



Published in final edited form as:

Expert Rev Vaccines. 2024 ; 23(1): 789–795. doi:10.1080/14760584.2024.2395534.

Indirect protection from rotavirus vaccines: a systematic review

Tyler Chavers¹, Jordan Cates^{1,*}, Eleanor Burnett¹, Umesh D. Parashar¹, Jacqueline E. Tate¹

¹Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

Introduction: Rotavirus vaccines may provide indirect protection by reducing transmission in the population and thus reducing disease burden.

Methods: This systematic review summarizes estimates of indirect protection from rotavirus vaccines and the methods used to obtain these estimates.

Results: We identified 71 studies published between 2009 and 2022 that provided 399 estimates of indirect protection from rotavirus vaccine. Most estimates (73%) evaluated hospitalizations due to rotavirus gastroenteritis as the outcome and unvaccinated children <5 years old as the age group (64%), but there was considerable variability in methods to evaluate indirect protection. For hospitalizations due to rotavirus gastroenteritis among unvaccinated children <5 years old, the median incidence rate ratio was 0.60 (IQR: 0.40–0.87, n=110 estimates), the median relative percent change in percent positivity was 25% (IQR: 13–44%, n=49 estimates), and the median relative percent change in absolute number of rotavirus positive tests or rotavirus-specific International Classification of Diseases codes was 42% (IQR: 16–66%, n=40 estimates).

Conclusions: These findings broadly suggest rotavirus vaccines provide some indirect protection. There is a need to standardize measurement of indirect rotavirus vaccine protection, particularly using consistent outcomes and metrics, and stratifying results by standardized age groups and years since vaccine introduction.

1. Introduction

Rotavirus vaccines have prevented substantial morbidity and mortality due to severe rotavirus gastroenteritis in children for nearly two decades since their licensure [1,2]. Studies have measured the direct protection of these vaccines, primarily through clinical trials and observational studies that compare outcomes between immunized and nonimmunized individuals. Vaccination may also indirectly protect vaccinated and unvaccinated members of a population by reducing overall transmission of rotavirus in the population [3].

Indirect protection (also referred to as herd or community immunity) can bolster the overall impact of a vaccination program by reducing cases, hospitalizations, and deaths

*Corresponding author: Jordan Cates, ntm6@cdc.gov.

Author contribution statement: All authors should have substantially contributed to the conception and design of the review article and interpreting the relevant literature and were involved in writing the review article or revised it for intellectual content.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position the Centers for Disease Control and Prevention.

among whole populations [4], and both direct and indirect protection play a role in the programmatic level vaccine decision-making process. For example, cost-effectiveness analyses rely on predictive models and vaccine effectiveness (VE) studies to estimate reductions in population-level disease burden. The total costs associated with care decline as vaccine effects increase and several analyses have noted that rotavirus vaccines become cost-effective or even cost-saving with the inclusion of an indirect protection term into their models [5–9].

While understanding indirect protection is important to measure a vaccine's overall performance, a standardized approach for measuring the indirect protection from rotavirus vaccines has not been consistently implemented. Among three recent systematic reviews and meta-analyses that looked at indirect protection from rotavirus vaccines, none generated an estimate of the indirect protection for a specific age group, outcome, and metric (e.g. incidence) as has been done in meta-analyses of direct protection [10–12]. Further, estimates of indirect protection are challenging to define and compare across setting, as they require assumptions around transmission conditions and population immunity which are often poorly characterized [13–15].

Heterogeneity across the literature leaves indirect protection from rotavirus vaccines vaguely defined and estimates range across various age groups, outcomes, surveillance methods, and number of years post-vaccine introduction. Given the various factors that influence indirect protection, we performed a systematic review to describe available methods and estimates that quantify indirect protection from rotavirus vaccines.

2. Methods

2.1. Literature search strategy and inclusion criteria

To evaluate published post-licensure studies of indirect protection from rotavirus vaccine, we performed a literature review of articles indexed in PubMed, Embase, CINAHL, and Scopus databases. We used search terms ((rotavirus AND (vaccin* OR immuni*)) OR ((herd immunity OR herd protection OR indirect immunity OR indirect protection) and (RotaTeq OR Rotarix OR Rotavac OR Rotasiil))) from 1 January 2006 to 31 December 2022. We excluded any reviews, presentations, non-primary research, and publications that did not include estimates specific to internationally licensed human rotavirus. We did not restrict the search by language.

2.2. Data abstraction and definitions

We abstracted information from articles using a standardized collection form in Microsoft Excel. We defined indirect protection as any estimate of the change in rotavirus morbidity among unvaccinated individuals in settings with rotavirus vaccine introduction compared to all individuals in settings without rotavirus vaccine introduction. Any metric that evaluated indirect protection was abstracted, including incidence rate ratios, relative percent change in the proportion of acute gastroenteritis stool specimens positive for rotavirus (henceforth referred to as percent positivity), or relative change in absolute numbers of positive rotavirus tests or medical encounters with an International Classification of Diseases (ICD) code for

rotavirus. Incidence rate ratios were directly abstracted if available, back-calculated from VE estimates, or calculated as the ratio of incidence rates. Relative changes in percent positivity or in absolute numbers of rotavirus positive tests or of ICD codes were either directly abstracted or calculated using reported frequencies. We abstracted data on the type of outcome (i.e. hospitalizations, emergency department visits, laboratory detections, outpatient visits, nosocomial infections, mixed medical encounters, community infections, asymptomatic infections). We abstracted estimates stratified by outcome, age, and years since vaccine introduction.

2.3. Analysis

We summarized the frequency and proportion of studies by several factors: World Health Organization (WHO) region, the childhood mortality strata of the country of study, group evaluated for indirect protection (age-eligible unvaccinated, age-ineligible, or both), whether comparisons were made temporally or geographically, the data source, and the methods for ascertaining rotavirus infection. We categorized countries into three child mortality strata: lowest quartile (“low”); 2nd quartile (“medium”); and the 3rd and 4th quartiles (“high”), using the 2014 (median study period year) estimates of <5 year old child mortality from UNICEF [16]. Taiwan was considered to be low mortality based on locally published mortality rates [17]. Data sources were categorized as active hospital surveillance, administrative data with ICD codes, laboratory surveillance, nationally notifiable case database, case-control study, or cluster randomized trial. The methods for ascertaining rotavirus infection included ICD-9 or ICD-10 codes or laboratory tests including enzyme immunoassays (EIA), polymerase chain reactions (PCR), immunochromatography, polyacrylamide gel electrophoresis (PAGE), or unspecified laboratory methods. We summarized incidence rate ratios, relative percent change in percent positivity, and relative percent change in absolute number of rotavirus positive tests or rotavirus-specific ICD codes by age category, outcome, years since introduction, and whether the study collected data annually or only during rotavirus seasons. We sorted the age groups into six strata: infants <2 months, children <5 years, children ≥5 years (maximum age between 5 and 19 years), children and adults ≥5 years (maximum age not specified), adults 18–64 years of age, and older adults ≥65 years of age. Any age groups ranging over multiple age categories were assigned to the category with the most overlap (Supplemental Table 1). For data stratified by single years since vaccine introduction, we evaluated years 0 and 1 since vaccine introduction as single year periods and grouped years 2–4 and 5–12 since vaccine introduction given the sparse data in these later time periods. Given the heterogeneity in the study designs and data quality, we did not use fixed- or random-effects models to pool estimates [18]. Instead, the distributions of incidence rate ratios, relative percent changes in percent positivity, and relative percent change in absolute numbers were summarized as medians and interquartile ranges (IQR). The primary analysis summarized distributions of estimates of indirect protection against hospitalizations due to rotavirus gastroenteritis among unvaccinated children <5 years old, as the majority of estimates were for this outcome and age category. The median and IQR incidence rate ratio for hospitalizations due to rotavirus gastroenteritis among unvaccinated children <5 years old was also stratified by child mortality, given evidence of lower direct protection from rotavirus vaccination in countries with medium and high child mortality [19]. Sensitivity analyses were conducted

stratifying estimates by age groups and years since introduction. Private-market rotavirus introduction and seasonal data collection were also considered to be associated with a higher risk of bias and studies with these characteristics were excluded in sensitivity analyses. Data source was also considered a factor that may influence the risk of bias in a study, especially for studies that relied on administrative databases using ICD codes or laboratory surveillance that may not systematically identify cases, thus a sensitivity was also conducted stratifying estimates by data source.

Protocol registration: This protocol was registered with PROSPERO, registration no. CRD42024499399, and aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

3. Results

3.1. Study selection and study characteristics

Our search criteria yielded 2,293 publications, of which 71 met the inclusion criteria (Figure 1). Among the 71 included studies published between 2009 and 2022, there were 399 estimates of indirect protection from rotavirus vaccines that could be abstracted, stratified by metric, outcome, age group, and years since vaccine introduction. The median number of available estimates per study was 3 (IQR: 2–6.5, range 1–30) (Supplemental Table 1). The majority of studies were from the European Region (42%), the Region of the Americas (23%), and the African region (17%), and were primarily from countries with low childhood mortality (68%) (Table 1). Most studies were among adult and child populations that were age-ineligible at the time of the study for rotavirus vaccination (87%), though 6% of studies were for unvaccinated age-eligible children and 7% of studies included both age-ineligible and age-eligible unvaccinated populations. A variety of data sources and methods were used for ascertaining rotavirus infection. Data came from active hospital surveillance (44%), administrative databases (32%), laboratory surveillance (19%), nationally notifiable case surveillance (3%), case-control study (1%), and cluster randomized trial (1%), while 32% of studies used ICD codes only, 3% of studies used ICD codes and laboratory methods, and 65% used a laboratory method only to determine rotavirus infection.

3.2. Estimate characteristics

Thirty-six studies provided 229 incidence rate ratios, 27 studies provided 88 estimates of relative percent change in rotavirus percent positivity, and 14 studies provided 82 estimates of relative percent change in absolute number of rotavirus positive tests or rotavirus-specific ICD codes (Table 2).

While more than half of estimates used hospitalizations due to rotavirus gastroenteritis as the outcome (71% of incidence rate ratios, 68% of relative percent change in percent positivity, and 83% of relative percent change in absolute rotavirus positive tests or rotavirus-specific ICD codes) and children <5 years old as the age group (62% of incidence rate ratios, 72% of relative percent change in percent rotavirus positive, and 61% of relative percent change in absolute rotavirus positive tests or rotavirus-specific ICD codes), there was considerable variability in metrics, outcomes, and age categories used to evaluate indirect protection

(Table 1). For example, there were 21 different age groupings in which authors measured indirect protection among unvaccinated children <5 years of age (Supplemental Table 2). There were 52 estimates among adults 18–64 years of age and older adults ≥65 years of age, of which 22 (42%) were from administrative databases with ICD codes, 16 (31%) were from laboratory surveillance, and 14 (27%) were from nationally notifiable case-based surveillance; there were no active surveillance studies with indirect protection estimates among adult populations. Most estimates were from the very early post-introduction period (e.g. 206 [52%] estimates were from 0 or 1 years since vaccine introduction) and there were 35 (9%) estimates from studies that collected data seasonally. There were very few (n=23, 6%) estimates 5 or more years after vaccine introduction.

3.3. Indirect protection estimate summaries

For hospitalizations due to rotavirus gastroenteritis among unvaccinated children <5 years old, the median incidence rate ratio was 0.60 (IQR: 0.40–0.87, n=110 estimates), the median relative percent change in percent positivity was 25% (IQR: 13–44%, n=49 estimates), and the median relative percent change in absolute number of rotavirus positive tests or rotavirus-specific ICD codes was 42% (IQR: 16–66%, n=40 estimates) (Figure 2). When stratified by under-five mortality strata, the median incidence rate ratio in hospitalized children <5 years old was 0.60 (IQR: 0.40–0.86, n=88 estimates) among 19 low-mortality countries, 0.56 (IQR: 0.34–0.62, n=12 estimates) among three medium mortality countries, and 0.83 (IQR: 0.64–1.11, n=10 estimates) among two high-mortality countries (Figure 3). Compared to children <5 years old, the median incidence rate ratios were closer to the null and there were wider interquartile ranges in studies of indirect protection among unvaccinated children ≥5 years old (median incidence rate ratio 0.74 [IQR: 0.45, 1.07], n=24 estimates), adults (median incidence rate ratio 1.17 [IQR: 0.50, 1.54], n=17 estimates), and older adults (median incidence rate ratio 1.20 [IQR: 0.89, 1.66], n=11 estimates) (Supplemental Table 3). Excluding year 0 data, seasonal estimates, and private market introductions had no substantive impact on the indirect protection estimates against for hospitalization for all ages (Supplemental Table 3) or among children <5 years of age (Supplemental Table 4). There was some variability in the distributions of estimates by data source; the median relative percent change in percent positivity and relative percent change in absolute numbers of rotavirus positive tests or of ICD codes was lower among administrative databases with ICD codes compared with active hospital surveillance among all ages (Supplemental Table 3) and among children <5 years of age (Supplemental Table 4).

4. Discussion

Rotavirus vaccine's indirect protection may contribute to declines in rotavirus disease among populations where the vaccine is available, including non-vaccinated groups, especially unvaccinated children <5 years old. This review aimed to describe the full spectrum of literature quantifying indirect protection from observational studies, but most studies estimated reductions in hospitalizations due to rotavirus among unvaccinated children <5 years of age in low- and medium-childhood mortality countries. Evidence of indirect protection against rotavirus hospitalization among children <5 years of age was consistent across three different metrics abstracted (incidence rate ratios, relative percent

change in percent rotavirus positivity, and relative percent change in absolute number of rotavirus positive tests or ICD codes). However, meaningfully synthesizing the full spectrum of literature and comparing results was challenging because of the variety of methods used. This variety likely accounts for the wide range of estimates, including some that showed an increase in rotavirus in unvaccinated populations, which could be better contextualized with standardized methodologies. Our summary of the characteristics and methods used by these studies can help to inform future evaluations. Researchers may focus on incidence of hospitalization and report yearly age and number of years post-vaccine introduction for comparability to existing estimates.

Our finding of a median incidence rate ratio of 0.60 (which can also be represented as a 40% indirect vaccine effectiveness estimate) for rotavirus hospitalization among unvaccinated children <5 years of age is consistent with prior systematic reviews. Specifically, a meta-analysis by Rosettie et al using data through June 2017 that restricted to studies with reported confidence intervals found a pooled indirect VE of 48% (95% CI: 39–55%) [12]. The consistency of findings is reassuring and strengthens the evidence of indirect protection due to rotavirus vaccination in this population. However, even among this relatively limited and standardized population, caution is needed in interpreting these descriptive summaries, given the lack of comparability across settings with variable vaccine coverage and population immunity.

Similar to Rosettie et al, our review found evidence of variation in the estimates of indirect protection by country childhood mortality strata, with somewhat lower indirect protection in high childhood mortality compared to low- and medium-mortality countries, though more data are needed from high childhood mortality settings to confirm a true difference in indirect protection. This potential differential indirect protection may be correlated with documented differential direct protection from rotavirus vaccine [21] but could be related to additional factors including vaccine coverage and rotavirus exposure frequency and intensity. Furthermore, these estimates of indirect protection were based on relative reductions, thus high-childhood mortality settings may still see a large absolute reduction among unvaccinated individuals due to a high rotavirus burden.

This review also included estimates of indirect protection among older children and adults. While there were fewer studies among children ≥5 years old compared to children <5 years old, estimates among individuals ≥5 years old also showed consistent evidence of indirect protection with all three summarized estimates. However, when stratifying the estimates from adult populations, evidence of indirect protection among adults 18–64 years old and older adults ≥65 years old was mixed, consistent with prior systematic reviews [22]. While some studies among adults and older adults found evidence of indirect protection, there were a similar number of studies that found no protection or evidence of increased burden of rotavirus indirectly due to rotavirus vaccination. However, the methodologies of studies among adult populations were often limited to administrative databases based on rotavirus-specific ICD codes which raises concerns around accuracy of rotavirus estimation due to changes in testing or coding practices. In the post-rotavirus vaccination era, there may have been an increased awareness of rotavirus and thus increased testing in adult populations, potentially biasing results. The absolute number of hospitalized adults were typically very

small, thus robust comparisons may be limited by small sample sizes in this population. Evidence of indirect protection among adult populations remains inconsistent.

This review has several limitations. It serves as a broad overview that compares all estimates regardless of study duration, sampling methods, diagnostics, and severity. To summarize findings, we made several generalizations when values overlapped multiple age groups, post-vaccine years, or outcomes. We also performed descriptive analyses based on the most frequently reported parameters from the literature, including age, outcome, country childhood mortality strata, and number of post-introduction years. Other parameters were not included but may be associated with indirect protection such as population immunity and vaccine coverage. Years since vaccination may be an imperfect proxy variable for vaccine coverage. However, it is reassuring that our analyses stratified by year after vaccine introduction were largely consistent with the overall summarized estimates. Time-varying confounders are of potential concern, such as changes in surveillance, testing, or coding practices; we were unable to assess or account for these factors as part of this literature assessment. We intentionally refrained from pooling estimates in fixed- or random-effect models given the heterogeneity in the methods used in these observational studies. Finally, when individual articles presented multiple estimates in the same stratified analysis, we did not attempt to weight the estimates. This may lead to some bias if certain studies had an inflated representation in some estimates.

5. Conclusions

These findings demonstrate the need to standardize measurement of indirect protection from rotavirus vaccine. Factors such as age, outcome measured, metric used, vaccine coverage in the population, rotavirus identification method, and year post-vaccine introduction should all be considered when developing new studies or summary analyses. Additional evaluations of indirect protection in medium and high childhood mortality settings are needed to better understand rotavirus vaccine performance in these settings. Rotavirus vaccines remain an effective tool in reducing disease burden and may benefit some non-target groups as shown in this review. Understanding indirect immunity on a broader scale through expanded studies and meta-analyses may better inform remaining vaccine introductions and promote increasing coverage of existing vaccination programs.

6. Expert opinion

Our review found considerable variation in target populations, definitions of rotavirus, and analytic methods used in the quantification of indirect protection from rotavirus vaccination. Researchers considering rotavirus vaccine indirect protection questions should consider how best to align their protocols with the existing literature for comparability. Additionally, there are a lack of data among older age groups, in high child mortality countries, and long-term post-rotavirus vaccine introduction. Quantifying the indirect impacts of rotavirus vaccination across the lifespan can improve cost effectiveness estimates used for vaccine decision making. Better understanding the indirect protection of rotavirus vaccines may also help us better understand rotavirus epidemiology in the post-vaccine era, including outbreaks and differences in performance by country. Understanding indirect protection of

rotavirus vaccines will continue to be an important area for investigation as new rotavirus vaccines become widely used and as more countries introduce these vaccines into their routine immunization programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Declarations of Interests:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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pooled indirect vaccine effectiveness against hospitalization of 48% (95% CI: 39–55%) among unvaccinated children <5 years of age

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Article highlights:

- This systematic review summarized 71 studies reporting data on indirect protection from rotavirus vaccines, identifying considerable variability in methods used to evaluate indirect protection.
- Findings broadly suggest rotavirus vaccines provide some indirect protection, especially among unvaccinated children <5 years old.
- There is a need to standardize measurement of indirect rotavirus vaccine protection, particularly using consistent outcomes, metrics, and stratifications.

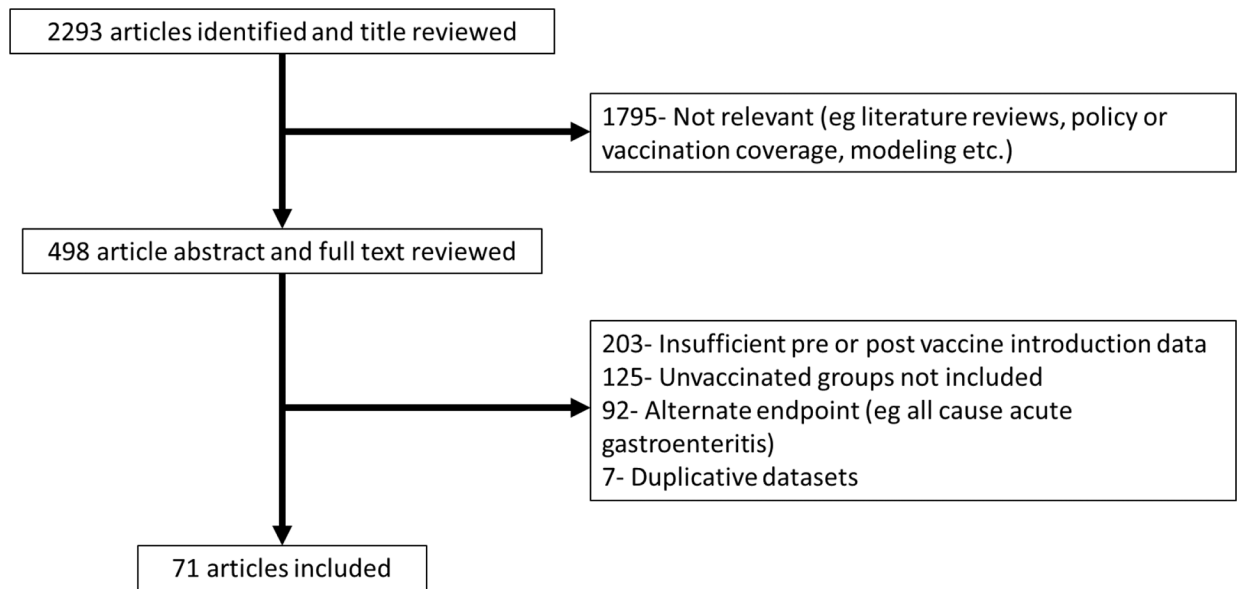


Figure 1. Article selection and breakdown of studies published between 2009 and 2022 identified in a systematic review of indirect protection provided by rotavirus vaccines.

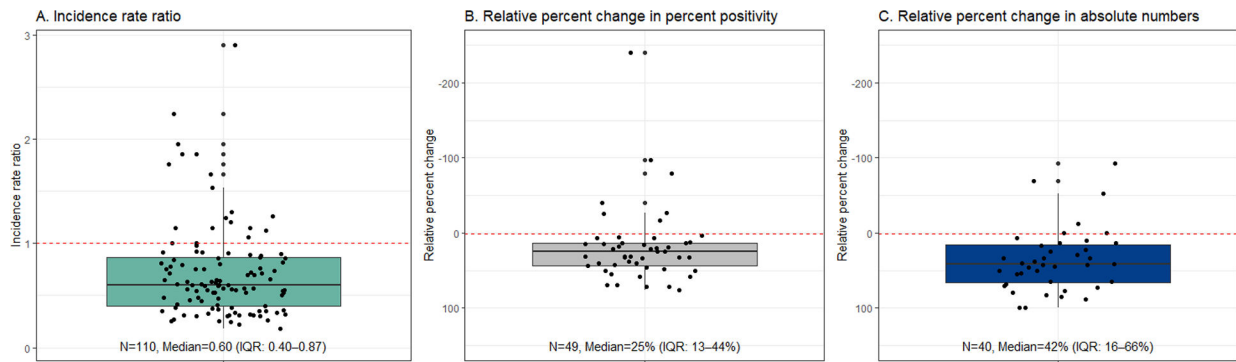


Figure 2.

Distributions of three metrics of indirect protection of rotavirus vaccine: incidence rate ratios of rotavirus hospitalization (N=110), relative percent change in the percent positivity of rotavirus among hospitalizations (N=49), and relative percent change in the absolute number of rotavirus positive tests or ICD codes (N=40) among hospitalized children less than 5 years of age from studies published between 2009 and 2022 identified in a systematic review of indirect protection provided by rotavirus vaccines. IQR=interquartile range

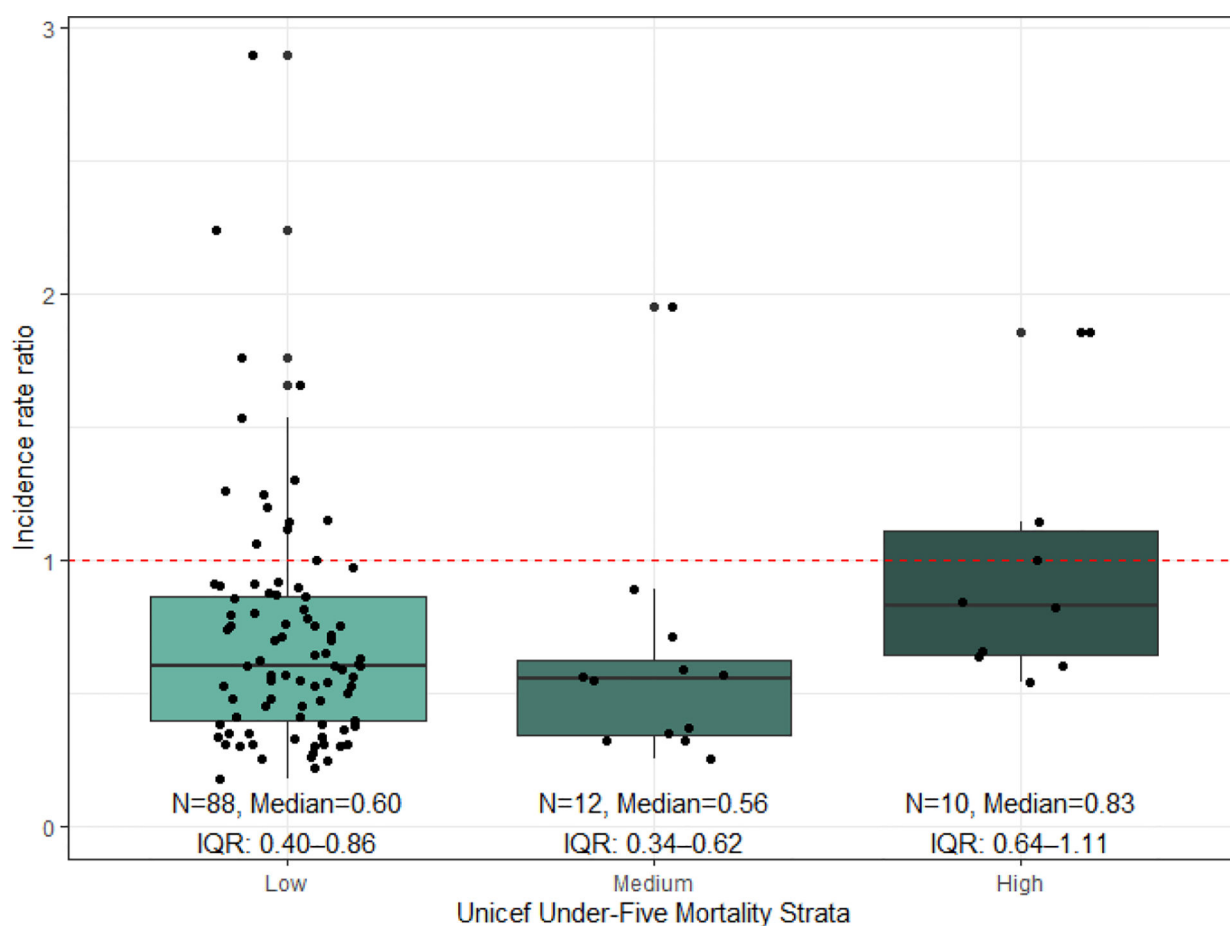


Figure 3.

Distributions of indirect protection incidence rate ratios of rotavirus hospitalization among unvaccinated children <5 years of age stratified by country-level child mortality strata from studies published between 2009 and 2022 identified in a systematic review of indirect protection provided by rotavirus vaccines. IQR=Interquartile range

Table 1.

Characteristics of studies published between 2009 and 2022 identified in a systematic review of indirect protection provided by rotavirus vaccines.

Number of unique studies	N=71
WHO Region	
African (AFR)	12 (17%)
Region of the Americas (AMR)	16 (23%)
South-East Asian Region (SEAR)	5 (7%)
European Region (EUR)	30 (42%)
Easter Mediterranean Region (EMR)	0 (0%)
Western Pacific Region (WPR)	8 (11%)
Rotavirus vaccine introduction	
National	67 (94%)
Private-market	4 (6%)
Child mortality strata	
Low-mortality	48 (68%)
Medium-mortality	6 (8%)
High-mortality	17 (24%)
Group evaluated for indirect protection	
Age-eligible unvaccinated	4 (6%)
Age-ineligible	62 (87%)
Age-ineligible and age-eligible unvaccinated	5 (7%)
Comparing rotavirus burden over time or by geography	
Time	69 (97%)
Geography	2 (3%)
Data Source *	
Active hospital surveillance	31 (44%)
Administrative databases with ICD codes	23 (32%)
Laboratory surveillance	14 (19%)
Nationally notifiable case database	2 (3%)
Case-control study	1 (1%)
Cluster randomized trial	1 (1%)
Method for ascertaining rotavirus *	
ICD-9 or ICD-10 codes	23 (32%)
EIA	40 (56%)
PCR	7 (10%)
Immunochromatography	7 (10%)
PAGE	1 (1%)
Laboratory-confirmed, method unspecified	5 (7%)

EIA=enzyme immunoassay; ICD= International Classification of Diseases; PAGE= polyacrylamide gel electrophoresis; PCR= polymerase chain reaction; WHO=World Health Organization

* Some studies used data from multiple data source or had multiple methods for ascertaining rotavirus, thus the responses in these categories are not mutually exclusive and do not sum to 100%. Twenty-three (32%) studies used ICD codes only, two (3%) studies used ICD codes and laboratory methods, and 46 (65%) used laboratory methods only.

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Table 2.

Characteristics of estimates of indirect protection provided by rotavirus vaccines from studies published between 2009 and 2022 identified in a systematic review. Estimates were abstracted, when available, or calculated, stratified by metric, outcome, age group, and years since introduction.

	Stratified by metric of indirect protection		
	Incidence rate ratio	Relative percent change* in percent positivity	Relative percent change* in absolute number of rotavirus positive tests or ICD codes [†]
Total number of estimates	N=229	N=88	N=82
Description of estimates			
Outcome			
Hospitalizations [‡]	163 (71%)	60 (68%)	68 (83%)
Emergency department visits	5 (2%)	0 (0%)	0 (0%)
Laboratory detections	21 (9%)	3 (3%)	9 (11%)
Outpatient visits	12 (5%)	11 (12%)	0 (0%)
Nosocomial infections	5 (2%)	0 (0%)	0 (0%)
Mixed medical encounters	22 (10%)	14 (16%)	5 (6%)
Community infections	0 (0%)	0 (0%)	0 (0%)
Asymptomatic infections	1 (0%)	0 (0%)	0 (0%)
Age category[§]			
<2 months	1 (0%)	1 (1%)	17 (21%)
Children <5 years old	141 (62%)	63 (72%)	50 (61%)
Children ≥5 years old	43 (19%)	8 (9%)	8 (10%)
Children and adults ≥5 years old	8 (4%)	0 (0%)	7 (9%)
Adults 18–64 years of age	22 (10%)	14 (16%)	0 (0%)
Older adults ≥65 years of age	14 (6%)	2 (2%)	0 (0%)
Years since vaccine introduction			
Single year data			
0	47 (21%)	29 (33%)	17 (21%)
1	63 (28%)	25 (28%)	25 (30%)
2–4 [#]	69 (30%)	19 (22%)	25 (30%)
5–12 [#]	12 (5%)	1 (1%)	10 (12%)
Grouped year data between 0–8 years^{**}	38 (17%)	14 (16%)	5 (6%)
Collected data annually or seasonally			
Annual	212 (93%)	81 (92%)	71 (87%)
Seasonal	17 (7%)	7 (8%)	11 (13%)

ICD= International Classification of Diseases

* Relative percent change= 100*(percent positivity or absolute numbers in the control group [e.g., population prior to vaccine introduction] minus percent positivity or absolute numbers in the comparator group [e.g., post-vaccine program unvaccinated population], divided by the percent positivity or absolute numbers in the control group)

^fIncludes absolute number of outcomes (n=78), mean annual number of outcomes (n=2), and absolute number of extrapolated outcomes (n=2).

[‡]Studies with emergency department and hospitalization were grouped under hospitalizations

[§]These age categories include any age groups that fell within this category. For example, the children <5 years age category includes both estimates for children 5–23 months as well as children 24–35 months. There were 5 different age groups within the broader category of infants <2 months, 21 different age groups within the broader category of children <5 years, 16 different age groups within the children ≥5 years category, 3 different age groups within the children and adults ≥5 years category, 10 age groups within the adults category, and 2 age groups within the older adults category (Supplemental Table 1).

[#]single year data available; years 2–4 and 5–12 since vaccine introduction were grouped due to sparse data in these time periods

^{**}Year groupings include 0–1 (n=5), 0–2 (n=1), 0–3 (n=4), 0–4 (n=23), 0–6 (n=5), 1–3 (n=5), 1–7 (n=2), 2–5 (n=2), 2–8 (n=1), 4–8 (n=2), 5–6 (n=2)