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Global impact of rotavirus vaccination on diarrhea hospitalizations and deaths among children <5 years old: 2006–2019

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Abstract

Since 2006, more than 100 countries have introduced rotavirus vaccine into their immunization programs. We reviewed published data on relative reductions of rotavirus hospitalizations, acute gastroenteritis (AGE) hospitalizations, and AGE deaths among children <5 years old. Articles published from 1 January 2006 to 31 December 2019 with at least 12 months of data before and after rotavirus vaccine introduction were included. Relative reductions were abstracted into a standardized form. Descriptive statistics are presented as medians and interquartile ranges (IQR). We reviewed 1827 total records and included 105 articles from 49 countries. Among children <5 years old, there was a median reduction of 59% (IQR: 46, 74) in rotavirus hospitalizations, 36% (IQR: 23, 47) in AGE hospitalizations, and 36% (IQR: 28, 46) AGE mortality. Reductions were larger in countries with low child mortality, among younger age groups, and in countries with higher coverage. The median percentage of specimens that tested positive for rotavirus among children <5 years old hospitalized for diarrhea was 40% (IQR: 28, 45) before rotavirus vaccine introduction and 20% (IQR: 20, 20) 4 years after introduction. Overall, we found sustained impact on rotavirus and AGE hospitalizations and deaths. These results should encourage countries still considering rotavirus vaccine implementation.

Summary:

105 peer-reviewed articles from the first 14 years of rotavirus vaccine implementation show substantial reductions in rotavirus and acute gastroenteritis hospitalizations, with the largest decreases in countries with low child mortality and higher coverage, and among younger age groups.

Keywords

Rotavirus; acute gastroenteritis; rotavirus vaccine; impact; literature review

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Introduction

In 2013, more than 200,000 estimated deaths due to rotavirus occurred among children <5 years old worldwide, representing 37% of diarrhea deaths in this age group [1]. Since 2 live, oral rotavirus vaccines (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium and RotaTeq Merck & Co., West Point, PA, USA) were first licensed in 2006 and rotavirus vaccines were recommended for all countries by the World Health Organization (WHO) in 2009, more than 100 countries have introduced rotavirus vaccine into their routine infant immunization schedule [2, 3]. There has been a notable impact on rotavirus disease and all-cause acute gastroenteritis (AGE) in countries that have implemented rotavirus vaccination. Data from the WHO-coordinated Global Rotavirus Surveillance Network reported a 40% relative decline in rotavirus positive specimens among children <5 years old hospitalized for diarrhea and an earlier systematic literature review found a median 80% reduction in rotavirus hospitalizations among children <1 year old [4, 5].

Since our last review of the impact of rotavirus vaccines on rotavirus and AGE hospitalizations and deaths, about 20 additional countries have introduced a rotavirus vaccine and more than 50 additional articles on rotavirus vaccine impact have been published. In particular, evidence of vaccine impact from high-burden settings in Africa has greatly increased. In this literature review, we summarize the published relative reductions of rotavirus hospitalizations, AGE hospitalizations, and AGE deaths among children <5 years old after rotavirus vaccine implementation from individual countries.

Methods

Literature search and selection criteria

We searched PubMed for articles published in English from 1 January 2006 to 31 December 2019 that included the terms “rotavirus” and either “vaccin*” or “immuni*” in the title. As Rotasiil (Serum Institute of India Pvt. Ltd., Pune, India), and ROTAVAC (Bharat Biotech International Ltd., Hyderabad, India) are newly WHO pre-qualified and Rotavin (PolyVac, Hanoi, Vietnam) and Lanzhou lamb rotavirus vaccine (Lanzhou Institute of Biological Products, Lanzhou, China) are not available outside of Vietnam and China, respectively, this review includes data only from places where Rotarix and/or RotaTeq were used. We excluded articles that did not present primary data; were guidelines, coverage findings, or programmatic descriptions; or otherwise were irrelevant to this review’s objectives. We included articles that had at least 12 months of data from before and after rotavirus vaccine introduction for children <5 years old; articles reporting analyses of only partial years data for months associated with the rotavirus season were excluded. Findings for age groups other than <1 year old, 12–23 months, 24–59 months, and <5 years old were included if the results were presented in a way that allowed us to calculate the results for these standardized age groups. We also excluded subpopulations that may not be representative of the general pediatric population, such as NICU patients. We included data where the outcome was death or hospitalizations and emergency department visits (collectively referred to as hospitalizations) due to community-acquired rotavirus or AGE; we excluded data where the outcome was outpatient visits or other healthcare seeking, such as google searches and telephone triage, and where the outcome was hospital-acquired rotavirus or AGE.

In cases where multiple articles presented findings from the same dataset, we included all articles that had at least one unique datapoint by outcome, time period, or subpopulation; when more than one article presented the same analysis, we only included the datapoint from the most recent article. In articles that included more than one population within a country without an aggregated impact estimate or more than one country, all findings meeting our analysis criteria were included with each place as a separate observation. Where summary results from multiple countries were not disaggregated, we excluded the article. Subnational introductions, situations where rotavirus vaccine is only available on the private market, and demonstration projects were included if they met the other criteria.

Data abstraction and definitions

A Microsoft Excel data entry form was developed which captured the relative reductions for each outcome, age group, and year normalized for rotavirus vaccine introduction as well as the percentage of rotavirus positive specimens by age group and normalized year. The data entry form included other information from each article such as the country where the evaluation was conducted; the vaccine brand in use and date of introduction; estimated coverage of the complete rotavirus vaccination series; whether changes in the age distribution, seasons, and length of hospital stay were noted the article; and whether the original data were rates, relative proportions, or absolute numbers of hospitalizations. Data was abstracted by one reviewer (EB).

We supplemented information abstracted from the selected articles with 2017 estimates of <5 year old child mortality from Unicef and annual coverage of the completed rotavirus vaccination series from Wuenic [6, 7]. We categorized countries into 3 child mortality strata: lowest quartile (“low”); 2nd quartile (“medium”); and the 3rd and 4th quartiles (“high”). We considered Taiwan and Hong Kong to be low mortality, based on locally published mortality rates [8]. For vaccine coverage, we selected the higher coverage estimate between Wuenic and article-reported rotavirus vaccination coverage for each year of surveillance because coverage is often heterogenic within countries and we assumed the catchment areas of sentinel surveillance hospitals may have better healthcare infrastructure than the country overall. We created 3 programmatically-relevant coverage categories: <65%, 65– 84%, and ≥85%. As the coverage analysis considered each surveillance year separately, one observation could have datapoints from different years included in more than one coverage category.

Analysis

All descriptive statistics are presented as medians and interquartile ranges (IQR) or numbers and percentages. For analyses that present data summarized over multiple years, medians for individual observations were calculated from presented findings, excluding the year of rotavirus vaccine introduction, where a summary was not provided by the article. Similarly, if an observation presented annual data for any years relative to rotavirus vaccine introduction, it was included in the relevant analyses. The analysis of relative reductions by rotavirus vaccine coverage is limited to observations where the original data was presented as a rate in low mortality strata countries.

As a sensitivity analysis, we compared median relative reductions within a child mortality strata by data type where there were at least 3 observations in each data type category (absolute number, proportion of hospitalizations, and rate) for one hospitalization outcome. We also assessed the correlation between data type and child mortality strata using Pearson's correlation coefficients and considered a p-value of <0.05 to be significant.

All analyses were performed using SAS v9.4 and R v3.5.2.

Results

This literature review included 105 articles that present ecological impact of rotavirus vaccine on rotavirus and AGE deaths or hospitalizations. We reviewed 1,827 total records and read 437 abstracts (Figure 1). Of the 162 full text articles reviewed, 20 presented data from the same dataset and time period as a more recent article, 18 presented partial year or seasonal data, 14 used an alternative method of assessing impact, and 5 presented estimates for alternate <5 year old age groups. In total, we included 128 unique observations from 49 countries (Figure 2). There were 66 (52%) observations from countries in the low child mortality strata, 20 (16%) from the medium child mortality strata, and 42 (33%) from the high child mortality strata. Nearly all (90%, n=115) were from countries with universal rotavirus vaccine introduction, 2 (2%) were in demonstration project settings, and 11 (9%) in settings where rotavirus vaccine was available on the private market. Fifty-seven (45%) observations used rates and rate ratios, 43 (34%) used percentages, and 36 (28%) used absolute numbers to calculate relative reductions in AGE or rotavirus hospitalizations. The full list of articles is included in supplementary table 1.

Overall reductions by mortality strata

Among children <1 year old, there was a median reduction of 70% (IQR: 55, 83) in rotavirus hospitalizations, 34% (IQR: 24, 47) in AGE hospitalizations, and 31% (IQR: 18, 45) in AGE mortality compared with before rotavirus vaccine introduction (Figure 3a). The median reduction in rotavirus hospitalizations was 78% (IQR: 65, 85) in the low child mortality strata, 76% (IQR: 69, 79) in the medium strata, and 55% (IQR: 41, 64) in the high strata (Figure 4a). The median reduction in AGE hospitalizations was 39% (IQR: 27, 47) in the low child mortality strata, 31% (IQR: 26, 42) in the medium strata, and 26% (IQR: 20, 46) in the high strata (Figure 4b). The median reduction in AGE mortality was 38% (IQR: 17, 45) in the medium strata and 30% (IQR: 22, 32) in the high strata (Figure 4c). Among children <5 years old, there was a median reduction of 59% (IQR: 46, 74) in rotavirus hospitalizations, 36% (IQR: 23, 47) in AGE hospitalizations, and 36% (IQR: 28, 46) AGE mortality compared with before introduction (Figure 3b). The median reduction in rotavirus hospitalizations was 66% (IQR: 49, 76) in the low child mortality strata, 59% (IQR: 49, 59) in the medium strata, and 50% (IQR: 41, 65) in the high strata (Figure 4d). The median reduction in AGE hospitalizations was 38% (IQR: 26, 44) in the low child mortality strata, 30% (IQR: 20, 39) in the medium strata, and 36% (IQR: 20, 50) in the high strata (Figure 4e). The median reduction in AGE mortality was 36% (IQR: 34, 50) in the medium strata and 37% (IQR: 24, 41) in the high strata (Figure 4f).

Annual percentage positive by age group

The median percentage of specimens that tested positive for rotavirus among children <5 years old hospitalized for diarrhea was 40% (IQR: 28, 45) before rotavirus vaccine introduction (Figure 5a), 27% (IQR: 19, 34) the year of vaccine introduction, 20% (IQR: 14,29) 1 year after introduction, 19% (IQR: 11, 25) 2 years after introduction, 23% (IQR: 16, 27) 3 years after introduction, and 20% (IQR: 20, 20) 4 years after introduction. The median percent rotavirus positive among children <1 year old was 43% (IQR: 30, 47) before rotavirus vaccine introduction (Figure 5b), 29% (IQR: 23, 38) in the year of vaccine introduction, 19% (IQR: 10,29) in year 1, 17% (IQR: 12, 24) in year 2, 18% (IQR: 15, 25) in year 3, and 14% (IQR: 13, 21) in year 4 post-vaccine introduction. The median percent positive among children 12–23 months old was 38% (IQR: 31, 47) before rotavirus vaccine introduction (Figure 5c), 31% (IQR: 28, 34) in the year of vaccine introduction, 26% (IQR: 21, 28) in year 1, 17% (IQR: 12, 24) in year 2, 23% (IQR: 19, 36) in year 3, and 20% (IQR: 13, 30) in year 4 post-vaccine introduction. The median percent positive among children 24–59 months old was 28% (IQR: 18, 35) before rotavirus vaccine introduction (Figure 5d), 25% (IQR: 17, 30) in the year of vaccine introduction, 17% (IQR: 14, 26) in year 1, 14% (IQR: 8, 15) in year 2, 15% (IQR: 15, 25) in year 3, and 17% (IQR: 12, 19) in year 4 post-vaccine introduction. Although the percentage positive was highest in the high child mortality group each year, the observed trend in children <5 years old was consistent across the 3 child mortality strata (Supplementary figure 1); there was insufficient data to repeat the age group analysis by child mortality strata.

Reductions by year and age group

AGE hospitalizations were reduced by a median of 20% among children <1 year old the year rotavirus vaccine was introduced, 31% in year 1 which was the first year all children <1 year old would have been eligible for vaccination, and 62% after 7 complete years of rotavirus vaccine availability (Figure 6a). Among children 12–23 months old, AGE hospitalizations were reduced by a median of 7% the year rotavirus vaccine was introduced, 27% the first year all children 12–23 months would have been eligible for vaccination (year 2), and 76% in year 7. Among children 24–59 months old, AGE hospitalizations were reduced by a median of 2% the year rotavirus vaccine was introduced, 47% the first year all children 24–59 months would have been eligible for vaccination (year 6), and 61% in year 7. Among children <1 year old, rotavirus hospitalizations were reduced by a median of 47% the year rotavirus vaccine was introduced, 70% in year 1, and 97% in year 7 (Figure 6b). Among children 12–23 months old, rotavirus hospitalizations were reduced by a median of 32% the year rotavirus vaccine was introduced, 56% in year 2, and 99% in year 7. Among children 24–59 months old, rotavirus hospitalizations were reduced by a median of 32% the year rotavirus vaccine was introduced, 80% in year 6, and 97% in year 7.

Rate reductions by coverage

Among children <1 year old, there was a median 30% (IQR: 28, 32) rate reduction in AGE hospitalizations where rotavirus vaccine coverage was <65%, 37% (IQR: 29, 52) where coverage was 65–84%, and 47% (IQR: 38, 50) where coverage was ≥85% (Supplementary Figure 2a). There was a median 43% (IQR: 38, 58) rate reduction in rotavirus

hospitalizations where rotavirus vaccine coverage was <65%, 79% (IQR: 63, 82) where coverage was 65–84%, and 85% (IQR: 75, 94) where coverage was ≥85% (Supplementary Figure 2b). There was insufficient data in each of the coverage groups to repeat the analysis for the other mortality strata or using reductions calculated from proportion positive.

Sensitivity analysis

There was a statistically significant correlation between child mortality strata and both AGE hospitalization reduction data type (correlation coefficient: 0.38; $p<0.01$) and rotavirus hospitalization reduction data type (correlation coefficient: 0.65; $p<0.01$). Three analyses met the inclusion criteria for our sensitivity analysis, that is had at least 3 observations for each of 3 data types within 1 outcome and mortality strata: AGE hospitalizations among children <1 year old and <5 years old in high child mortality strata and rotavirus hospitalizations among children <5 years old in low child mortality strata. In the high mortality strata, the median reduction in AGE hospitalizations among children <1 year old was 25% (IQR: 24, 32) using absolute numbers, 42% (IQR: 33, 49) using AGE as a percentage of all hospitalizations, and 20% (IQR: 16, 42) using rates; among children <5 years old it was 36% (IQR: 19, 52) using absolute numbers, 36% (24, 37) using percent of all hospitalizations, and 31% (11, 53) using rates. In the low mortality strata, the median reduction in rotavirus hospitalizations among children <5 years old was 74% (IQR: 71, 82) using absolute numbers, 68% (IQR: 57, 84) using percent of specimens that tested positive, and 58% (IQR: 47, 76) using rates.

Discussion

In this literature review of rotavirus vaccine impact including 101 articles from 47 countries across different child mortality strata, we calculated a median relative reductions of 59% in rotavirus hospitalizations and of approximately 36% in AGE hospitalizations and mortality among children <5 years old following rotavirus vaccine introduction. Reductions in AGE and rotavirus hospitalizations increased over time after rotavirus vaccine introduction and were highest in settings with the highest rotavirus vaccine coverage. We found the median percentage of stool specimens that tested positive for rotavirus among children <5 years old was about 40% and declined to 20% after rotavirus vaccine introduction, which is comparable to multi-country findings from the WHO-coordinated Global Rotavirus Surveillance Network [4]. In all analyses, reductions in rotavirus hospitalizations were higher than AGE hospitalizations, which further supports that the declines are attributable to rotavirus vaccine as it only targets a specific pathogen compared to other interventions that target diarrhea generally, such as sanitation improvements and access to rehydration therapy.

As infants are targeted for rotavirus vaccination and this age group accounts for the greatest burden of rotavirus among young children, the finding that children <1 year old experience the fastest and largest reductions in hospitalizations is expected. However, our results also suggest that herd immunity may protect older children before the age cohorts would have been eligible for rotavirus vaccination. For example, we found the percentage of specimens that tested positive for rotavirus declined by 48% among children 12–23 months and 22% among children 24–59 months the first year after rotavirus vaccine introduction, when

neither age group would have been eligible to receive the vaccine. Similarly, median reductions were over 20% among children 12–23 months old for AGE hospitalizations the first year after rotavirus vaccine introduction. Some publications have documented reductions even in older children and adults after rotavirus vaccine introduction [9–12].

Our findings suggest a gradient in the reductions in hospitalizations by child mortality strata, with larger declines in the low mortality strata than the high mortality strata. This trend is consistent with differential vaccine effectiveness by child mortality strata [13]. Other differences in methodologies and setting likely also contribute to the magnitude and this difference should be interpreted with care. Data type was strongly correlated with child mortality strata in our data and reductions calculated from percentages consistently estimated a higher reduction that data calculated from rates within a child mortality strata for the same outcome. Nonetheless, the median reductions we found in countries with high child mortality represent substantial reductions in disease burden and hospitalizations. Future evaluations should carefully consider the available data and future systematic reviews may find analyses limited by data type are more appropriate for their specific objectives.

This literature review has a few other limitations. First, the data that contributed to this literature review were ecological data. While we tried to limit to articles that used similar methods and measured the same outcomes, all of the variation may not be well-accounted for in our analysis. Additionally, the summary findings represent a variable number of years since rotavirus vaccine introduction, which likely overrepresents early years of rotavirus vaccine implementation and may underestimate the true, long term ecological impact. Second, there are subsets of these data that can be sparse and limit the generalizability. For example, there are fewer articles that present impact >2 years after rotavirus vaccine introduction, from countries in the medium <5 year old child mortality strata, and from 12–23 month olds and 24–59 month olds. Our findings would be stronger with additional data from these subgroups. Additionally, we were unable to repeat some analyses by child mortality strata due to limited data. Finally, we also did not assess outcomes other than annual hospitalizations and deaths, such as outpatient visits, hospital-acquired infections, and length of hospital stay. These outcomes could provide additional information for decisionmakers.

We found a substantial and sustained impact on rotavirus and AGE hospitalizations and deaths with the introduction of rotavirus vaccines in age cohort eligible to have received the vaccine, with as expected greater reductions in low compared with high mortality settings. We also found evidence suggesting indirect effects on older pediatric age groups. These results should encourage countries still considering routine rotavirus vaccine implementation. Programs that have already introduced rotavirus vaccine should continue to strive for high rotavirus vaccination coverage as larger declines were found in settings with high rotavirus vaccine coverage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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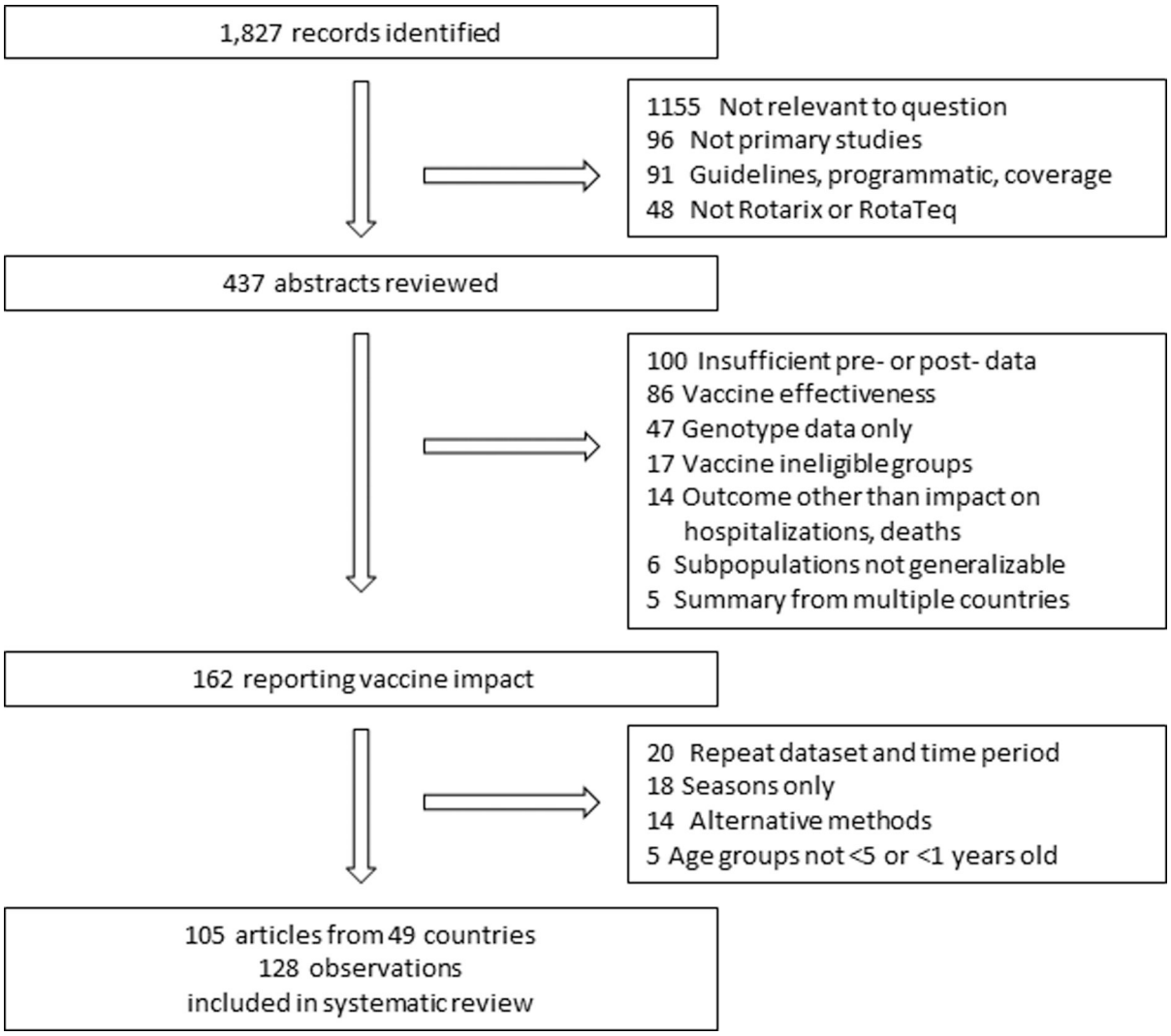

Figure 1.
Summary of literature search and selection criteria.

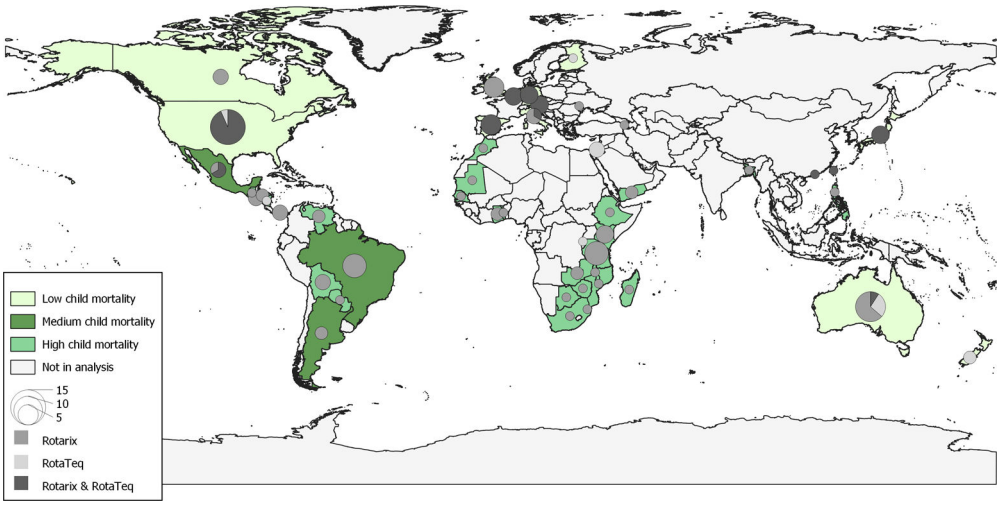

Figure 2.

Global map showing countries that contributed data by child mortality strata and the number of data points by vaccine type.

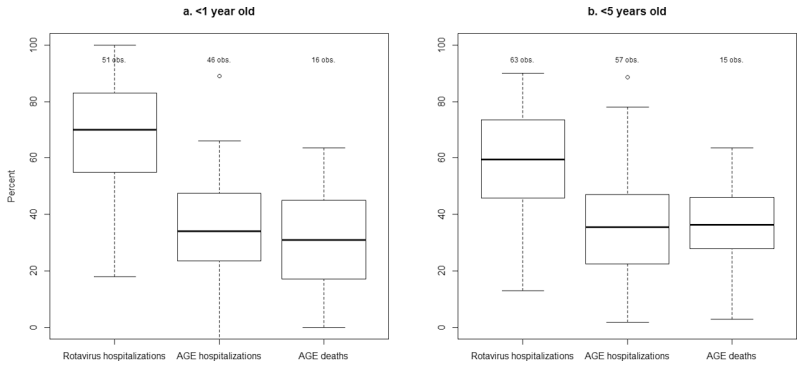

Figure 3.

Median reduction in rotavirus hospitalizations, acute gastroenteritis hospitalizations, and acute gastroenteritis deaths among children <1 year and <5 years.

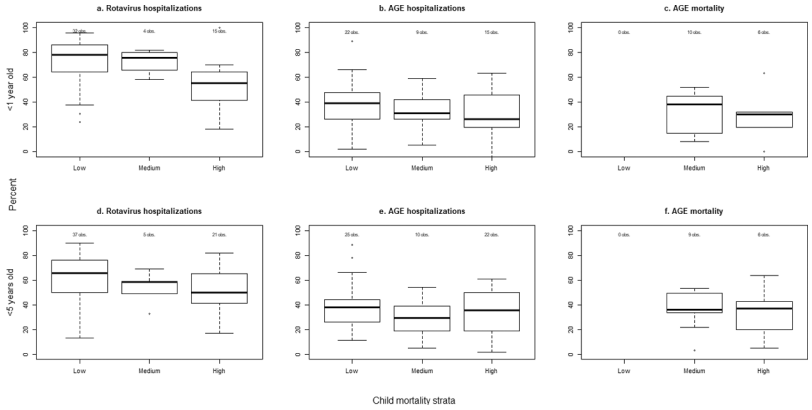

Figure 4.

Percentage reduction of acute gastroenteritis and rotavirus hospitalizations by national <5 year old child mortality level among children <1 and <5 years old

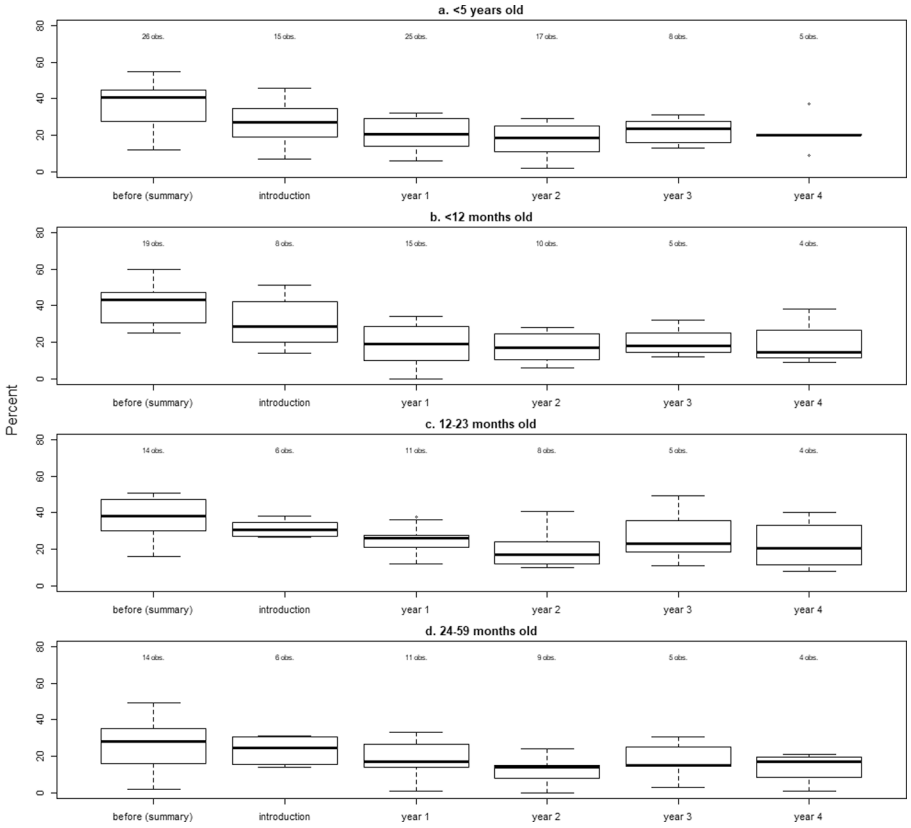

Figure 5.

Percentage of specimens that tested positive for rotavirus among children hospitalized for diarrhea by year relative to rotavirus vaccine introduction among 4 age groups.

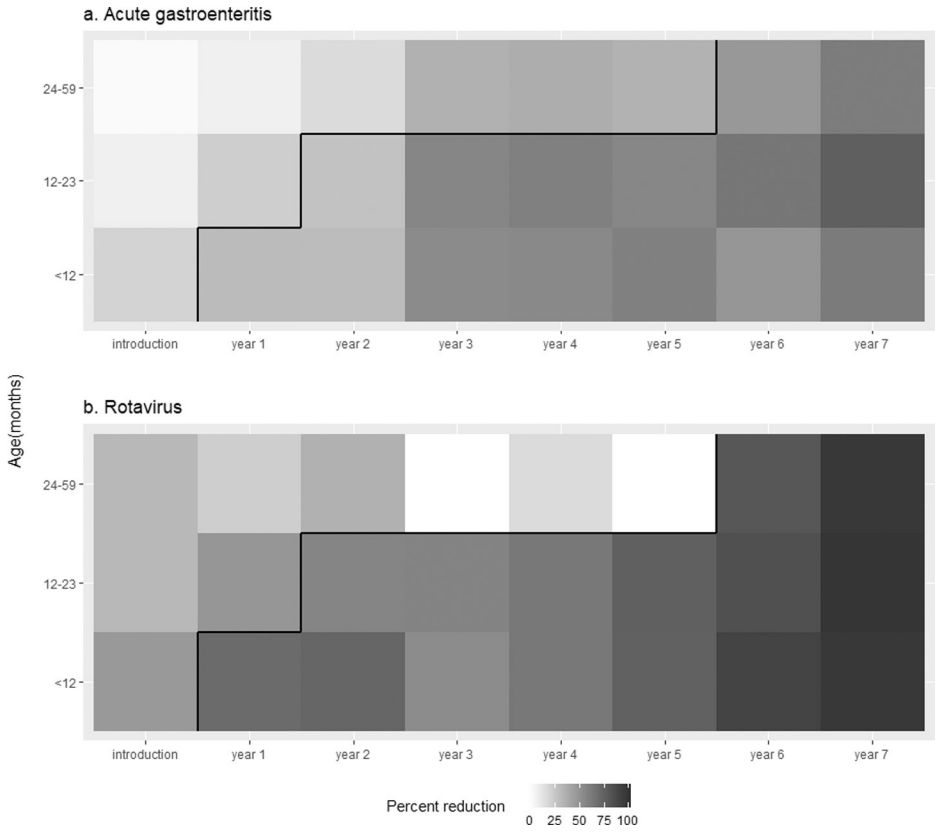

Figure 6.

Median percent reduction in acute gastroenteritis and rotavirus hospitalizations from the pre-rotavirus vaccine introduction baseline by age group and year relative to rotavirus vaccine introduction. The area below and to the right of the black line indicates when an entire age group would be eligible for vaccination.

Table 1.

Characteristics of the dataset.

	n=128	%
Year of publication (median, IQR)	2016	2013, 2018
Settings		
WHO Region		
Africa	27	21
Americas	46	36
Eastern Mediterranean	3	2
Europe	31	24
South-East Asia	1	1
Western Pacific	20	16
Child mortality strata		
Low	66	52
Medium	20	16
High	42	33
Vaccine information		
Year of vaccine introduction (median, IQR)	2009	2006, 2013
Vaccine		
Rotarix	75	59
RotaTeq	12	9
Both	41	32
Gavi supported introductions	33	26
National introductions	115	90
Demonstration projects	2	2
Private market only	11	9