District Hospital, and University Teaching Hospital Butare). In September, 2012, rotavirus surveillance was started at three more district hospitals (Kabgayi District Hospital, Kabutare District Hospital, and Muhima District Hospital), bringing the number of hospital surveillance sites to eight. Briefly, children younger than 5 years who presented to a sentinel hospital and met the case definition for diarrhoea (occurrence of three or more episodes of diarrhoea [stools of a less formed character than usual] within a 24 h period that began fewer than 7 days before the hospital visit) were enrolled and a stool specimen was collected within 48 h of admission to avoid detection of nosocomial infections. Stool specimens were refrigerated until testing for rotavirus antigen by enzyme immunoassay at the University Teaching Hospital Kigali laboratory, Kigali, Rwanda. Trends in rotavirus-specific admissions to hospital were studied at one hospital that had done surveillance continuously from Jan 1, 2011, through Dec 31, 2014, under technical supervision and support of WHO. Changes in rotavirus epidemiology

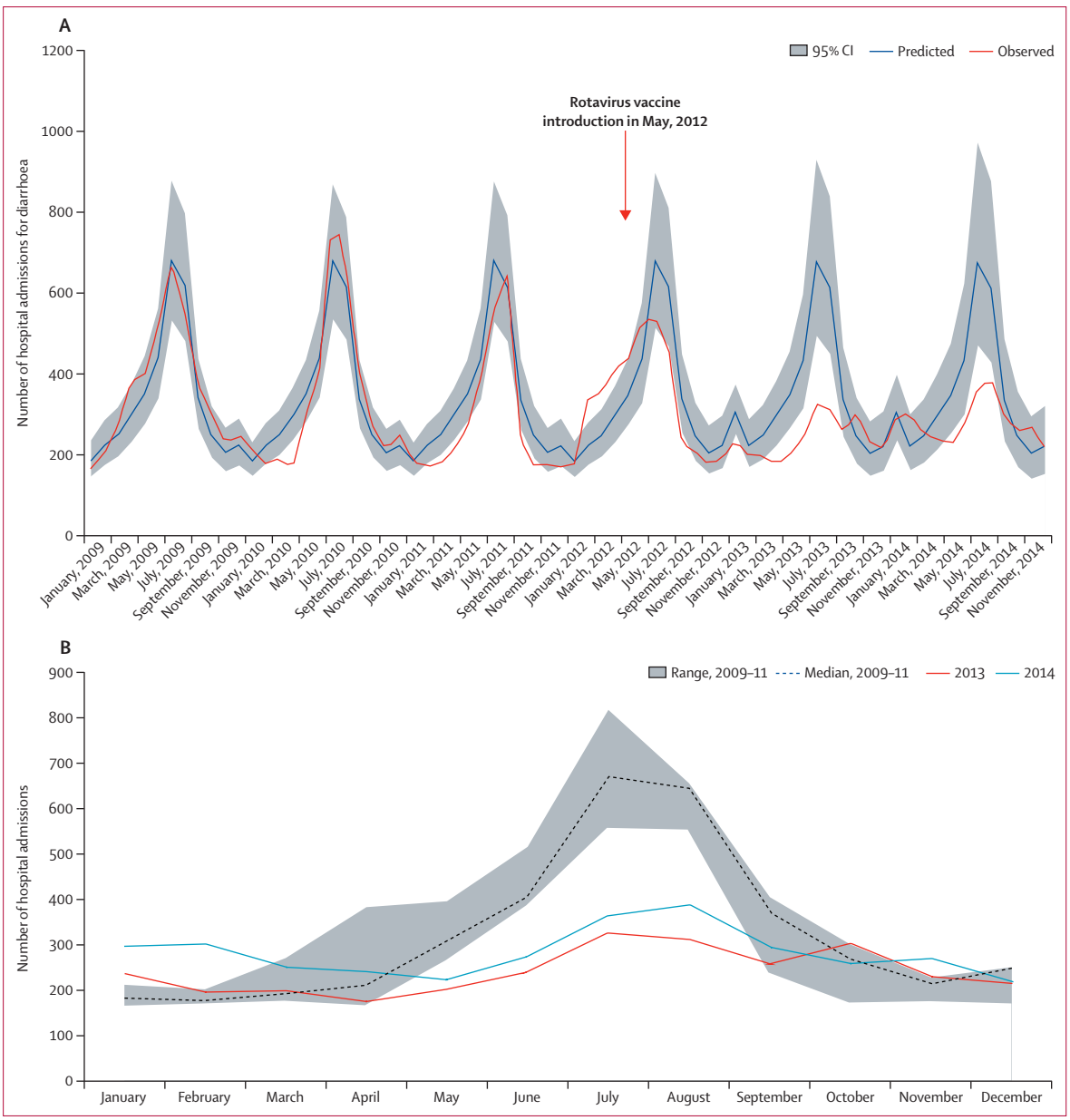

Figure 1: **Hospital admissions for diarrhoea before rotavirus vaccine introduction (2009–11) and after rotavirus vaccine introduction (2013 and 2014)**
(A) Predicted and observed number of hospital admissions for diarrhoea by month. (B) Number of hospital admissions for diarrhoea before rotavirus vaccine introduction (2009–11) and after rotavirus vaccine introduction (2013, 2014). Data (range; min–max) for children younger than 5 years at 24 district hospitals that continuously reported to Health Management Information System, January, 2009, to December, 2014.

including changes in the proportion positive and in the age distribution of rotavirus positive cases were assessed using data from all eight surveillance hospitals.

Statistical analysis

To predict the monthly incidence of all-cause diarrhoea hospital admissions that would be expected to happen if rotavirus vaccine had not been introduced, we did a time-series analysis. Because Poisson models showed overdispersion, we fitted a negative binomial model to the prevaccine Health Management Information System data for all-cause diarrhoea hospitalisation and adjusted for seasonality by including calendar month and for secular trends by including calendar year. We assessed model fit with the Pearson χ^2 statistic. We then plotted the expected number of hospital admissions for diarrhoea against the number of recorded admittances. To calculate the percentage reduction in the recorded number of all-cause diarrhoea hospital admittances and associated 95% confidence intervals (CIs) relative to the expected

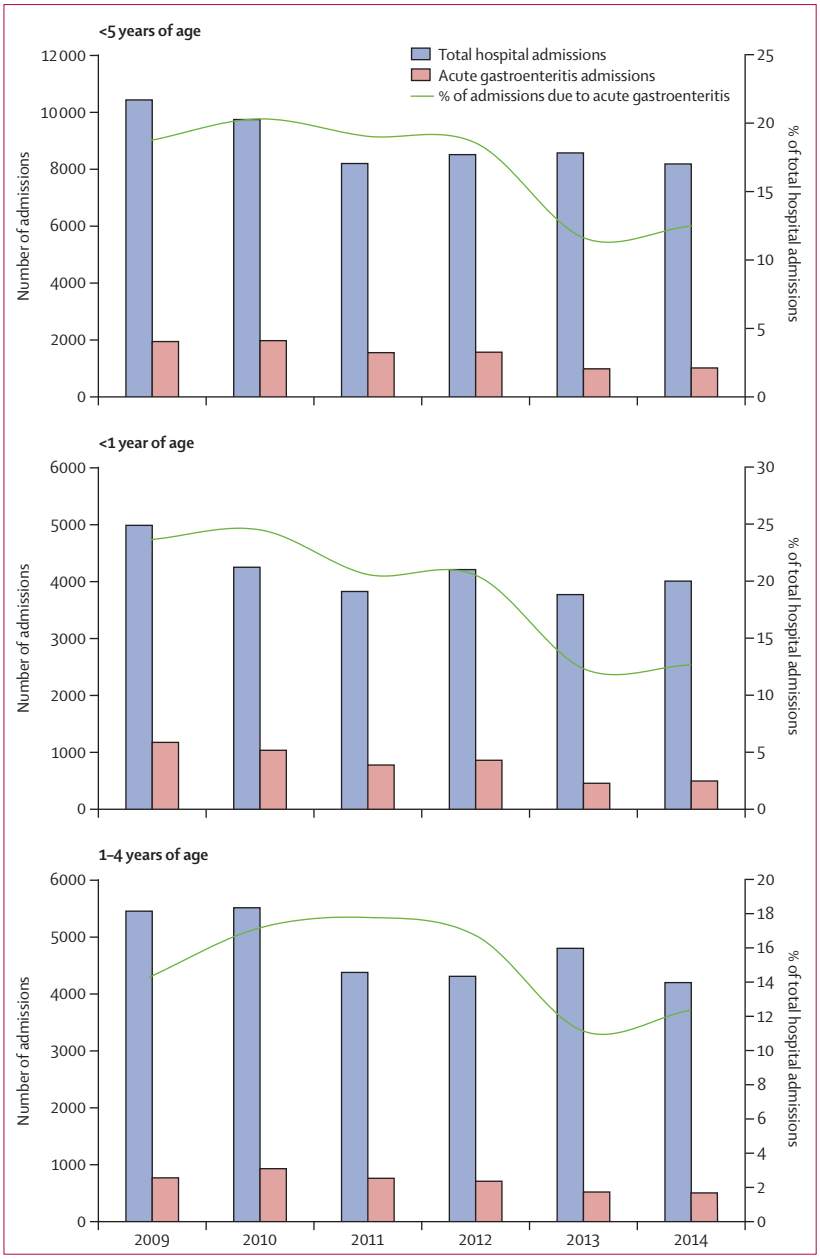

Figure 2: **Total hospital and acute gastroenteritis admissions and proportion of total hospital admissions for diarrhoea in children at four district and two teaching hospitals, 2009–14**

number, we included an indicator for the time after rotavirus vaccine introduction in a model including prevaccine and post-vaccine introduction data while controlling for seasonal and secular trends. We exponentiated the β of the indicator variable and its associated Wald 95% CI to work out the percentage reduction associated with vaccine introduction. We used χ^2 tests to compare the proportion of total admissions to hospital because of diarrhoea for the registry review and the proportion of admissions for diarrhoea because of rotavirus in the active surveillance data before and after the rotavirus vaccine introduction. To compare the number of hospital admissions because of rotavirus before and after the introduction of the rotavirus vaccine using the rotavirus surveillance data for the continuously reporting hospital from 2011 through 2014, we used a Wilcoxon rank sum test to compare the number of hospital admissions per month before (2011) and after (2013 and 2014) rotavirus vaccine introduction. Because rotavirus vaccine was introduced in May, 2012, we regarded 2012 as a transition year with rapidly changing vaccine coverage, and excluded 2012 data from the post-vaccine introduction analyses.

Analyses were done in SAS (version 9.3). The protocol was approved by the National Ethics Committee of Rwanda.

Role of the funding source

The Gavi, the Vaccine Alliance had no role in study design, data collection or analysis, data interpretation, or writing of the report. The Government of Rwanda provided in-kind support through staff time and logistics. Ministry of Health staff were involved in the study design, data collection, data interpretation, and writing of the report. All authors had full access to the data and take full responsibility for the integrity of the findings.

Results

24 of 46 district hospitals reported the number of hospital admissions for diarrhoea captured by the Health Management Information System every month between Jan 1, 2009, and Dec 31, 2014. We excluded about 560 children admitted to hospital with bloody diarrhoea or diarrhoea caused by chronic opportunistic infections, which combined accounted for 2–3% of hospital admissions for all-cause diarrhoea per year and showed no clear seasonality. In the prevaccine years (2009–11) at these hospitals, we recorded a median of 4051 (min–max range 3347–4301) hospital admissions for diarrhoea in children younger than 5 years per year. We noted a strong seasonal pattern: more hospital admissions for diarrhoea coincided with the rotavirus season from May to September during each prevaccine year from 2009 to 2011, with a peak in July (figure 1). In 2013, the first full year after rotavirus vaccine introduction, hospital admissions for diarrhoea in children younger than 5 years fell by 29% to 2881 admissions, and in 2014, decreased by 17% to 3371, compared with the prevaccine introduction median. Compared with the predicted number of hospital admissions for diarrhoea from the time-series model, the recorded number was 21% (95% CI –2 to 39) lower in 2013 and 4% (–32 to 30) lower in 2014 (figure 2). We noted significant seasonality during April to September. When we restricted the analysis to these months, the number of hospital admissions for diarrhoea was 40% (95% CI 17 to 56) lower in 2013, and 27% (–9 to 51) lower in 2014, compared with the predicted number of admissions. In both 2013 and 2014, the fall in hospital admissions for

diarrhoea was restricted to the rotavirus season months from May to September (figure 1). Between May and September, the median number of hospital admissions for diarrhoea during the prevaccine period 2009–11 was 2506; this number declined by 47% (N=1333) in 2013 and by 39% (N=1539) in 2014.

In our review of registries from the paediatric admission wards at four large district hospitals and two referral teaching hospitals, the proportion of total hospital admissions for diarrhoea in 2013 and 2014 in all age groups significantly decreased from the median prevaccine baseline ($p<0·01$ for each age group for each year; appendix). In the prevaccine era, a median of 9784 (min–max range 8225–10 462) hospital admissions were recorded per year in children younger than 5 years. Of these, a median of 1968 (min–max range 1572–1994) admissions (19%, 19–20%) were due to diarrhoea (figure 2). Compared with the prevaccine median from 2009–11, the number of hospital admissions for diarrhoea in children younger than 5 years fell by 49% to 1004 admissions in 2013 and by 48% to 1030 in 2014, accounting for 12% and 13% of total admissions in the 2 post-vaccine years, respectively (figure 3).

Of children younger than 1 year, the prevaccine median number of total hospital admissions was 4257 (range 3835–4999) and of these, a median of 1044 (range 790–1183) were due to diarrhoea (ie, 21–25% of total hospital admissions; figure 2). The number of hospital admissions for diarrhoea in children younger than 1 year decreased by 55% to 466 in 2013, and by 51% to 508 in 2014, compared with the prevaccine baseline, accounting for 12% and 13% of total hospital admissions in the 2 post-vaccine years, respectively (figure 3). Similarly in children aged 1–4 years, we noted a pre-vaccine median of 5463 (min–max range 4390–5527) total hospital admissions and, of these, a median of 785 (782–950) due to diarrhoea, accounting for 14–18% of total admissions in this age group (figure 2). The number of hospital admissions for diarrhoea in children aged 1–4 years fell by 31% to 538 in 2013, and by 34% to 522 in 2014, compared with the prevaccine baseline, accounting for 11% and 12% of total admissions in the 2 post-vaccine years, respectively (figure 3). The seasonal peak was blunted in all age groups after vaccine introduction.

With regard to trends in rotavirus-specific hospital admissions and changes in rotavirus epidemiology, one sentinel hospital located in eastern province undertook active surveillance for rotavirus continuously from January, 2011, to December, 2014 (figure 4). The number of rotavirus detections increased from May to September of each year. After the introduction of rotavirus vaccine in May, 2012, the annual peak in admittances to hospital because of rotavirus in eastern province was blunted in 2013 and 2014, with a 61% and 70% fall in the number of admissions because of rotavirus in 2013 and 2014, respectively, compared with the prevaccine year of 2011 ($p=0·04$).

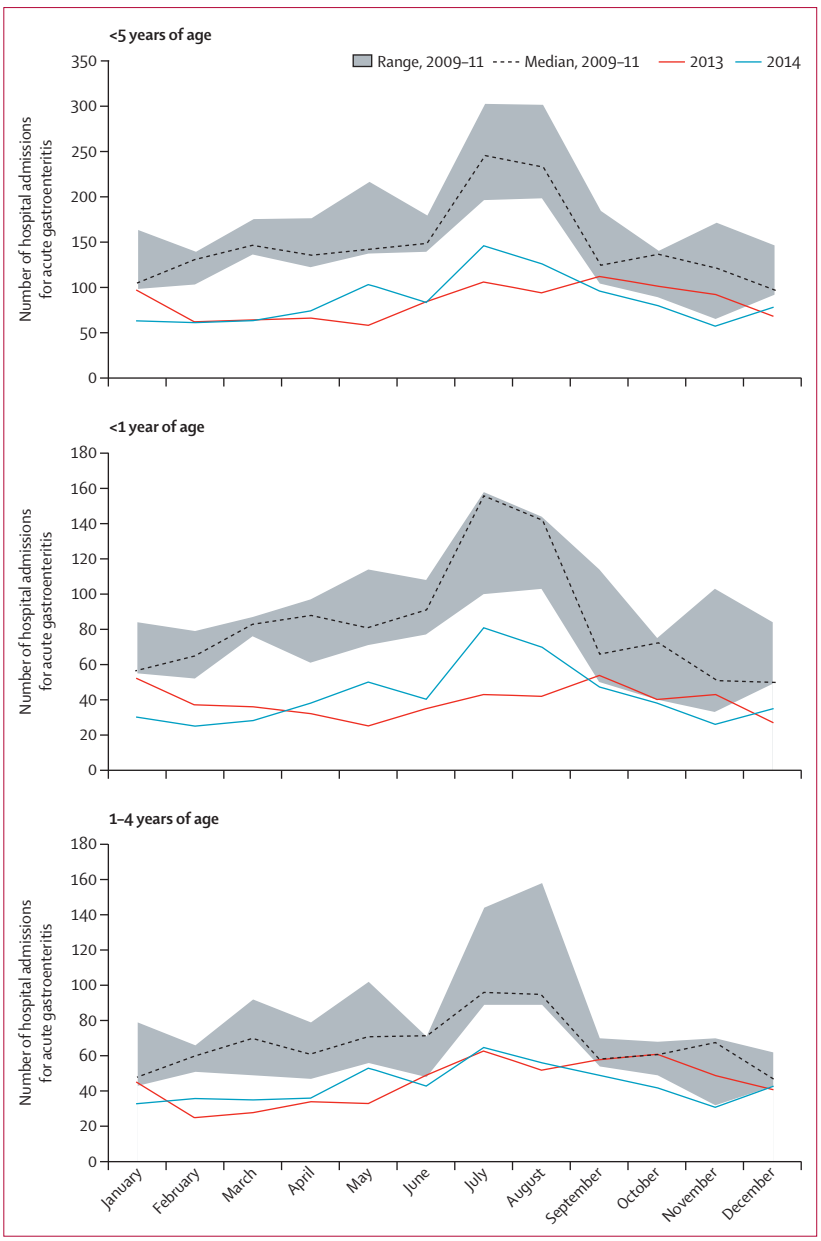

Figure 3: **Median and range (min–max) of the number of acute gastroenteritis hospital admissions by month before vaccine introduction (2009–11) and in 2013 and 2014 in children at four district and two teaching hospitals**

Using data from all eight surveillance hospitals, the proportion of children younger than 5 years admitted to hospital for diarrhoea caused by rotavirus fell from 52% in 2011, to 24% in 2013 ($p<0·0001$) and 23% in 2014 ($p<0·0001$). This decrease in the proportion of hospital admissions for diarrhoea that were rotavirus-positive was noted across almost all age groups, but the greatest effect was recorded in children directly protected by the vaccine (children aged 3–11 months in 2013, and 3–23 months in 2014; figure 5). In 2011, 56% (74/133) of all admittances to hospital because of rotavirus happened in children younger

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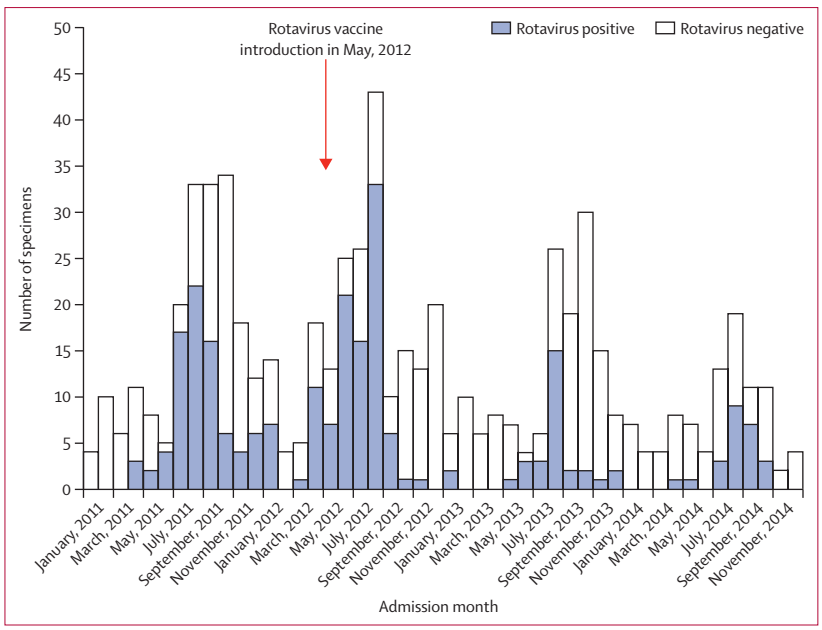

Figure 4: **Rotavirus detections by month in children aged <5 years admitted to one district hospital, January, 2011–December, 2014**

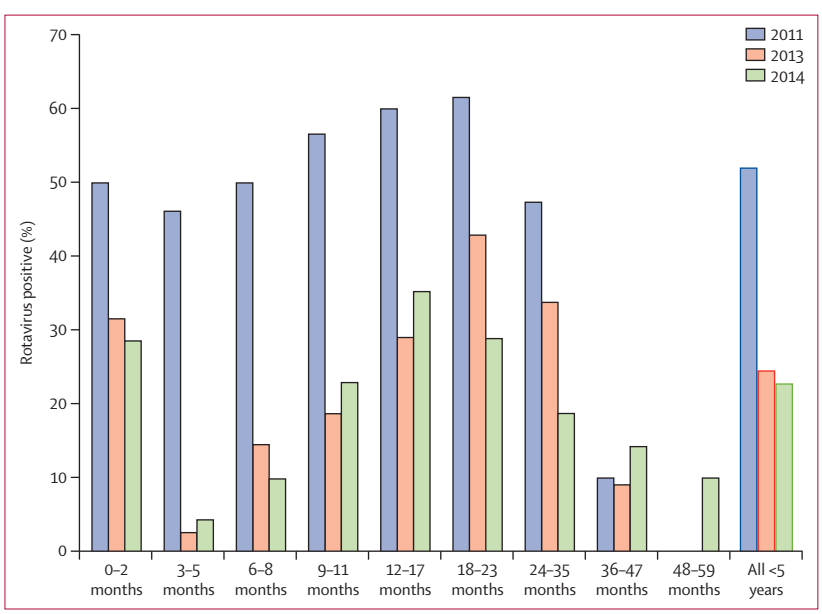

Figure 5: **Rotavirus positivity by age group before vaccine introduction (2011) and after vaccine introduction (2013 and 2014)**

than 1 year. In 2013, the cumulative age distribution shifted to the right, with 31% (58/185) of rotavirus hospital admissions happening before the age of 1 year. In 2014, 37 (36%) of 103 of hospital admissions because of rotavirus happened in children younger than 1 year.

Discussion

As an early introducer of rotavirus vaccine into its expanded programme on immunisation, Rwanda is one of the first low-income countries in sub-Saharan Africa to document the effect of rotavirus vaccine and the first to assess RV5. The introduction of the rotavirus vaccine resulted in rapid and substantial reductions in admissions to hospital for acute, non-bloody diarrhoea, and for rotavirus in children younger than 5 years. Similar to other countries with seasonal rotavirus disease, Rwanda observed a significant blunting in the seasonal peaks of hospital admissions for diarrhoea after the introduction of rotavirus vaccine into the national expanded programme on immunisation. We noted the biggest effect in children age-eligible to be vaccinated, resulting in a shift of the age distribution of hospital admissions for rotavirus to older-age children immediately after rotavirus vaccine introduction. However, a decrease in the proportion of children with diarrhoea testing positive for rotavirus was recorded in almost every age group, including children too young and too old to be vaccinated; this decrease might suggest that these children are indirectly protected by the vaccine through reduced transmission of rotavirus in the population.

Findings of the assessment of vaccine effectiveness after the introduction of RV1 into the routine immunisation programmes in South Africa and Malawi showed that the vaccine was 57–64% effective against hospital admissions for rotavirus and reduced the prevalence of rotavirus in young children.[50–52] We report the first data for the effect of routine RV5 vaccination in Africa. The strong seasonal peaks in hospital admissions for diarrhoea combined with a high rotavirus detection rate in the prevaccine period help accentuate the effect of the vaccine, as most of the reduction in diarrheal disease happened during these seasonal peaks. The fall in hospital admissions for diarrhoea noted in Rwanda is similar to decreases recorded in Brazil, Mexico, and Panama, and the decreased hospital admissions for rotavirus are similar to those reported in Brazil and El Salvador after the implementation of rotavirus vaccine in these countries.[7,26–30]

We noted a greater reduction in the number of hospital admissions for diarrhoea in 2013 compared with 2014. This phenomenon of alternating years of larger and smaller reductions has been recorded over 7 post-introduction years in the USA and is probably the result of the accumulation of susceptible children over successive seasons resulting in increased transmission.[53,54] With only 2 years of post-vaccine data from Rwanda, it is too early to establish whether such a pattern is happening in this high disease burden setting, but continued monitoring of trends in hospital admissions for diarrhoea in the post-vaccination era will provide data to study this trend. Finally, indirect protection of children too old to have been vaccinated with rotavirus vaccine has been previously reported in several high-income and middle-income countries including the USA, Australia, Austria, and El Salvador.[23,24,26,55–58] We provide the first possible evidence of indirect protection from rotavirus vaccination in a high-burden, low-income setting.

This study has some limitations. First, the Health Management Information System was strengthened and expanded in January, 2012, immediately before rotavirus vaccine introduction in May, 2012. Additional hospitals began reporting to the system. To maintain comparability between 2009 and 2014, we restricted the analyses to district hospitals that were included in both 2009–11 and 2012–14 and that reported the number of hospital admissions for diarrhoea to the Health Management Information System every month from January, 2009, to December, 2014. The strengthening of the system could have resulted in more complete reporting during the post-vaccine era, which would have lowered the estimates of vaccine effect. To further validate our results, we compared two district hospitals that had both Health Management Information System data and data from the registry review and noted that both data sources showed similar trends in diarrhoea disease during the 6 year time period (appendix). Second, hospital admissions for diarrhoea for the Health Management Information System analysis and the registry review were based on hospital admissions defined as related to diarrhoea at the site level rather than based on a standardised national case definition, and some variability could have existed between hospitals. However, for each analysis we captured a standard set of discharge diagnoses for diarrhoea and acute gastroenteritis. Third, we excluded bloody and chronic diarrhoea from the Health Management Information System analysis; however, this process probably had little effect on our results because bloody and chronic diarrhoea accounted for only 2–3% of hospital admissions for diarrhoea every year and showed no trends in seasonality. Finally, we only had 1 complete year of active rotavirus surveillance from one site before vaccine introduction. However, this site enrolled more than 150 children admitted to hospital for diarrhoea before vaccine introduction and so was able to provide a stable baseline. Furthermore, despite their individual limitations, the compatibility in trends recorded across the three surveillance platforms is reassuring that these platforms were probably internally consistent over time and provide additional confidence in our findings. The sharp decrease in hospital admissions for diarrhoea, with the largest effect recorded in children age-eligible to be vaccinated and which occurred coincident with the introduction of rotavirus vaccine, suggests that the decrease in hospital admissions for diarrhoea during this period is the result of the introduction of rotavirus vaccine and not incremental improvements in sanitation, hygiene, or clean water. By 2013, three-dose rotavirus vaccine coverage in children younger than 1 year was estimated to reach 99% and remained high at 98% in 2014.[54]

In summary, hospital admissions for diarrhoea and rotavirus in Rwanda decreased substantially after rotavirus vaccine implementation. We noted decreases not only in children who were eligible to be vaccinated, but also in children age-ineligible to have received the vaccine, suggesting that these children were indirectly protected through reduced transmission of rotavirus in the population. These data support the continued use of rotavirus vaccine in Rwanda and highlight the benefits of routine vaccination against rotavirus in low-income settings.

Contributors

FN, JET, MG, CR, JMM, and UDP came up with the idea for and designed the study; FN and MG acquired the data; FN, JET, MG, CR, PD, PL, JMM, AB, and UDP analysed and interpreted the data; JET came up with the first draft of the report; and FN, MG, CR, PD, PL, JMM, AB, and UDP critically reviewed the report.

Declaration of interests

The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC). AB is on the International Advisory Board for *The Lancet Global Health* and is the Minister of Health of Rwanda. None of the other authors declare any competing interests.

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