Published in final edited form as:

Lancet Glob Health. 2019 July ; 7(7): e893–e903. doi:10.1016/S2214-109X(19)30207-4.

Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network

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NA, JET, ALC, FS, CY, and UDP created the outline for the analysis. SA and NA prepared the data for analysis. NA and JET did the analyses. NA, JET, SA, ALC, FS, CY, TN, and UDP prepared the manuscript. DSD, KFo, JH, TC, MA, AW, JM, JMM, JNMB, DC, GW, DV, SS, LHdO, GR-B, NJS, VG, NB, FJP, NT, KFa, HA, HAR, PRW, and JBLL provided critical feedback to the analysis and manuscript.

Declaration of interests

JH reports and owns stock in GlaxoSmithKline and Merck. All remaining authors declare no competing interests.

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Abstract

Background—Rotavirus vaccine use in national immunisation programmes has led to declines in hospital admissions for rotavirus gastroenteritis among children; however, the global impact of rotavirus vaccine introduction has not been described using primary data. We describe the impact of rotavirus vaccine introduction on admissions for acute rotavirus gastroenteritis in primarily low-income and middle-income countries, using 9 years of data from the WHO-coordinated Global Rotavirus Surveillance Network (GRSN).

Methods—Between Jan 1, 2008, and Dec 31, 2016, children younger than 5 years of age who were admitted to hospital with acute gastroenteritis were prospectively enrolled in GRSN sites. We included sites that enrolled children and collected stool specimens monthly and tested at least 100 specimens annually in the impact analysis, with a separate analysis taking into account site continuity. We compared proportions of acute gastroenteritis cases positive for rotavirus in the pre-vaccine and post-vaccine periods and calculated mean proportion changes for WHO regions, with 95% CIs; these findings were then compared with interrupted time series analyses. We did further sensitivity analyses to account for rotavirus vaccination coverage levels and sites that collected specimens for at least 11 months per year and tested at least 80 specimens per year. We also analysed the age distribution of rotavirus-positive cases before and after vaccine introduction.

Findings—403 140 children younger than 5 years of age admitted to hospital with acute gastroenteritis from 349 sites in 82 countries were enrolled over the study period, of whom 132 736 (32.9%) were positive for rotavirus. We included 305 789 children from 198 sites in 69 countries in the impact analysis. In countries that had not introduced rotavirus vaccine in their national immunisation programmes, rotavirus was detected in 38.0% (95% CI 4.8–73.4) of admissions for acute gastroenteritis annually whereas in those that have introduced the vaccine, rotavirus was detected in 23.0% (0.7–57.7) of admissions for acute gastroenteritis, showing a 39.6% (35.4–43.8) relative decline following introduction. Interrupted time series analyses confirmed these findings. Reductions by WHO regions ranged from 26.4% (15.0–37.8) in the Eastern Mediterranean Region to 55.2% (43.0–67.4) in the European Region and were sustained in

nine countries (contributing up to 31 sites) for 6–10 years. The age distribution of children with rotavirus gastroenteritis shifted towards older children after rotavirus vaccine introduction.

Interpretation—A significant and sustained reduction in the proportion of hospital admissions for acute gastroenteritis due to rotavirus was seen among children younger than 5 years in GRSN sites following rotavirus vaccine introduction. These findings highlight the need to incorporate rotavirus vaccines into immunisation programmes in countries that have not yet introduced them and underline the importance of high-quality surveillance.

Introduction

Rotavirus gastroenteritis is responsible for substantial morbidity and mortality among children younger than 5 years of age. Rotavirus gastroenteritis has previously accounted for an estimated 1·9 million episodes per year of severe acute gastroenteritis requiring hospital admission among children younger than 5 years of age;[1] in 2013 alone, an estimated 215 000 deaths related to rotavirus gastroenteritis occurred in this age group, with four countries (Nigeria, Pakistan, India, and Democratic Republic of the Congo) accounting for 49% of these deaths.[2] However, hospital admissions and deaths from rotavirus gastroenteritis and all-cause acute gastroenteritis have declined following the increasing incorporation of rotavirus vaccines into national immunisation programmes. Reductions in under-5 mortality from all-cause acute gastroenteritis in countries following rotavirus vaccine introduction range from 22% to 45%,[3–6] with some findings indicating a sustained reduction 7 years after introduction.[7] In these same countries, hospital admissions for acute gastroenteritis in this age group have declined substantially, with a recent systematic review showing an overall 38% reduction.[8] Individual country reports also indicate reductions in hospital admissions for rotavirus gastroenteritis among children younger than 5 years, ranging from 23% to 69% in diverse settings worldwide.[3,7,9–12]

WHO recommends the use of rotavirus vaccines in all national immunisation programmes globally, particularly in countries with high diarrhoeal mortality among children.[13] Two rotavirus vaccines are currently in routine use globally: the monovalent Rotarix (RV1; GlaxoSmithKline, Rixensart, Belgium) and pentavalent RotaTeq (RV5; Merck, West Point, PA, USA). These vaccines have been shown to be effective globally in preventing hospital admissions for rotavirus gastroenteritis, with vaccine effectiveness ranging from 57% to 85% for RV1 and from 45% to 90% for RV5 based on countries' mortality strata, with higher vaccine effectiveness noted in countries with lower childhood mortality.[14]

High-quality surveillance data are crucial to accurately document rotavirus gastroenteritis burden and monitor the impact of the vaccines. To meet this need, the Global Rotavirus Surveillance Network (GRSN) was established by WHO in 2008, with funding from Gavi, the Vaccine Alliance, by unifying existing sentinel hospital rotavirus surveillance platforms from each of the six WHO regions (African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region). Standard surveillance and laboratory procedures were established across all participating sites.[15] Gavi provides assistance to immunisation programmes based on average gross national income per capita: during 2008–10, countries were eligible if their

gross national income was US$1000 per capita in 2003; this threshold was adjusted for annual inflation until 2015. Since 2015, countries are eligible if their average gross national income has been $1580 per capita or less for the 3 years prior to applying for Gavi assistance.[16] Countries can participate in the GRSN irrespective of Gavi eligibility status.

The GRSN generates local data for decision making regarding rotavirus vaccine use and monitoring trends in rotavirus burden. Rotavirus surveillance data from this network have contributed to a fundamental body of scientific literature documenting the regional[17,18] and global[19–21] rotavirus gastroenteritis burden. Although some participating countries have also provided data showing the impact of national rotavirus vaccine introductions,[10,11,22,23] the global impact of rotavirus vaccines using GRSN data has not yet been assessed. We describe the first 9 years of enrolment at sites participating in the GRSN and evaluate the global and regional impact of rotavirus vaccines on hospital admissions for rotavirus gastroenteritis among children younger than 5 years of age.

Methods

GRSN case enrolment and testing

Sentinel surveillance sites were selected to be part of the GRSN if they treated at least 250–500 children annually and had access to laboratory facilities.[15] With a conservative estimate of 30% of acute gastroenteritis cases being due to rotavirus prior to vaccine introduction, this requirement would yield at least 75–150 cases of rotavirus gastroenteritis per year per site. From Jan 1, 2008, to Dec 31, 2016, using a standard case definition and case- based data collection tool,[15,24] staff at participating sentinel sites prospectively identified children younger than 5 years of age admitted to the hospital or emergency unit with acute gastroenteritis, which is defined as three or more episodes of loose stools in a 24-h period, lasting no more than 14 days. Children presenting with bloody diarrhoea were excluded as this is not consistent with rotavirus gastroenteritis. Basic demographic information was collected upon enrolment and stool specimens were collected within 48 h of enrolment. Specimens were tested for rotavirus using a commercial ELISA (Premier Rotaclone [Meridian Bioscience; Cincinnati, OH, USA], ProSpecT [Oxoid; Basingstoke, UK], or RIDaSCREEN [R-Biopharm; Darmstadt, Germany]) at enrolling hospital laboratories or national reference laboratories in participating countries. External quality assurance assessments were done annually to ensure accuracy of laboratory diagnoses.

Data collection and reporting to the GRSN occurs as part of routine public health surveillance in participating countries and does not require human subjects review.

Main analyses

Countries included in the analyses, as well as the number of countries introducing rotavirus vaccine per year, are listed in the appendix. We did three separate analyses using different subsets of GRSN enrollees in these countries: a descriptive analysis, a vaccine impact analysis, and an age distribution analysis.

For the descriptive analysis, we included all sites reporting to the GRSN for any length of time during 2008–16 and all sites that met inclusion criteria for the impact analysis

(described below). We report the number of reporting countries, sites, and site-years; number of Gavi-eligible countries; number of acute gastroenteritis cases; and proportion of cases positive for rotavirus. A country was classified as Gavi eligible if it had ever met eligibility criteria during the surveillance period.

To accurately assess vaccine impact, the seasonal nature of rotavirus disease in many parts of the world[25] has to be taken into account: continuous surveillance throughout the year is necessary to capture complete seasons and limit potential bias from enrolment of partial seasons. For this reason, sites were included in the vaccine impact analysis only if they enrolled children and tested specimens every month of a calendar year with at least 100 specimens tested in that year. Individual surveillance sites could drop in and out of the analysis over the course of the 9-year surveillance period depending on their meeting of the annual inclusion criteria. Within the analysis, sites were characterised as pre-vaccine or post-vaccine for each year on the basis of the year of rotavirus vaccine introduction in their country. The year of introduction was ascertained from WHO, PATH, and Gavi websites. In our analysis, the year variable did not refer to calendar year but indicated the number of years before or after vaccine introduction: the year of introduction was year 0, with pre-vaccine years given negative values and post-vaccine years given positive values. The year of vaccine introduction was included in the pre-vaccine period (ie, year ≤0) because coverage in the under-5 population would have been low during this year. Among included sites, the annual proportion of children admitted to hospital with acute gastroenteritis who were found positive for rotavirus was calculated by site and the mean proportion across sites was calculated and reported by region. We also report the annual median proportion of hospitalised children positive for rotavirus for sites in countries with and without routine rotavirus vaccine use. For countries without routine rotavirus vaccine use, this included both sites that had not introduced rotavirus vaccine in the national immunisation programme as well as the pre-vaccine introduction years in sites that had introduced rotavirus vaccine. The mean proportion of children with acute gastroenteritis who were positive for rotavirus in the pre-vaccine period was compared with that of the post-vaccine period, globally and regionally, and the relative reduction in the proportion with rotavirus gastroenteritis is reported with 95% CIs. Relative reductions in the proportion of children with rotavirus gastroenteritis in sites with both pre-vaccine and post-vaccine data were also reported by Gavi eligibility status for the regions that had this data available.

Finally, we analysed the age distribution of rotavirus positive cases after vaccine introduction: we present the age distribution of children with rotavirus gastroenteritis for whom age or date of birth was available for countries in the periods before and after introduction of rotavirus vaccine and compare proportions of individual age groups in these periods.

We used the Wilcoxon rank-sum test to compare median ages and the χ^2 test to compare proportions throughout our analyses. p values smaller than 0·05 were considered statistically significant. We used SAS 9.4, Microsoft Excel 2016, and R version 3.5.1 for our analyses.

Sensitivity analyses

We did three sensitivity analyses on vaccine impact. The first analysis aimed to account for the fact that the routine surveillance sites included in the main vaccine impact analysis could drop in and out of the analysis if they did not meet the site inclusion for a particular year. Data were analysed from sites that had enrolled children and tested their specimens in at least 1 pre-vaccine and 1 post-vaccine year. In addition to comparing proportions before and after vaccine introduction, we did an interrupted time-series analysis using Poisson regression techniques to compare with our impact findings. Among countries with both pre-vaccine and post-vaccine data, a generalised linear model was fit assuming the annual number of hospital admissions for rotavirus gastroenteritis followed a negative binomial distribution and we used the log of the total number of children tested as the offset term. The covariates were region, country, pre-vaccine and post-vaccine status, the number of years since vaccine introduction, the number of site-years, and Gavi eligibility status. In a second model, we did not include the number of years since vaccine introduction (ie, we considered the entire pre-vaccine and post-vaccine periods as a whole) but otherwise had the same terms in the model. For both models, we report the proportion change in cases of acute gastroenteritis found positive for rotavirus with 95% CIs.

We also did two sensitivity analyses on vaccine impact in which the proportions of children hospitalised who tested positive for rotavirus gastroenteritis were compared in the pre-vaccine and post-vaccine periods for different subgroups. The first subgroup analysis accounted for the fact that rotavirus vaccine impact on hospital admissions for rotavirus gastroenteritis might be tempered in countries with low rotavirus vaccine coverage. For this subgroup, the post-vaccine period was restricted to countries that had attained full-dose rotavirus vaccine coverage of at least 60% based on WHO/UNICEF national estimates.[26] This cutoff was chosen because it was the coverage level at which impact was first noted in the USA.[27] The second subgroup analysis accounted for smaller sites with lower enrolment. For this subgroup, the inclusion criteria were relaxed and sites that had enrolled children and tested specimens for at least 11 months of a calendar year and collected and tested at least 80 specimens in a year were included. We were not able to combine the criteria for the sensitivity analyses into one analysis as the sample size would have been too small.

Role of the funding source

Funding for the GRSN is provided by Gavi. Gavi had no role in the study design, collection, analysis, or interpretation of the data. The corresponding author (NA) had full access to the data and took the decision to submit for publication, with agreement from all coauthors.

Results

Globally, 405 916 children younger than 5 years enrolled in 350 surveillance sites in 82 countries from all six WHO regions were reported to the GRSN during 2008–16 (figures 1, 2). Of these children, 403 140 (99·3%) from 349 sites met the acute gastroenteritis case definition and were included in the descriptive analysis (table 1). 132 736 (32·9%) of these children had rotavirus gastroenteritis. Of the reported cases included in the descriptive analysis, 305 789 (75·9%) met inclusion criteria for the main impact analysis. The

proportion of site-years contributed by each WHO region to the main impact analysis, in descending order of contribution, were the Region of the Americas (30·3%), the African Region (24·0%), and the Eastern Mediterranean Region (18·1%), with the European Region (12·1%), Western Pacific Region (11·9%), and South-East Asia Region (3·6%) contributing smaller proportions (table 1). Among the 151 sites (905 site-years) excluded from the main analysis, the highest proportion of site-years were also contributed by the Region of the Americas (36·0%, 326 site-years) and the African Region (25.6%, 232 site-years) and Eastern Mediterranean Region (26.6%, 241 site-years); however, the European Region's contribution decreased to 1.8% (16 site-years) and Western Pacific Region's contribution decreased to 5.1% (46 site-years). The proportion of site- years excluded from the main analysis from the South-East Asia Region (4.9%, 44 site-years) was similar to that for the included site-years. Of cases meeting the inclusion criteria, 31.5% tested positive for rotavirus gastroenteritis, with variation by region from 25.6% to 44.3% (table 1). 123 (62%) of 198 sites in the impact analysis were from 46 Gavi-eligible countries.

In countries that had not introduced rotavirus vaccine (ie, using data from countries that have not introduced the vaccine and data from the pre-rotavirus vaccine period in countries that have introduced the vaccine), the median annual proportion of acute gastroenteritis cases positive for rotavirus remained stable over time globally, at around 40% (figure 3). When assessed regionally, a similar trend was seen in the South-East Asia Region and the Western Pacific Region, who only reported pre-vaccine data to the GRSN (data not shown).

In countries where rotavirus vaccines have been introduced into the national immunisation programme, the average proportion of acute gastroenteritis cases positive for rotavirus decreased in all regions after routine rotavirus vaccine introduction compared with the pre-vaccine era (table 2). Globally, there was a 39.6% (95% CI 35.4–43.8) relative reduction in the proportion of hospitalised children found positive for rotavirus; regional relative reductions ranged from 26.4% (15.0–37.8) in the Eastern Mediterranean Region to 55.2% (43.0–67.4) in the European Region (table 2; figures 4, 5). These reductions were sustained in nine countries (which contributed up to 31 sites), all in the Region of the Americas, for 6–10 years after rotavirus vaccine introduction (figures 4, 5). The European Region documented the largest percentage decrease in rotavirus positivity after vaccine introduction (table 2).

Two regions, the African Region and the Region of the Americas, had pre-vaccine and post-vaccine data available from sites in both Gavi-eligible and Gavi-ineligible countries. When analysis was restricted to these regions and stratified by Gavi eligibility, the proportion of children hospitalised who were positive for rotavirus in these two regions combined declined by 35.1% (95% CI 28.9–41.2) in Gavi-eligible sites, from 38.6% in the pre-vaccine period to 25.0% in the post-vaccine period ($p<0.0001$). By contrast, there was a 41.5% (95% CI 29.0–54.1) relative reduction in rotavirus gastroenteritis hospitalisations in Gavi-ineligible sites, from 35.9% in the pre-vaccine period to 21.0% in the post-vaccine period ($p<0.0001$). When comparing the mean percentage change among Gavi-eligible countries with that for Gavi-ineligible countries, these confidence limits overlapped.

In our first sensitivity analysis, considering sites that met the inclusion criteria and contributed data in both the pre-vaccine and post-vaccine periods, similar reductions were seen in the proportions of children hospitalised who had rotavirus gastroenteritis, with a 35·1% (95% CI 28·8–41·3) relative reduction overall, ranging from 23.5% (12.6–34.3) in the Eastern Mediterranean Region to 53.0% (39.8–66.3) in the European Region (table 2). A time series analysis confirmed these findings, with a 26.9% (13.9–37.9) reduction in admissions for rotavirus gastroenteritis noted in the post-vaccine period compared with the pre-vaccine period, when controlling for region, country, pre-vaccine and post-vaccine status, site-years, Gavi eligibility status, and the number of years since rotavirus vaccine introduction. When the number of years since rotavirus vaccine introduction were excluded from the model, we saw a 40.7% (33.9–46.7) reduction in admissions for rotavirus gastroenteritis. Similar reductions in the proportion of children hospitalised with acute gastroenteritis positive for rotavirus were observed in the remaining sensitivity analyses (table 2).

Of the 132 736 reported cases of rotavirus gastroenteritis, age was reported in 86 434 (65.1%). There was variability in the proportion of of these cases contributed by each region, with fewer cases from the South-East Asia Region and the Region of the Americas. Among rotavirus gastroenteritis cases in the pre-vaccine period, the median age of rotavirus gastroenteritis cases was 12 months (IQR 7–20), whereas after vaccine introduction, the median age was 15 months (9–25; $p<0.0001$). These figures did not appreciably change when the analysis was restricted to countries providing both pre-vaccine and post-vaccine data (data not shown). In the pre-vaccine period, 17.8% of rotavirus gastroenteritis cases occurred in the 0–5-month age group, 38.8% in the 6–11-month age group, 29.7% in the 12–23-month age group, and 13.7% in the 24–59-month age group (figure 6). In the post-vaccine period, the proportion of rotavirus gastroenteritis cases occurring in the 0–5-month age group decreased to 12.9% and that for 6–11-month age group decreased to 31.9%, whereas the proportion increased for both the 12–23-month age group (to 36.4%) and the 24–59-month age group (to 18.8%; $p<0.0001$).

Discussion

Globally, rotavirus prevalence among children younger than 5 years of age admitted with acute gastroenteritis to hospitals or emergency units decreased by nearly 40% in countries after introduction of rotavirus vaccines into their national immunisation programmes, whereas no such reduction was observed in regions where it was not introduced. This decline is similar to the reduction of 38% reported in a recent global literature review.[8] Previous impact analyses have shown declines in rotavirus gastroenteritis hospitalisations of 43–70% in African,[9,28,29] 67–69% in European,[10,11] 59–81% in Latin American,[30] and 40% in eastern Mediterranean[31] countries that have introduced rotavirus vaccines. In our study, the WHO European Region and the Region of the Americas similarly saw the greatest declines, which might be due to the higher vaccine effectiveness noted in these settings as compared with other regions.[14] Nevertheless, our data do not reach the magnitude of reduction seen in country-specific analyses; this discrepancy might be due to variability in the number of GRSN sites that contributed to the analysis over time. Length of time reporting to the GRSN, measured as site-years of data, varied by region. Some regions

contributed nearly equal numbers of site-years in the pre-vaccine and post-vaccine periods for some of the analyses, but one—the Region of the Americas—contributed substantially more site-years after rotavirus vaccine introduction owing to the early introduction of rotavirus vaccine in this region.[32] Regardless, all regions showed a decline in prevalence in nearly all years during the post-vaccine period. Nine countries showed sustained reductions for 6–10 years (the endpoint of the surveillance period analysed) following rotavirus vaccine introduction. Analysis with further years of surveillance data will determine longer term trends in these declines.

Most (62%) sites were from lower-income or middle- income settings, as defined by their Gavi eligibility. When stratifying the vaccine impact analysis by Gavi eligibility, we observed significant reductions in the proportion of children admitted to hospital with acute gastroenteritis who were positive for rotavirus in both eligible and ineligible countries, although Gavi-ineligible countries had slightly higher reductions in rotavirus positivity. This decline among Gavi-ineligible countries might result from the higher vaccine efficacy and effectiveness reported in high-income versus lower-income settings.[33] As expected, in countries and regions that had not introduced rotavirus vaccine during the surveillance period analysed, we found a stable burden of rotavirus disease.

Reported vaccination coverage has increased steadily in most countries that have introduced rotavirus vaccines into their national immunisation programmes.[26] Countries with low rotavirus vaccine coverage would not be expected to have substantial reductions in admissions for rotavirus gastroenteritis, and our second sensitivity analysis applied the most stringent criteria to the GRSN population, taking into account only cases enrolled at sites with continuous enrolment and national rotavirus vaccine coverage of 60% or more in the post-vaccine introduction period. This analysis showed a similar overall reduction of nearly 40%, with greater reductions in some regions similar to the main analysis. This suggests two points: first, given that only four datapoints were excluded for not achieving this coverage cutoff, this is an indication of strong immunisation programmes in countries once rotavirus vaccine is introduced because the majority achieve coverage greater than 60%. Second, similar to the USA, where a reduction in admissions for rotavirus gastroenteritis was seen at around 60% coverage, even moderate coverage would expect to yield a significant decrease in rotavirus gastroenteritis hospitalisations. This could have a profound impact on use of medical facilities and associated costs.

The age distribution of rotavirus infection shifted slightly upwards in the post-vaccine period. This shift has been described in countries with established rotavirus vaccine programmes. In Rwanda, the cumulative age distribution of rotavirus gastroenteritis cases showed a rightwards shift, with 56% of rotavirus gastroenteritis hospital admissions occurring among infants in the pre-vaccine period compared with 31% after rotavirus vaccine introduction.[29] Similarly, in Bolivia, there was a decrease in the proportion of rotavirus gastroenteritis cases occurring by 12 months of age, from 67% in the pre-vaccine period to 55% in the post-vaccine period.[34] This was also seen in Malawi[35] and in Brazil; data from the latter show the mean age of rotavirus infection increased by more than 7 months after rotavirus vaccine introduction.[36] Whether this shift in the proportion of rotavirus gastroenteritis cases to older ages is a reflection of improved protection shortly

after vaccination, whether this shift will diminish over time as all cohorts up to 5 years of age are vaccinated, or whether the absolute number of rotavirus gastroenteritis cases will change all remain to be seen. Additionally, there might be differential enrolment practices by age between pre-vaccine and post-vaccine countries that would affect this age distribution; this would need further study.

Our analysis is subject to several limitations. First, sites included in the impact analysis dropped in and out of the analysis over time as they succeeded or failed to meet the analytical inclusion criteria of enrolment and testing of children every month of a calendar year with at least 100 specimens per year. As such, the same sites and countries were not always included in both pre-vaccine and post-vaccine periods. We did a separate analysis with countries that had both pre-vaccine and post-vaccine data available and findings were similar.

Second, owing to the ecological design of this analysis, we were unable to determine the vaccination status of individual children and we classified our study population as pre-vaccine or post-vaccine based on rotavirus vaccine availability in the country's national immunisation programme. In post-vaccine periods, we assumed that coverage rates at the sentinel sites were equivalent to WHO/UNICEF national coverage estimates. In pre-vaccine periods, we were unable to account for children who might have received rotavirus vaccine in the private sector or in another country. We classified the year of vaccine introduction as part of the pre-vaccine period, which provided a more conservative estimate of rotavirus vaccine impact than if we had included it in the post-rotavirus vaccine period. This is because as rotavirus vaccine was introduced in a country and uptake steadily increased, the proportion of acute gastroenteritis cases due to rotavirus would be expected to decrease; this might have resulted in a larger reduction if rotavirus vaccine was introduced early in the year, and a high coverage was reached, whereas it would be smaller if rotavirus vaccine was introduced towards the end of the year and coverage levels were modest. Either way, our classification of the pre-vaccine and post-vaccine periods might have led to an underestimate of the true impact. Our estimates of rotavirus vaccine impact might also have been reduced in countries with low coverage in their national immunisation programmes or high coverage through the private market. We addressed the effect of countries with low rotavirus vaccine coverage with the second sensitivity analysis, where the study population was restricted to children from countries with annual rotavirus vaccine coverage of at least 60%, and found similar reductions as in the main analysis.

Third, although 198 of the 349 sites that participated in the GRSN during the surveillance period fulfilled criteria for inclusion into our impact analysis, 151 sites did not. The relative proportion of site-years contributed by region to the main analysis was similar to those excluded from the analysis, with the exception of the European Region and the Western Pacific Region. Both of these regions had smaller proportions of excluded site-years than proportions of site-years included in the main analysis. Any exclusion of site-years highlights the need to encourage high-quality surveillance year round.

Finally, we were unable to measure the impact of rotavirus vaccine on mortality through our data. Too few deaths were reported in the GRSN sites, for reasons that probably vary by

country, and diarrhoea deaths often occur in the community in lower-resource settings, which necessitates doing community-based studies[37] or relying on modelling activities to estimate the global impact of rotavirus vaccine on mortality.[38] Despite these limitations, we were able to show significant, consistent reductions in hospital admissions for acute gastroenteritis due to rotavirus in all subgroups. These findings, derived from our cohort of more than 400 000 children who were enrolled and tested by systematic, standardised methods, provide strong evidence for the impact of rotavirus vaccine in countries that have introduced them.

In conclusion, rotavirus vaccine introduction was followed by significant declines globally in the proportion of acute gastroenteritis cases caused by rotavirus among children younger than 5 years of age in sites reporting to the GRSN. This analysis highlights the importance of continuous, systematic surveillance in all regions for monitoring disease burden and documenting rotavirus vaccine impact. Our findings should encourage consideration of rotavirus vaccine introduction in countries that have not yet introduced the vaccine. Several countries in Africa and southeast Asia have introduced rotavirus vaccine after the surveillance period reported in this analysis, and other countries are planning to introduce the vaccine in the near future. As countries with high rotavirus gastroenteritis burden introduce rotavirus vaccines, high-quality, routine surveillance will continue to play a key role in showing the changing epidemiology of rotavirus gastroenteritis as well as the beneficial impact of rotavirus vaccine worldwide.[39]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Global Rotavirus Surveillance Network receives funding from Gavi, the Vaccine Alliance. No funding was provided for the preparation of this manuscript. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. We would like to acknowledge the Global and Regional Rotavirus Reference Laboratories, particularly Michael D Bowen, George Armah, Mapaseka L Seheri, Carl Kirkwood, Sarah Thomas, Elena Samoilovich, Gagandeep Kang, Jose Paolo G Leite, Hyesook Yeong, Duan Zhaojun, Liu Na, Ziqian Xu, and Dandi Li, for supporting the surveillance network.

Funding The GRSN receives funding from Gavi, the Vaccine Alliance and the US Centers for Disease Control and Prevention. No specific funding was provided for this Article.

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Research in context

Evidence before this study

We searched PubMed up to March, 2018, for systematic meta-analyses, literature reviews, and original research published in English using the search terms “rotavirus” and “rotavirus vaccine”. The introduction of rotavirus vaccines into national immunisation programmes worldwide has shown reductions in admissions to hospital for acute gastroenteritis in children younger than 5 years of age in country-specific analyses of vaccine impact. Additionally, literature reviews and systematic analyses from secondary sources have provided a global assessment of rotavirus vaccine impact.

Added value of this study

The establishment of WHO’s Global Rotavirus Surveillance Network (GRSN) in 2008 has allowed for standardised enrolment of children younger than 5 years of age for active hospital-based diarrhoea surveillance. Countries from all six WHO regions participate in the GRSN. To our knowledge, this Article provides the first analysis of global rotavirus vaccine impact using prospective active surveillance data from a globally representative set of primarily low-income and middle-income countries from all regions of the world. Using primary data in children younger than 5 years of age, we show significant reductions in the proportion of hospital admissions for acute gastroenteritis due to rotavirus in all WHO regions that have introduced rotavirus vaccines, with a global reduction of nearly 40%.

Implications of all the available evidence

The beneficial impact of rotavirus vaccines is shown globally; countries that have not yet introduced rotavirus vaccines into their national immunisation programmes should consider adding these life-saving vaccines. Additionally, countries with and without rotavirus vaccines should do high-quality surveillance to document burden of rotavirus acute gastroenteritis hospitalisations, both before and after vaccine introduction.

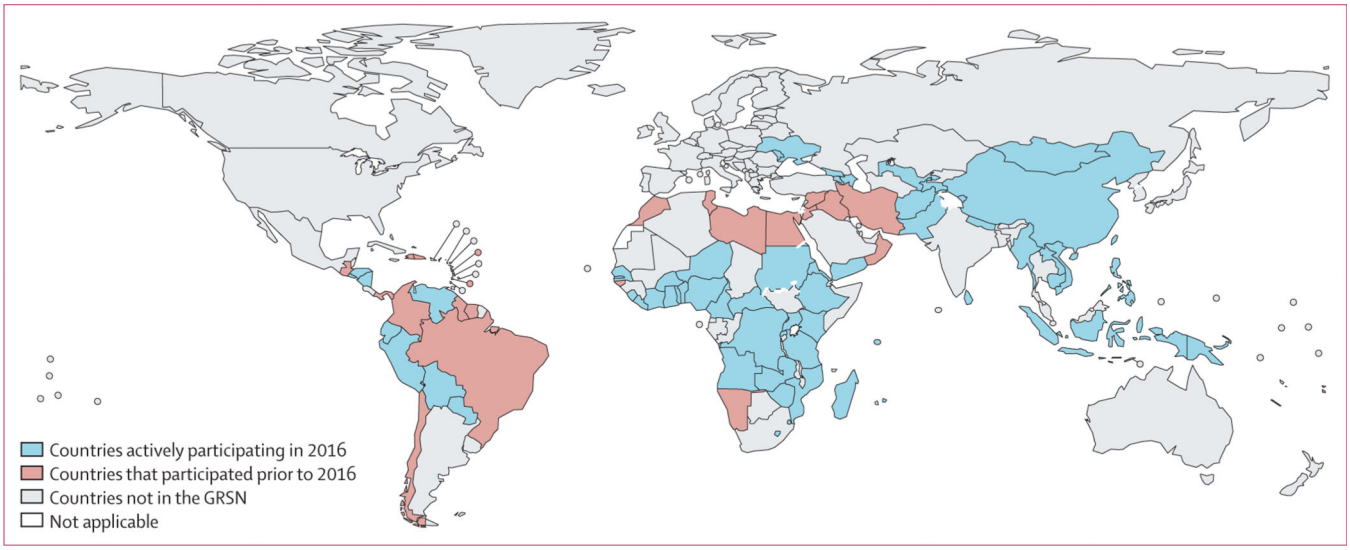

Figure 1: Countries participating in the GRSN

The map shows all countries that participated in 2016 and those that only participated during any of the years 2008–15, separately. Not applicable refers to disputed areas. GRSN=Global Rotavirus Surveillance Network.

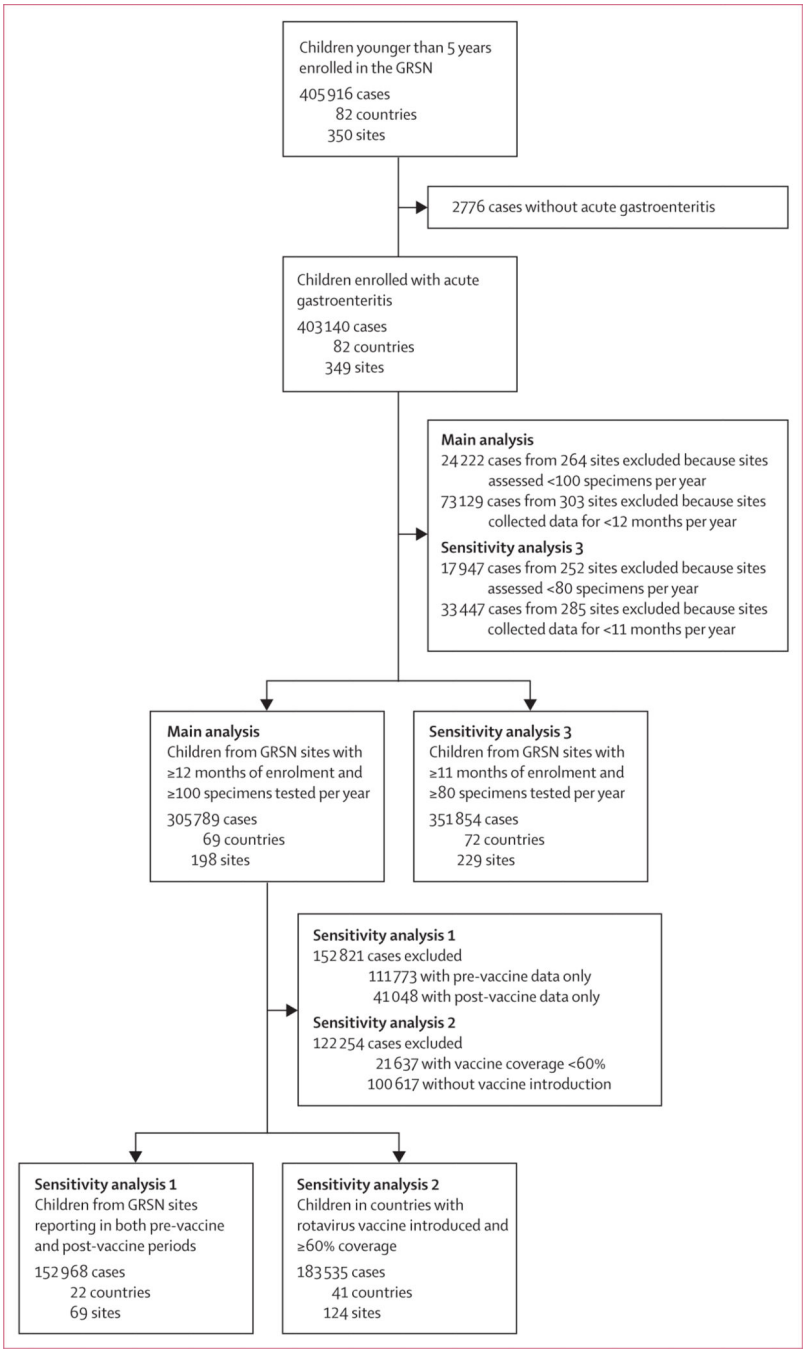

Figure 2: Data selection for analysis of global impact of rotavirus vaccine on acute gastroenteritis hospitalisations among children younger than 5 years of age enrolled in the GRSN, 2008–16

Sites could be excluded for more than one reason. GRSN=Global Rotavirus Surveillance Network.

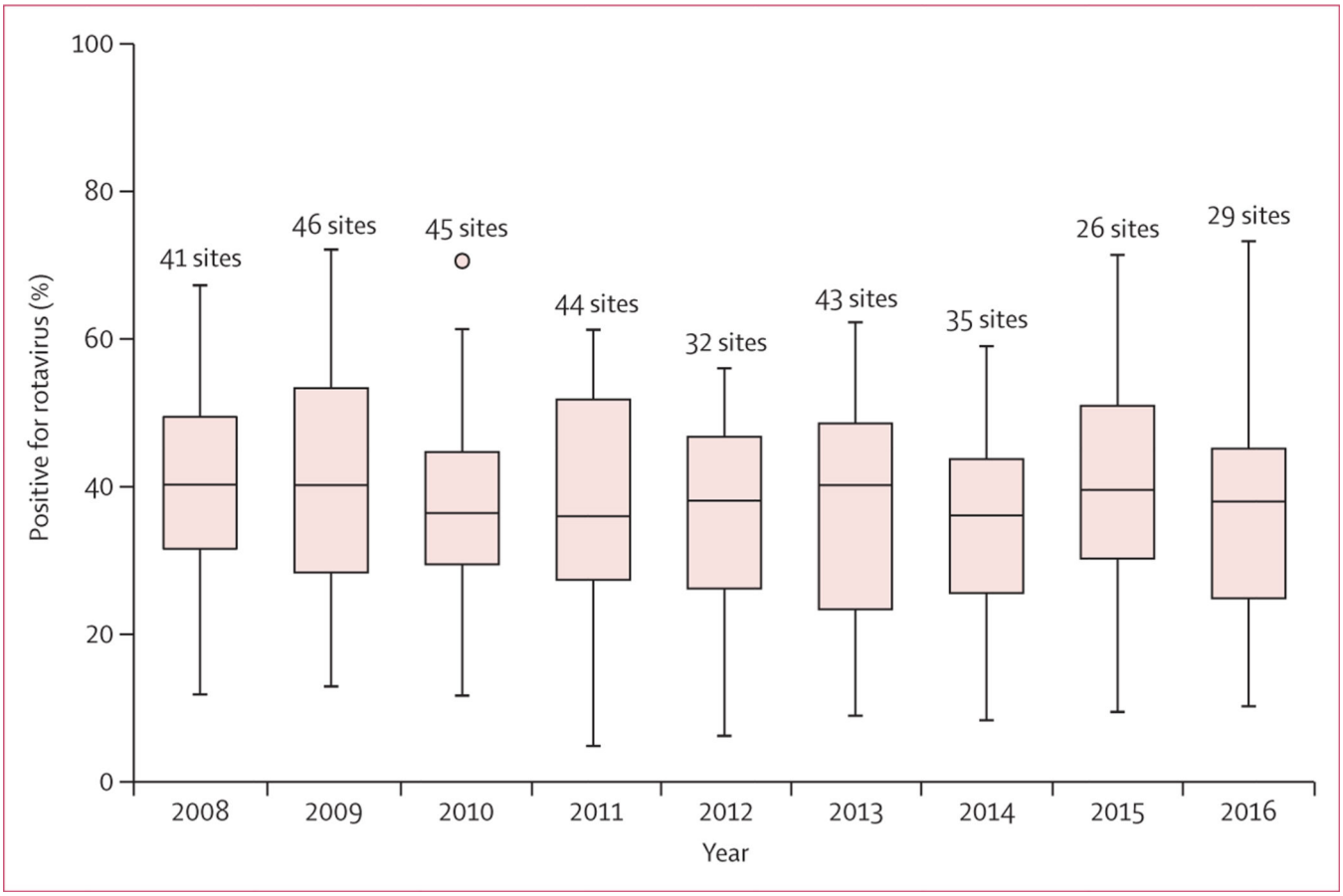

Figure 3: Rotavirus positivity in countries without rotavirus vaccine, 2008–16

Pre-vaccine data from countries that have introduced rotavirus vaccines as well as data from countries that have not yet introduced rotavirus vaccines. Data are from all sites in countries meeting inclusion criteria and reporting to the Global Rotavirus Surveillance Network. Boxplots depict median, 25th, and 75th percentile values. Whiskers denote variability beyond these upper and lower quartiles, with individual dots representing outliers.

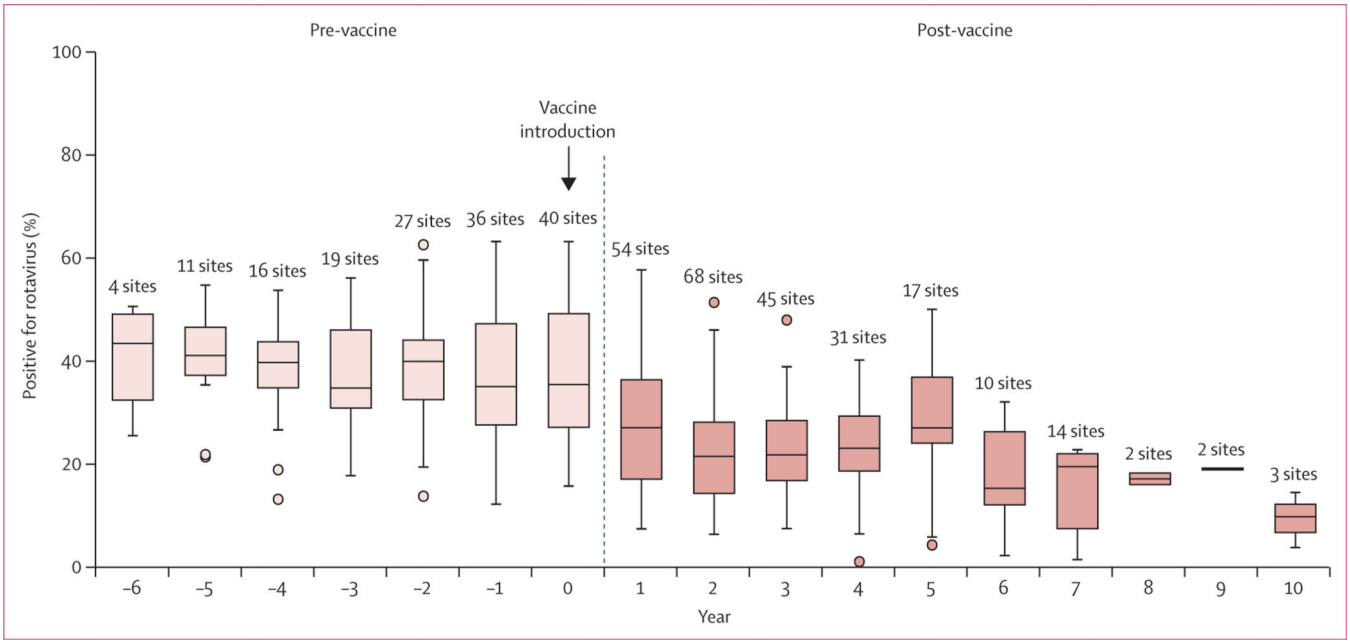

Figure 4: Rotavirus positivity in countries with rotavirus vaccine, 2008–16

Post-vaccine data are shown from countries that have introduced rotavirus vaccine. Year is calculated in reference to vaccine introduction year (year 0). Data are from all sites in countries meeting inclusion criteria and reporting to the Global Rotavirus Surveillance Network. Boxplots depict median, 25th, and 75th percentile values. Whiskers denote variability beyond these upper and lower quartiles, with individual dots representing outliers.

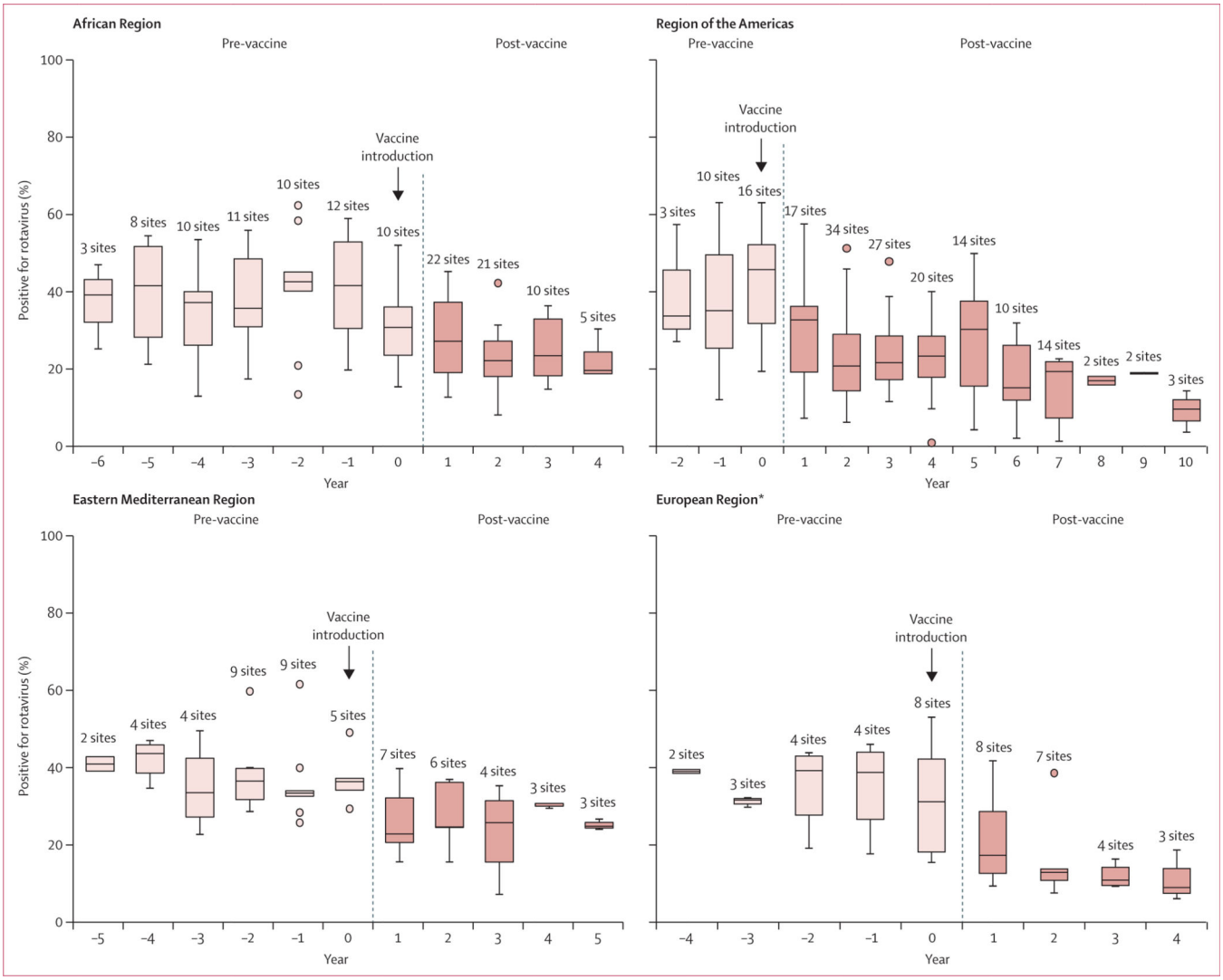

Figure 5: Rotavirus positivity in countries with rotavirus vaccine, by region, 2008–16

Year is calculated in reference to vaccine introduction year (year 0). Data are from sites in countries reporting to the Global Rotavirus Surveillance Network. Boxplots depict median, 25th, and 75th percentile values. Whiskers denote variability beyond these upper and lower quartiles, with individual dots representing outliers. *Two datapoints for pre-vaccine years −5 and −6 were removed from the figure for the European region given only one site contributed for each of these years.

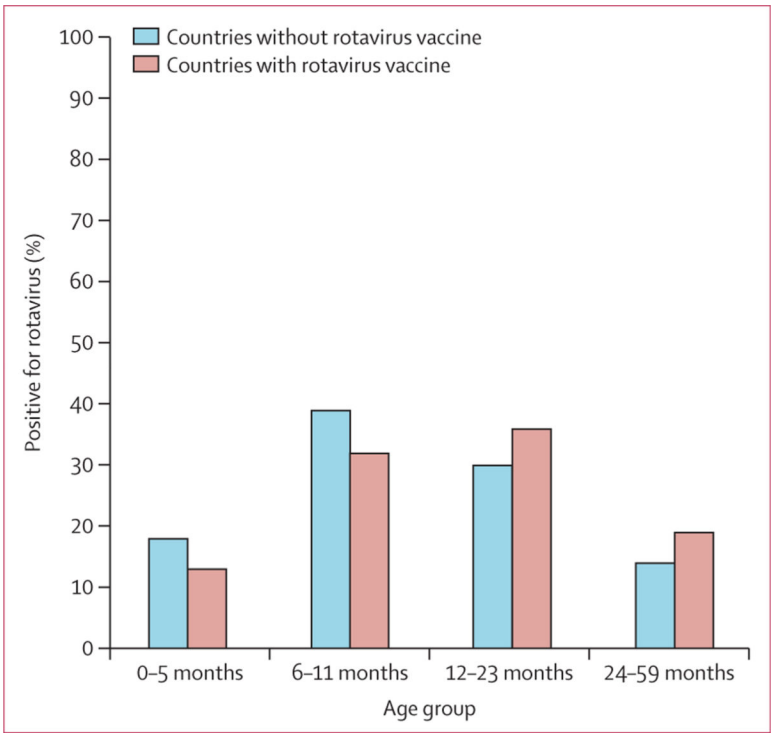

Figure 6: Age distribution of children positive for rotavirus in countries with and without rotavirus vaccine introduction reporting to the Global Rotavirus Surveillance Network, 2008–16

Countries with rotavirus vaccine comprise cases of rotavirus gastroenteritis from all countries that have introduced a rotavirus vaccine. Countries without rotavirus vaccine comprise cases of rotavirus gastroenteritis from countries that have not introduced a rotavirus vaccine and cases that occurred before introduction of the vaccine in those countries that have introduced a vaccine.

Table 1:

Description of hospital admissions for acute gastroenteritis among children aged 0–59 months by WHO region from all sites and sites meeting inclusion criteria, Global Rotavirus Surveillance Network, 2008–16

	All sites					Sites meeting inclusion criteria*				
	Site-years†	Countries (number Gavi eligible‡)	Sites (number Gavi eligible)	Participants tested	Positive for rotavirus	Site-years†	Countries (number Gavi eligible‡)	Sites (number Gavi eligible)	Participants tested	Positive for rotavirus
African Region	373	31 (27)	82 (74)	84 108	30 676 (36·5%)	141	24 (22)	48 (43)	56 301	19 318 (34·3%)
Region of the Americas	504	19 (4)	111 (23)	87 501	22 389 (25·6%)	178	14 (3)	65 (20)	60 433	15 466 (25·6%)
Eastern Mediterranean Region	347	13 (4)	94 (22)	78 787	27 454 (34·8%)	106	12 (4)	35 (17)	56 530	18 493 (32·7%)
European Region	87	7 (7)	17 (17)	96 411	26 831 (27·8%)	71	7 (7)	16 (16)	87 561	23 727 (27·1%)
South-East Asia Region	65	4 (4)	18 (18)	13 126	6674 (50·8%)	21	4 (4)	11 (11)	9231	3359 (36·4%)
Western Pacific Region	116	8 (6)	27 (19)	43 207	18 712 (43·3%)	70	8 (6)	23 (16)	35 733	15 835 (44·3%)
All regions	1492	82 (52)	349 (173)	403 140	132 736 (32·9%)	587	69 (46)	198 (123)	305 789	96 198 (31·5%)

*Inclusion criteria were sites enrolling, collecting, and testing ≥100 specimens per year for 12 months per year.

†Site-years are the cumulative total number of years contributed by sites during the surveillance period.

‡Countries were classified as Gavi eligible if they had ever qualified for Gavi funding during the surveillance period.

Table 2:

Rotavirus testing and positivity by WHO region and rotavirus vaccine introduction status among children for main analysis and sensitivity analyses, Global Rotavirus Surveillance Network, 2008–16

	African Region		Region of the Americas		Eastern Mediterranean Region		European Region		South-East Asia Region (pre-vaccine)	Western Pacific Region (pre-vaccine)*	All regions	
	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine			Pre-vaccine	Post-vaccine
Main analysis: all sites meeting inclusion criteria												
Site-years	83	58	35	143	83	23	49	22	21	70	341	246
Children tested	35194	21107	11940	48493	39158	17372	55364	32197	9231	35733	186 620	119169
Positive for rotavirus	13 881	5437	4333	11133	13 878	4615	19486	4241	3359	15 835	70 772	25426
Mean proportion of children positive for rotavirus (range) †	38–2% (12·9–66·2)	25–0% (8·0–45·5)	37·5 (4·8–63·2) NJ ^	22·7% (0·7–57·7)	35·7% (8·3–73·4)	26·3% (7·0–39·8)	36·3% (6·2–67·4)	16–3% (6·0–41·9)	37–2% (21·4–56·3)	42–3% (10·2–70·6)	38–0% (4·8–73·4)	23–0% (0·7–57·7)
Percentage reduction in proportion of children positive for rotavirus (95% Cl)	..	34–5% (27·0–42·0)	..	39·6% (29·7–49·4)	..	26·4% (15·0–37·8)	..	55–2% (43·0–67·4)	..	..	..	39–6% (35·4–43·8)
Sensitivity analysis 1: sites meeting inclusion criteria and reporting data from both pre-vaccine and post-vaccine introduction periods‡												
Site-years	52	28	29	66	21	23	23	22	..	..	125	139
Children tested	20551	10090	8417	18462	17135	17372	28744	32197	..	..	74 847	78121
Positive for rotavirus	8159	2366	3476	5149	5928	4615	9571	4241	..	..	27134	16371
Mean proportion of children positive for rotavirus (range) †	36–8% (12·9–62·4)	23–0% (8–45·5)	409% (11·8–63·2)	26–1% (1·0–57·7)	34–4% (22–5-49–0)	26–3% (7·0–39·8)	34–6% (15·3–53·2)	16–3% (6·0–41·9)	..	..	36–9% (11·8–63·2)	24–0% (1·0–57·7)
Percentage reduction in proportion of children positive	..	37·3% (26·6–48·0)	..	36·1% (25·0–47·2)	..	23·5% (12·6–34·3)	..	53·0% (39·8–66·3)	..	..	..	35·1% (28·8–41·3)

	African Region		Region of the Americas		Eastern Mediterranean Region		European Region		South-East Asia Region (pre-vaccine)	Western Pacific Region (pre-vaccine)*	All regions	
	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine	Pre-vaccine	Post-vaccine			Pre-vaccine	Post-vaccine
for rotavirus (95% Cl)												
Sensitivity analysis 2: sites meeting inclusion criteria and with national full-dose rotavirus vaccine coverage ≥60% in the post-vaccine introduction periods												
Site-years	58	58	19	140	28	23	18	20	..	4	127	241
Children tested	25264	21107	5882	47626	14752	17372	20450	29983	..	1099	67 447	116088
Positive for rotavirus	10184	5437	2454	10992	5355	4615	7692	3775	..	382	26067	24819
Mean proportion of children positive for rotavirus (range) †	38–7% (12·9–62·4)	25·0% (8·0–45·4)	39·6% (11·8–63·2)	22·8% (0·7–57·7)	37·3% (22·5–61·4)	26·3% (7·0–39·8)	37·2% (17·5–53·2)	14·8% (6·0–38·6)	..	33·7% (21·9–49·6)	38·2% (11·8–63·2)	23·0% (0·7–57·7)
Percentage reduction in proportion of children positive for rotavirus (95% Cl)	..	35·3% (27·3–43·3)	..	42–5% (31·3–53·7)	..	29·6% (19·0–40·1)	..	60–1% (49·3–70·9)	..	..	..	39·8% (34·5–44·5)
Sensitivity analysis 3: sites enrolling and testing ≥80 children per year and for a minimum of 11 months per calendar year during the surveillance period												
Site-years	133	71	52	197	116	25	56	22	31	84	472	315
Children tested	46 862	23429	14729	58559	47 5 83	17992	60 981	32197	10788	38626	219569	132177
Positive for rotavi rus	18483	6054	5209	13500	17484	4764	21364	4241	4177	17005	83722	28559
Mean proportion of children positive for rotavirus (range) †	39·3% (12·0–73·1)	25·2% (3·0–64·6)	32–7% (1·3–77·4)	22–9% (0·7–63·1)	37–1% (8·3–73·4)	26–7% (7·0–45·3)	36–0% (6·2–68·0)	16–3% (6·0–41·9)	42·1% (21·4–68·0)	41–8% (8·0–70·6)	38–3% (1·3–77·4)	23–2% (0·7–64·6)
Percentage reduction in proportion of children positive for rotavirus (95% Cl)	..	35·9% (28·7–43·2)	..	29·9% (18·1–41·8)	..	28·2% (17·5–38·9)	..	54·8% (42·5–67·1)	..	..	..	39·3% (35·4–43·2)

All percentage reductions were significant (p <0–0001) compared with pre-vaccine introduction using χ^2 testing.

* One site in the Western Pacific region had introduced rotavirus vaccine and had data available from the pre-vaccine period only.

† Average of the calculated means for all included sites.

‡ Vaccine introduction year included in the pre-vaccine period.