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Direct, Indirect, Total, and Overall Effectiveness of the Rotavirus Vaccines for the Prevention of Gastroenteritis Hospitalizations in Privately Insured US Children, 2007–2010

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We demonstrate how direct, indirect, total, and overall effectiveness estimates and absolute benefits of rotavirus vaccines vary through the years following vaccine introduction. Privately insured US children in a large claims database were followed from age 8 months until they 1) experienced a hospitalization for rotavirus or acute gastroenteritis; 2) lost continuous health plan enrollment; 3) turned 20 months of age; or 4) reached the end of the study period. Vaccine effectiveness estimates in preventing rotavirus and acute gastroenteritis hospitalizations were estimated using Cox proportional hazards regression, stratified by calendar year and adjusted for birth month. Incidence rate differences were estimated to determine the absolute number of gastroenteritis hospitalizations prevented in the cohort. Among 905,718 children, 51%, 66%, 80%, and 86% received 1 or more doses of rotavirus vaccine in each year from 2007 to 2010. The direct vaccine effectiveness of 1 or more doses of rotavirus vaccine in preventing rotavirus gastroenteritis hospitalizations ranged from 87% to 92% each year. Accounting for indirect protection increased estimates of vaccine effectiveness by an additional 3%–8% among those vaccinated. Failing to account for population-level vaccine benefits in 2010, when circulation of rotavirus was low, could underestimate the sustained impact of the vaccine program.

diarrhea; gastroenteritis; immunity, herd; pharmacoepidemiology; program effectiveness; rotavirus; rotavirus vaccines; use-effectiveness

Abbreviations: AGE, acute gastroenteritis; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; IRD, incidence rate difference; RGE, rotavirus gastroenteritis; RV1, rotavirus monovalent vaccine; RV5, rotavirus pentavalent vaccine; VE, vaccine effectiveness.

Most phase III vaccine efficacy trials determine the direct vaccine effectiveness (VE), generally measured as 1 minus the relative risk in the vaccinated group compared with the unvaccinated group. Some clinical trials and many postlicensure studies also measure herd protection, or indirect VE, defined as population-level effects of widespread vaccination on people not receiving the vaccine (1). Two additional population-level measures of VE, total and overall VE, account for both the direct and indirect effectiveness of a vaccine (Figure 1). Total VE combines the direct and indirect VE on individuals receiving the vaccine, whereas the overall VE weights the average of the total VE on individuals receiving the vaccine with the indirect VE on individuals not receiving the vaccine (1). Total VE can thus be interpreted as the complete benefit of vaccination in vaccine recipients, and overall VE can be interpreted as the public health benefit of vaccination. Despite challenges in estimating the 4 types of VE, they are essential to understanding the real-world impact of a vaccine (1–3).

Rotavirus was the leading cause of gastroenteritis in infants and young children, implicated in 55,000–70,000 hospitalizations in the United States prior to the availability of a rotavirus vaccine (4). Rotavirus vaccination is currently

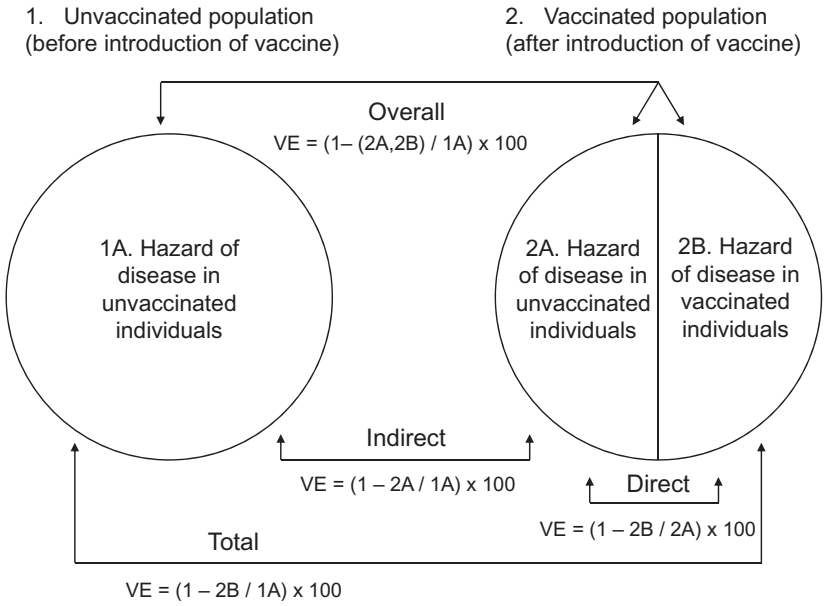

Figure 1. Types of vaccine effectiveness as described by Halloran et al. (1). A vaccinated population will still have some individuals within the population who are unvaccinated because 100% vaccination coverage is generally never achieved. VE, vaccine effectiveness.

recommended by the Centers for Disease Control and Prevention (Atlanta, Georgia), and 2 vaccines are marketed in the United States (5). The pentavalent rotavirus vaccine (RV5), RotaTeq (Merck & Co., Inc., Whitehouse Station, New Jersey), administered orally in 3 doses at ages 2, 4, and 6 months, has been licensed since February 2006, and the monovalent rotavirus vaccine (RV1), Rotarix (GlaxoSmithKline Biologics, Research Triangle Park, North Carolina), administered orally in 2 doses at ages 2 months and 4 months, has been licensed since April 2008.

We compared direct, indirect, total, and overall rotavirus VE estimates for the prevention of rotavirus gastroenteritis (RGE) and acute gastroenteritis (AGE) hospitalizations from 2007 to 2010 to determine how these 4 VE estimates varied through the years after vaccine introduction. We also examined how the absolute number of gastroenteritis hospitalizations varied through the years.

METHODS

Data source

The MarketScan Research Databases (Truven Health Analytics, Inc., Ann Arbor, Michigan) contain data from more than 111 million individuals throughout the United States with commercial health insurance. In 2010, the database included approximately 920,000 infants, corresponding to approximately 25% of the US birth cohort and 50% of the US birth cohort with commercial insurance (6, 7).

Design and population

Data on infants with continuous insurance enrollment during infancy, at least 1 outpatient claim for any service or diagnosis, and an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), code for a livebirth between May 1, 2000, and April 30, 2005, or May 1, 2006, and April 30, 2010, were extracted from the databases (Table 1). If an infant or mother had a claim for a livebirth on multiple dates within a short period of time, the date of the first claim was used as the birth date. Follow-up for RGE began when infants turned 8 months of age and continued until a maximum age of 20 months. Infants younger than 8 months and infants receiving doses of rotavirus vaccine after 8 months were excluded so that rotavirus vaccine status could be treated as a single point exposure.

Infants with commercial insurance who failed to receive vaccines with high coverage rates (≥95%) may differ from infants receiving such vaccines with respect to unmeasured confounding factors, so we required all infants in our study to be vaccinated with at least 1 dose of diphtheria, tetanus, and acellular pertussis vaccine using Current Procedural Terminology codes (8).

Outcome, exposure, and covariate measurements

Outcomes of RGE and AGE were identified using ICD-9-CM codes. Any of the 15 diagnosis fields in the inpatient files of the databases was used to capture the ICD-9-CM code 008.61 for gastroenteritis due to rotavirus. Rotavirus-coded events underestimate the true burden of rotavirus disease because of lack of routine laboratory testing and coding; therefore, we performed sensitivity analyses, assuming 25% and 50% sensitivity of the 008.61 code (9, 10), and extracted and examined outcomes related to AGE (11–13). Emergency department and outpatient visits for RGE and AGE were not included in the analysis.

Table 1. ICD-9-CM and CPT Codes Used in Analyses of US Commercially Insured Infants and Children 8–20 Months of Age (11–13)

Description by Type of Code	Code
CPT code	
Rotavirus vaccine (RV5, RV1)	90680, 90681
DTaP vaccine or related vaccines, including combinations	90696, 90698, 90700, 90701, 90702, 90714, 90715, 90718, 90720, 90721, 90723
ICD-9-CM code	
Livebirth (singleton or multiple)	V30–V39
Rotavirus gastroenteritis	008.61
Acute gastroenteritis	
Bacterial	001–005 (excluding 003.2), 008.0–008.5
Parasitic	006–007 (excluding 006.3–006.6)
Viral	008.6, 008.8
Undetermined etiology (infectious)	009.0–009.3
Undetermined etiology (noninfectious)	558.9
Diarrhea not otherwise specified	787.91

Abbreviations: CPT, Current Procedural Terminology; DTaP, diphtheria, tetanus, acellular pertussis vaccine; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

RV5 and RV1 vaccination status at 8 months of age was classified using the Current Procedural Terminology codes 90680 and 90681. To increase the sensitivity of vaccination status, we excluded infants living in states with state-funded rotavirus immunization programs (Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, and Wyoming) (13).

To account for household-level variation in rotavirus vaccine coverage, disease, and mixing behaviors, we examined the number of other dependent children less than 10 years of age covered by the same insurance holder as the infant (considered to be older siblings). To account for geographical variation, we included the region and rurality of the child's residence, as defined by the US Department of Agriculture, Economic Research Service (14). To characterize general infant health and potential differences in susceptibility to rotavirus disease, we compared the percentage of infants who had overnight hospital stays unrelated to AGE prior to 2 months of age.

Data analysis

We used Cox proportional hazard regression models to estimate hazard ratios, comparing the hazard of RGE or AGE hospitalization among vaccinated infants to that among unvaccinated infants entering the cohort in 2007, 2008, 2009, or 2010 and subtracting the result from 1 to obtain estimates of direct VE by calendar year. We similarly estimated the indirect, total, and overall VE, varying the comparison cohorts accordingly. For indirect VE, we compared unvaccinated infants followed during each calendar year of the rotavirus vaccine period, 2007–2010, with (unvaccinated) infants followed during the baseline period, 2001–2005. For total VE, we compared vaccinated infants followed during each calendar year of the rotavirus vaccine period with (unvaccinated) infants followed during the baseline period. For overall or average VE, we compared all vaccinated and unvaccinated infants during each calendar year of the rotavirus vaccine period with (unvaccinated) infants followed during the baseline period.

In all regression analyses, age served as the underlying time scale, and infants were censored when they experienced a RGE or AGE hospitalization, lost continuous enrollment, reached 20 months of age, or reached the end of the study period on December 31, 2005, or December 31, 2010, whichever occurred first. Results were stratified by year to account for increasing vaccination coverage and possible variations in rotavirus transmission by year and adjusted for month of birth to account for the seasonality of rotavirus. Infants and children were allowed to contribute person-time during 2 calendar years. For example, an infant who turned 8 months of age on October 1, 2007, would contribute up to 3 person-months in 2007 and reenter the cohort on January 1, 2008, at age 11 months, to contribute up to 9 more calendar months of person-time in 2008. Infants followed during 2 calendar years in the baseline period were followed continuously.

We estimated incidence rate differences (IRDs) on the basis of the case count and person-years in the population and performed additional analyses assuming 25% and 50% sensitivity and 100% specificity of the RGE and AGE ICD-9-CM codes to determine the absolute number of RGE and AGE hospitalizations prevented by the rotavirus vaccine program in the cohort.

All analyses were conducted in SAS, version, 9.2, software (SAS Institute, Inc., Cary, North Carolina). This study was exempt from human subjects review by the institutional review board of the University of North Carolina at Chapel Hill (Chapel Hill, North Carolina).

RESULTS

Cohort

Approximately half (52%) of the 3.94 million infants identified in the enrollment files between January 2000 and December 2010 had a claim for a livebirth (Figure 2). After additional exclusions, 627,818 (78%) of the 905,718 children in the final cohort were born during the rotavirus vaccine period (476,576 were vaccinated with a rotavirus vaccine; 151,242 were unvaccinated). The other 277,900 children were born during the prevaccine baseline period. Among all 627,818 children followed during the rotavirus vaccine period, 379,262 (60%) were followed during parts of 2 calendar years.

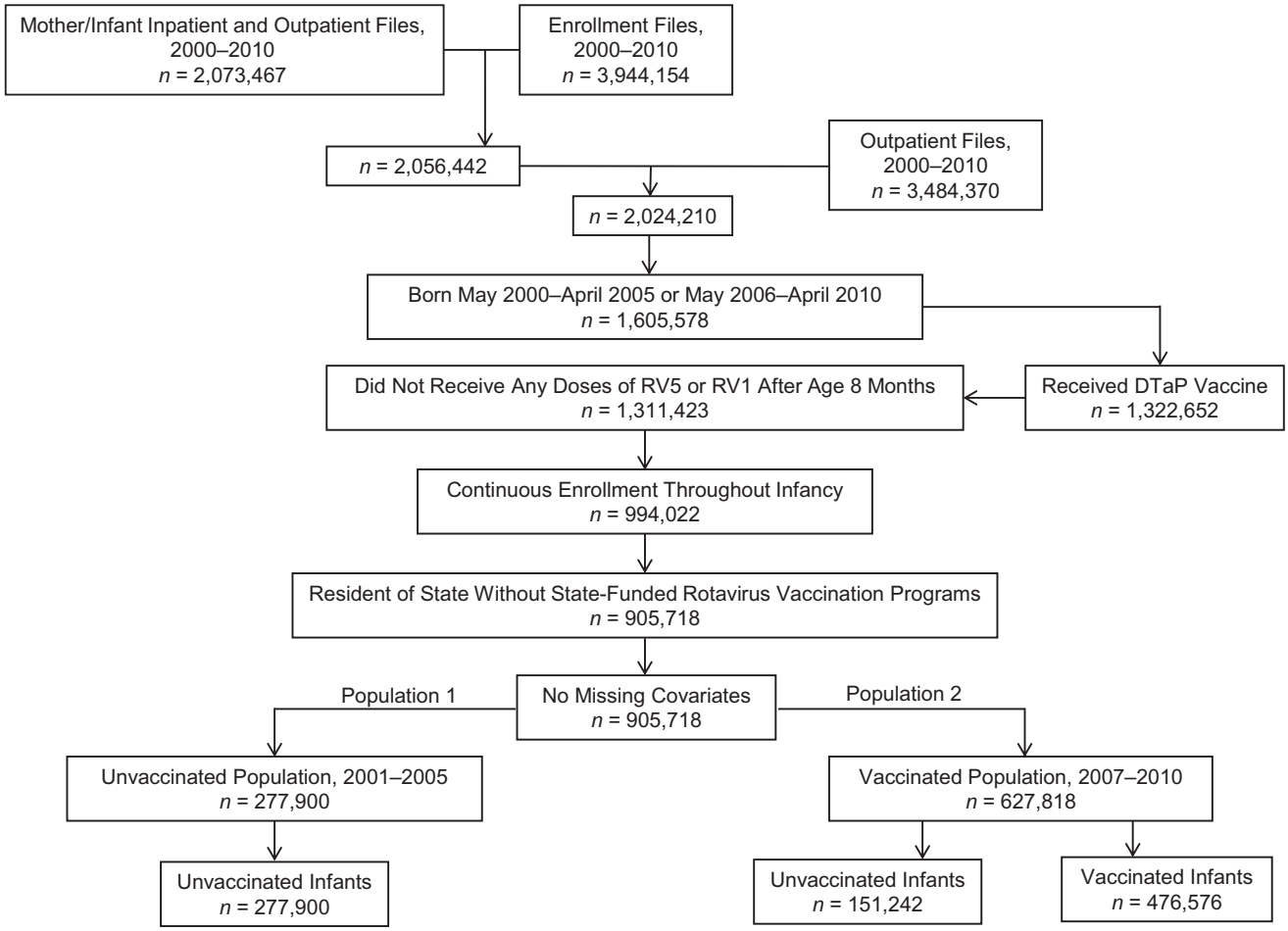

Figure 2. Derivation of the unvaccinated population (population 1) and the vaccinated population (population 2) in the rotavirus vaccine effectiveness cohort study of US commercially insured infants and children 8–20 months of age, 2001–2005 and 2007–2010. Births were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes in inpatient and outpatient records. These records were restricted to infants 0 years of age and to females 10–50 years of age. Twenty-three of 905,718 infants were excluded from this cohort in the final rotavirus gastroenteritis analysis because their cohort entry date (8-month birthday) equaled their cohort exit date (rotavirus gastroenteritis hospitalization date ($n = 4$) or loss of health plan enrollment date ($n = 19$)); for the same reasons, 40 infants were excluded from the final acute gastroenteritis analysis. DTaP, diphtheria, tetanus, and acellular pertussis vaccine; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

Characteristics of the cohort

Almost 76% of the children born during the rotavirus vaccine period received at least 1 dose of RV5 or RV1, of which 79% completed the series. Vaccination rates varied by calendar year, ranging from 51% in 2007 to 86% in 2010. Most vaccinated children (91%) received RV5, and more than 3% received doses of RV5 and RV1. The vaccinated and unvaccinated children were generally comparable (Table 2); however, children residing in the Western United States were better represented during the baseline years than in the vaccine years (19% vs. 11%).

RGE hospitalizations

The number of infants and children in the cohort hospitalized with RGE during follow-up was 1,016 (0.11%). The percentage of infants and children hospitalized for RGE decreased during each calendar period as follows: for 2001–2005, 722/277,899 (0.26%); for 2007, 63/133,309 (0.05%); for 2008, 114/266,941 (0.04%); for 2009, 96/311,253 (0.03%); and for 2010, 21/296,323 (0.01%). The incidence rate of RGE hospitalization in March, the traditional peak of rotavirus activity, ranged from 121 per 10,000 child-years (95% confidence interval (CI): 106, 137) during the prevaccine period to 1 per 10,000 child-years (95% CI: 0, 5) in 2010 (Figure 3).

AGE hospitalizations

Compared with the prevaccine period, the proportions of children hospitalized annually for gastroenteritis during the rotavirus vaccine period were generally consistent for viral (excluding rotavirus), bacterial, and presumed infectious

Table 2. Characteristics of 905,718 Commercially Insured US Infants and Children Vaccinated or Unvaccinated With RV5 or RV1, 2001–2005 and 2007–2010

Variable	Year								
	2001–2005	2007[a]		2008[a]		2009[a]		2010[a]	
	Prevaccine Period, % (*n* = 277,900)	Vaccinated, % (*n* = 68,380)	Not Vaccinated, % (*n* = 64,932)	Vaccinated, % (*n* = 175,768)	Not Vaccinated, % (*n* = 90,883)	Vaccinated, % (*n* = 249,840)	Not Vaccinated, % (*n* = 61,136)	Vaccinated, % (*n* = 254,249)	Not Vaccinated, % (*n* = 41,892)
Male	51.6	50.9	51.4	50.9	51.4	51.1	51.6	51.3	52.0
Hospitalized overnight for non-AGE (before 2 months of age)	3.9	4.0	4.0	3.9	4.0	3.6	4.0	3.5	4.0
No. of siblings	0.9 (1.0)[b]	0.8 (1.0)[b]	0.9 (1.0)[b]	0.8 (1.0)[b]	0.9 (1.0)[b]	0.8 (1.0)[b]	0.9 (1.1)[b]	0.8 (1.0)[b]	0.9 (1.1)[b]
US region of residence									
Northeast	10.4	6.9	9.4	8.4	10.9	11.4	16.7	13.9	22.0
North central	24.4	31.1	34.6	30.0	34.4	28.4	31.1	27.9	26.8
South	46.0	53.5	43.9	52.3	41.9	50.3	39.3	46.2	37.2
West	19.1	8.5	12.1	9.3	12.8	10.0	13.0	12.0	14.1
Population density of residence									
Metro with ≥1 million population	57.7	56.5	58.7	58.1	57.3	60.3	58.0	61.4	59.8
Metro with 250,000–1 million population	19.6	19.3	16.6	19.1	16.8	18.2	15.8	18.6	16.2
Metro with <250,000 population	9.9	11.8	9.6	10.5	9.8	9.9	9.5	9.4	9.0
Urban with ≥20,000 population, adjacent to metro area	3.8	3.8	4.1	3.6	4.1	3.4	4.2	3.3	4.0
Urban with ≥20,000 population, not adjacent to metro area	1.9	1.8	2.5	1.8	2.6	1.7	2.4	1.5	2.1
Urban with 2,500–19,999 population, adjacent to metro area	4.3	4.0	4.9	4.1	5.3	3.9	5.4	3.6	4.9
Urban with 2,500–19,999 population, not adjacent to metro area	1.8	1.8	2.6	1.9	3.0	1.8	3.5	1.6	2.9
Rural with <2,500 population, adjacent to metro area	0.6	0.6	0.6	0.5	0.6	0.5	0.6	0.5	0.4
Rural with <2,500 population, not adjacent to metro area	0.5	0.4	0.5	0.5	0.6	0.4	0.7	0.4	0.6

Abbreviations: AGE, acute gastroenteritis; metro, metropolitan; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.

[a] A total of 379,262 (60%) infants and children were counted during 2 consecutive calendar years during the vaccine period, 2007–2010.

[b] Value is mean (standard deviation).

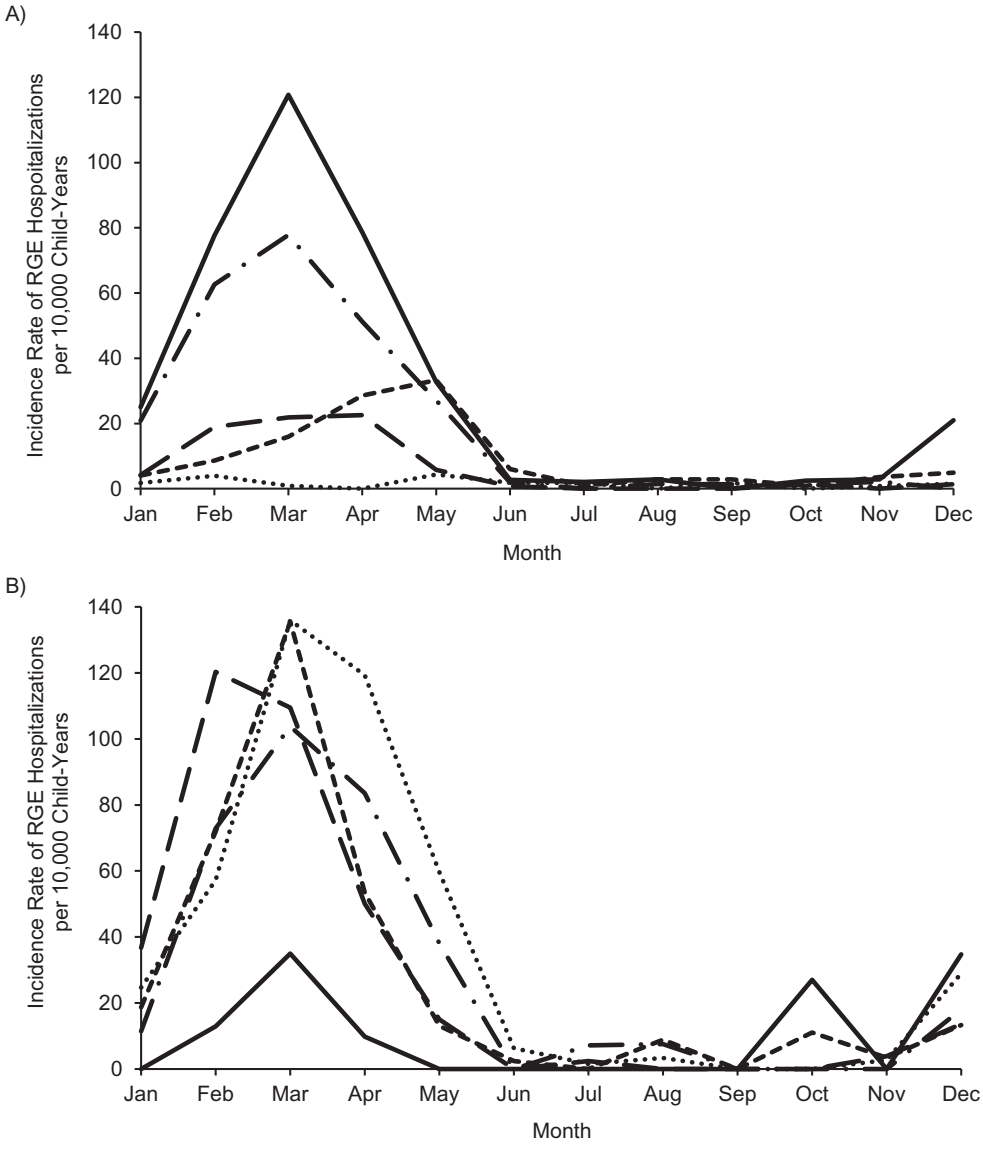

Figure 3. A) Incidence of rotavirus gastroenteritis (RGE) hospitalizations per 10,000 child-years among commercially insured US infants and children 8–20 months of age, individual years following vaccine introduction (2007–2010) versus prevaccine years combined (2001–2005). Solid line, 2001–2005; dashed and dotted line, 2007; small dashed line, 2008; large dashed line, 2009; dotted line, 2010. B) Incidence of RGE hospitalizations per 10,000 child-years among commercially insured US infants and children 8–20 months of age, individual prevaccine years (2001–2005). Solid line, 2001; dashed and dotted line, 2002; small dashed line, 2003; large dashed line, 2004; dotted line, 2005.

gastroenteritis, as well as for diarrhea from other causes, but decreased for rotavirus (as expected) and noninfectious diarrhea (Figure 4). Overall, the number of infants and children in the cohort with an AGE diagnosis was 4,483 (0.49%). The percentage of infants and children hospitalized for AGE during the prevaccine years was 0.73% (2,021/277,893). This percentage declined to 0.31% (413/133,306) in 2007 and continued to decline steadily during the vaccine years, reaching 0.17% (507/296,120) in 2010. Overall, nearly 1 quarter of the AGE diagnoses were coded as RGE. However, the proportion of children with AGE diagnostic codes that corresponded to RGE generally decreased with each successive calendar period (for 2001–2005, 36% (722/2,021); for 2007, 15% (63/413); for 2008, 16% (114/730); for 2009, 12% (96/812); and for 2010, 4% (21/507)). Despite the decline in the proportion of AGE diagnoses coded as RGE through the years, the monthly incidence rate of AGE by year followed a similar pattern as the monthly incidence rate of RGE by year (Figure 5).

Rotavirus VE

Direct VE of 1 or more doses of RV5 or RV1 in preventing RGE hospitalizations between ages 8–20 months ranged

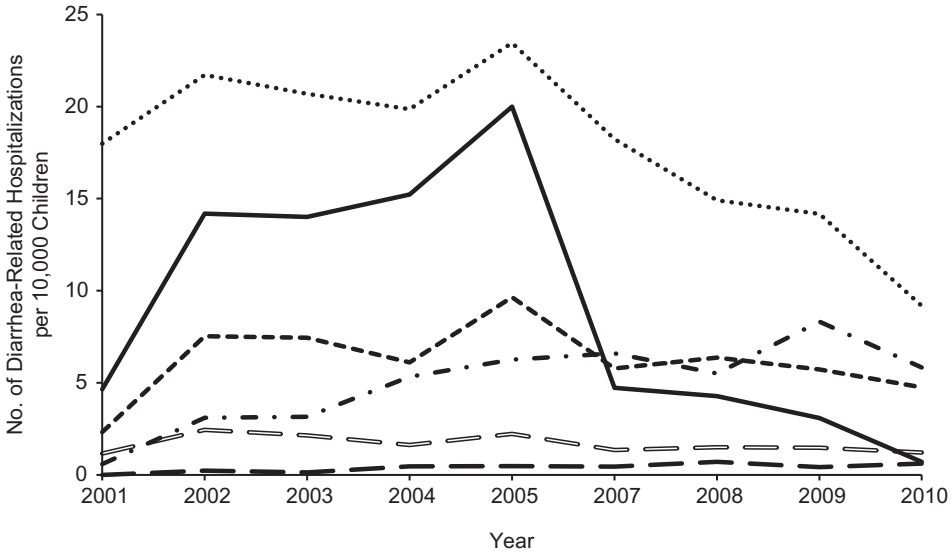

Figure 4. Diarrhea-related hospitalizations per 10,000 children among commercially insured US infants, 8–20 months of age, in the pre–rotavirus vaccine period (2001–2005) and rotavirus vaccine period (2007–2010). Solid black line, rotavirus (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), code 008.61); small black dashed line, viral excluding rotavirus (ICD-9-CM codes 008.6 and 008.8, excluding 008.61); large black dashed line, bacterial (ICD-9-CM codes 001–005 and 008.0–008.5, excluding 003.2); hollow dashed line, presumed infectious (ICD-9-CM codes 009.0–009.3); dotted line, presumed noninfectious (ICD-9-CM code 558.9); dashed and dotted line, diarrhea otherwise specified (ICD-9-CM code, 787.91).

from 87% (95% CI: 58%, 92%) in 2007 and 87% (95% CI: 80%, 92%) in 2008 to 92% (95% CI: 87%, 95%) in 2009 (Table 3). The indirect VE varied more widely, from 14% (95% CI: −14%, 36%) in 2007 to 82% (95% CI: 70%, 90%) in 2010. Accounting for both direct and indirect VE among the rotavirus-vaccinated infants yielded a total VE estimate that increased from 91% (95% CI: 73%, 97%) in 2007 to 98% (95% CI: 96%, 99%) in 2010. The overall VE ranged from 40% (95% CI: 20%, 54%) in 2007 to 96% (95% CI: 93%, 97%) in 2010. The overall VE estimate was low in 2007 compared with that in 2008–2010, but the direct and total VE estimates were high (≥87%) across all 4 calendar years. The rotavirus VE estimates were substantially lower in the prevention of AGE hospitalization, but generally followed a similar pattern to the VE estimates in the prevention of RGE hospitalization (Table 4). Exceptions included the direct VE estimates, which increased through 2009 and then decreased in 2010, and the total VE estimates, which increased 4-fold from 2007 to 2008.

Absolute benefits of rotavirus vaccination

Under the assumption of perfect sensitivity and specificity of the RGE ICD-9-CM code, 31–33 RGE hospitalizations per 10,000 child-years were prevented in vaccinated children, and 10–26 RGE hospitalizations per 10,000 child-years were prevented in unvaccinated children in the cohort during each calendar year from 2007–2010 (among vaccinated children, 6–21 hospitalizations were prevented by direct effects, and 10–26 hospitalizations were prevented by indirect effects) (Table 5). Considering the total effects in the vaccinated and indirect effects in the unvaccinated, to prevent 1 RGE hospitalization in our cohort, 315 $(31.8/10{,}000)^{-1}$ to 421 $(23.8/10{,}000)^{-1}$ children required a rotavirus vaccination. Assuming a more realistic scenario of 50% and 25% sensitivity of the RGE ICD-9-CM code, only 80 $(31.8 \times 4/10{,}000)^{-1}$ to 210 $(23.8 \times 2/10{,}000)^{-1}$ children may have required a rotavirus vaccination to prevent 1 RGE hospitalization. Compared with estimates relying on only RGE diagnostic codes, those using AGE diagnostic codes to estimate the number of RGE hospitalizations prevented in our cohort increased the number by 130%–180% among rotavirus-vaccinated children each calendar year (Table 6).

DISCUSSION

RV5 or RV1 was highly effective in preventing RGE hospitalizations in this population of commercially insured US infants and children aged 8–20 months. Direct VE was high across each calendar year, and indirect protection slightly increased the VE among rotavirus-vaccinated children. By comparison, in another study that examined RGE health care utilization in children under 5 years of age from January to June 2008 and January to June 2009 using the MarketScan Research Databases, high direct VE of 89% (95% CI: 79%, 94%) and 89% (95% CI: 84%, 93%) was also demonstrated (13). In clinical trials, a complete series (3 doses) of RV5 was 98% (95% CI: 88%, 100%) efficacious against severe RGE for the first full rotavirus season after vaccination among infants primarily in the United States and Finland, and a complete series (2 doses) of RV1 was 85% (95% CI: 70%, 94%) efficacious against hospitalizations

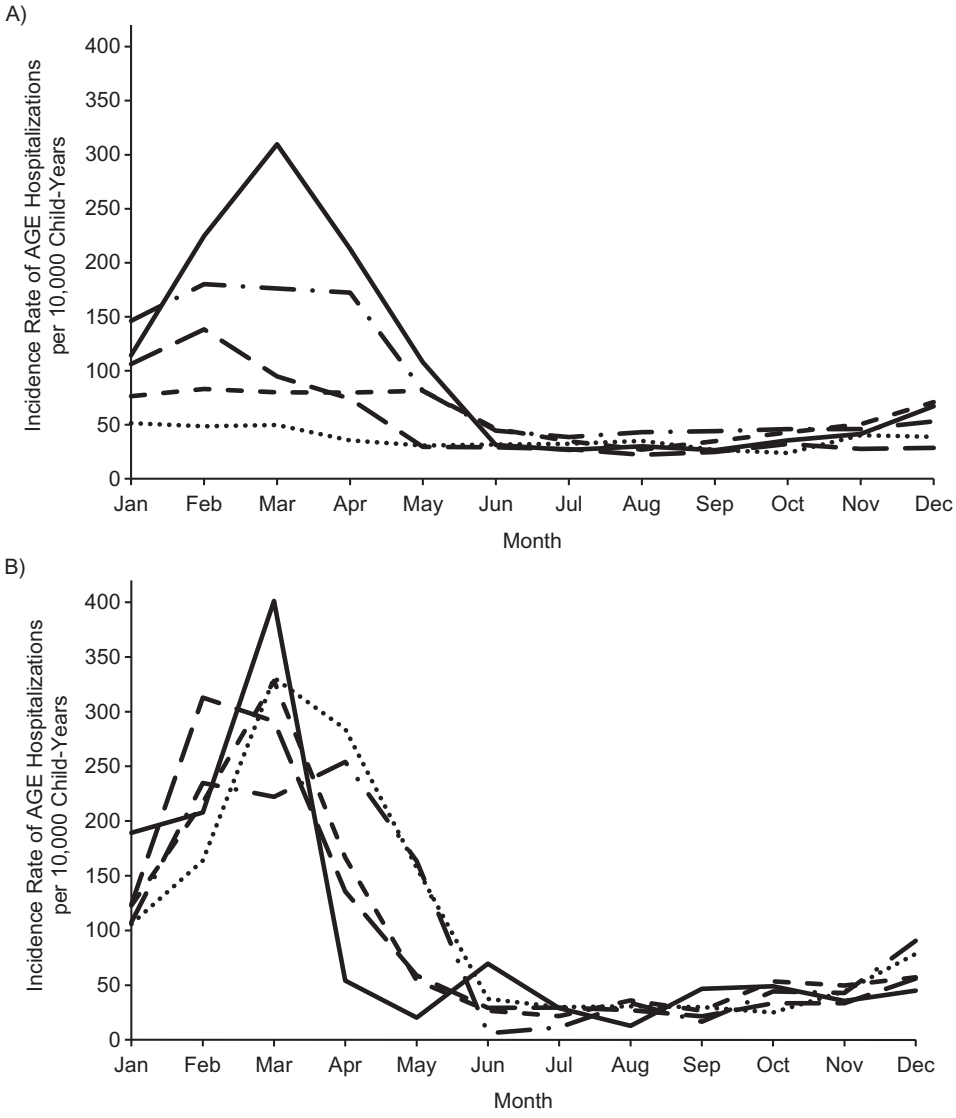

Figure 5. A) Incidence of acute gastroenteritis (AGE) hospitalizations per 10,000 child-years among commercially insured US infants and children, 8–20 months of age, individual years following vaccine introduction (2007–2010) versus prevaccine years combined (2001–2005). Solid line, 2001–2005; dashed and dotted line, 2007; small dashed line, 2008; large dashed line, 2009; dotted line, 2010. B) Incidence of AGE hospitalizations per 10,000 child-years among commercially insured US infants and children, 8–20 months of age, individual prevaccine years (2001–2005). Solid line, 2001; dashed and dotted line, 2002; small dashed line, 2003; large dashed line, 2004; dotted line, 2005.

for severe RGE from 2 weeks after the second dose until 1 year of age among infants in Latin America (15, 16). Our direct VE estimates were similar to those calculated in the aforementioned clinical trials, despite the fact that 21% of the infants in our postmarketing study did not complete a rotavirus vaccine series. In our view, this observation has 2 possible explanations.

First, partial completion of a rotavirus vaccine series may still result in high direct VE. This observation has been supported by other postmarketing studies, including an active, prospective, population-based case-control study of laboratory-confirmed RGE hospitalizations and emergency department visits in 3 US counties from January to June 2006 to January to June 2009. With rotavirus-negative AGE controls, the direct VEs of RV5 for 1-, 2-, and 3-dose rotavirus vaccine regimens were 74% (95% CI: 37%, 90%), 88% (95% CI: 66%, 96%), and 87% (95% CI: 71%, 94%) in children under 4 years of age (17). Another study that used a database from a large US health insurer to estimate 1- and 2-dose direct VE estimates in preventing RGE hospitalizations and emergency department visits for RV5 during the 2007 and 2008 rotavirus seasons found similarly high VE (for 1 dose, VE = 88%, 95% CI: 45%, 99%; for 2 doses, VE = 94%, 95% CI: 61%, 100%) (18).

An alternative explanation may be that our direct VE estimates are biased upward. A mathematical model showed that

Table 3. Rotavirus Vaccine Effectiveness Estimates Against Rotavirus Gastroenteritis Hospitalization[a] in US Commercially Insured Infants and Children 8–20 Months of Age, 2007–2010

Calendar Year by Effectiveness	Vaccinated With ≥1 Dose of RV5 or RV1, %	Vaccinated		Unvaccinated		Total (Vaccinated and Unvaccinated)		Vaccine Effectiveness[b]	95% CI
		No. of Events	Total No. of Children	No. of Events	Total No. of Children	No. of Events	Total No. of Children		
Direct effectiveness									
2007	51.3	3	68,380	60	64,929			87	58, 96
2008	65.9	23	175,890	91	91,051			87	80, 92
2009	80.3	22	250,035	74	61,218			92	87, 95
2010	85.9	8	254,377	13	41,946			90	75, 96
Indirect effectiveness									
2007	51.3			60	64,929			14	−14, 36
2008	65.9			91	91,051			44	30, 55
2009	80.3			74	61,218			40	24, 53
2010	85.9			13	41,946			82	70, 90
Total effectiveness									
2007	51.3	3	68,380					91	73, 97
2008	65.9	23	175,890					92	88, 95
2009	80.3	22	250,035					95	92, 97
2010	85.9	8	254,377					98	96, 99
Overall effectiveness									
2007	51.3					63	133,309	40	20, 54
2008	65.9					114	266,941	75	69, 79
2009	80.3					96	311,253	83	79, 86
2010	85.9					21	296,323	96	93, 97

Abbreviations: CI, confidence interval; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.
[a] During the prevaccine period (2001–2005), there were 722 events among 277,899 children.
[b] Adjusted for birth month and age using the formula, (1 − hazard ratio) × 100.

when a vaccine provides indirect protection, and the percent vaccinated in subpopulations is not equal (the likely scenario for most postmarketing studies), then direct VE estimates may be biased upward from clinical trial efficacy estimates because the vaccinated subpopulation will receive more indirect protection than the unvaccinated subpopulation (19). Thus, our direct VE estimates may in fact have included measures of indirect protection.

We expected indirect or "herd" protection against RGE hospitalizations to increase with each successive calendar year from 2007 to 2010, but this was not the case. The calendar year 2009 had a slightly lower indirect VE estimate than 2008 (44% vs. 40%). Although a lack of difference between these estimates cannot be ruled out given the overlapping confidence intervals, smaller or total absences of indirect protection in 1-year-olds in 2009 has been observed in other studies (11, 13, 20). Although some of these studies used external rates to estimate rotavirus vaccine coverage, and thus do not quantify measures of indirect VE, they have hypothesized that the low levels of rotavirus activity during the 2008 season allowed unvaccinated children to pass through the season without exposure to wild-type virus until 2009 (11, 20). However, because rotavirus activity in the United States was also curtailed in 2009, and the indirect VE estimate more than doubled to 82% in 2010 in our study, additional years of follow-up using the MarketScan Research Databases and other data sources may be needed to better establish time trends related to the indirect effectiveness of rotavirus vaccination in the United States. Rapid declines of rotavirus vaccine activity during the study period complicate the interpretation of the impact of indirect VE.

Compared with 2008 and 2009, in 2010, the more than 3-fold decrease in the direct IRD (despite high direct VE) and nearly 3-fold increase in the indirect IRD support our finding that rotavirus circulation was very limited in 2010 (Table 5, Figure 3). In such scenarios, reporting IRDs that incorporate impact at the population level (i.e., indirect, total, and overall) may be important if the objective is to measure the public health benefit rather than the clinical benefit. For instance, assuming perfect sensitivity and specificity, if the direct IRD in 2010 had been used rather than the overall IRD to calculate the number of children requiring a vaccine to prevent 1 RGE hospitalization, 1,613 children $((6.2/10{,}000)^{-1})$ or approximately 4–5 times as many would need to be vaccinated. From a clinical point of view, this estimate may be reasonable (i.e., physicians may be required to

Table 4. Rotavirus Vaccine Effectiveness Estimates Against Acute Gastroenteritis Hospitalization[a] in US Commercially Insured Infants and Children 8–20 Months of Age, 2007–2010

Calendar Year by Effectiveness	Vaccinated With ≥1 Dose of RV5 or RV1, %	Vaccinated		Unvaccinated		Total (Vaccinated and Unvaccinated)		Vaccine Effectiveness[b]	95% CI
		No. of Events	Total No. of Children	No. of Events	Total No. of Children	No. of Events	Total No. of Children		
Direct effectiveness									
2007	51.3	142	68,378	271	64,928			22	3, 37
2008	65.9	413	175,765	317	90,882			40	30, 48
2009	80.3	512	249,838	300	61,136			56	49, 62
2010	85.9	398	254,232	109	41,888			41	27, 53
Indirect effectiveness									
2007	51.3			271	64,928			−8	−24, 6
2008	65.9			317	90,882			24	15, 33
2009	80.3			300	61,136			9	−3, 19
2010	85.9			109	41,888			45	33, 54
Total effectiveness									
2007	51.3	142	68,378					12	−5, 27
2008	65.9	413	175,765					48	43, 53
2009	80.3	512	249,838					59	54, 62
2010	85.9	398	254,232					65	62, 69
Overall effectiveness									
2007	51.3					413	133,306	0	−13, 11
2008	65.9					730	266,647	40	35, 45
2009	80.3					812	310,974	48	44, 52
2010	85.9					507	296,120	62	58, 66

Abbreviations: CI, confidence interval; RV1, monovalent rotavirus vaccine; RV5, pentavalent rotavirus vaccine.
[a] During the prevaccine period (2001–2005), there were 2,021 events among 277,893 children.
[b] Adjusted for birth month and age using the formula, (1 − hazard ratio) × 100.

vaccinate a larger number of infants in 2010 compared with earlier years to prevent 1 RGE hospitalization); however, such use of the direct IRD in 2010 makes the rotavirus vaccine appear to be a less effective public health intervention when, in reality, the decreased circulation of rotavirus, which helped to substantially reduce the rate of hospitalizations in unvaccinated children, should be attributed to the vaccine, and in our view, accounted for in estimates when the public health perspective is of primary interest.

Our study has important strengths. First, across both time and vaccination status, the infants and children in the 5 calendar periods we examined were generally well balanced on selected covariates, which included proxies for health, potential sources of rotavirus infection, and population-level rotavirus vaccination coverage and mixing patterns. Because all cohort members were commercially insured and required to have at least 1 outpatient claim and at least 1 dose of diphtheria, tetanus, and acellular pertussis vaccine during infancy, such inclusion criteria may have led to the relatively good balance between the groups with regard to the measured, and hopefully, unmeasured, potential confounders. Second, because we used Cox proportional hazards regression, our analyses inherently adjusted for age. We also stratified by year to account for increasing vaccination coverage, and we adjusted for month of birth to account for the changing seasonality of rotavirus over the study period. Further adjustment using the covariates we described in Table 1 did not appreciably change our VE estimates (data not shown). This lack of change was not surprising because the groups seemed well balanced. Third, baseline rates (in 2001–2005) of RGE hospitalizations used to estimate indirect, total, and overall VE and corresponding IRDs in our study were the same as baseline rates from 2002 to 2006 in 1-year-olds in another study using MarketScan Research Databases (33 per 10,000 child-years) (13) and were similar to baseline rates from 2000 to 2006 in those aged 12–17 months in a State Inpatient Database study (32 per 10,000 child-years, 95% CI: 25, 40) (11). This finding was reassuring because 3 of the 4 VE and IRD measures relied on baseline estimates. Finally, our study provided some evidence that the decline of RGE hospitalizations from 2007 to 2010 was due to the rotavirus vaccines and not another extraneous cause. Figure 4 illustrates a sharp decline in the proportion of children hospitalized for RGE during the rotavirus vaccine period; however, proportions of children hospitalized from other infectious causes of gastroenteritis, including other viral and bacterial pathogens, remained consistent with pre–rotavirus vaccine years. This would be expected in the absence of time trends and when the rotavirus

Table 5. Absolute Reduction per 10,000 Child-Years of Rotavirus Gastroenteritis Hospitalizations Prevented by the Rotavirus Vaccination Program in Commercially Insured US Infants and Children 8–20 Months of Age, 2007–2010[a]

Calendar Year by Effectiveness	Observed No. of RGE Hospitalizations in Minuend	No. of Child-Years in Minuend	Rate Per 10,000 Child-Years (IR_1)	Observed No. of RGE Hospitalizations in Subtrahend	No. of Child-Years in Subtrahend	Rate Per 10,000 Child-Years (IR_0)	Observed IRD Per 10,000 Child-Years[b]	95% CI for IRD
Direct effectiveness: vaccinated versus unvaccinated in same year								
2007	3	28,250	1.1	60	37,791	15.9	−14.8	−19.0, −10.6
2008	23	85,452	2.7	91	39,447	23.1	−20.4	−25.2, −15.5
2009	22	131,381	1.7	74	32,292	22.9	−21.2	−26.5, −16.0
2010	8	118,708	0.7	13	18,981	6.8	−6.2	−9.9, −2.4
Indirect effectiveness: unvaccinated versus prevaccine period[c]								
2007	60	37,791	15.9	722	216,767	33.3	−17.4	−22.1, −12.7
2008	91	39,447	23.1	722	216,767	33.3	−10.2	−15.6, −4.9
2009	74	32,292	22.9	722	216,767	33.3	−10.4	−16.2, −4.6
2010	13	18,981	6.8	722	216,767	33.3	−26.5	−30.9, −22.0
Total effectiveness: vaccinated versus prevaccine period[c]								
2007	3	28,250	1.1	722	216,767	33.3	−32.3	−35.0, −29.5
2008	23	85,452	2.7	722	216,767	33.3	−30.6	−33.3, −28.0
2009	22	131,381	1.7	722	216,767	33.3	−31.6	−34.2, −29.1
2010	8	118,708	0.7	722	216,767	33.3	−32.6	−35.1, −30.2
Overall effectiveness: total in vaccine year versus prevaccine period[c]								
2007	63	66,041	9.5	722	216,767	33.3	−23.8	−27.2, −20.4
2008	114	124,899	9.1	722	216,767	33.3	−24.2	−27.1, −21.2
2009	96	163,673	5.9	722	216,767	33.3	−27.4	−30.1, −24.7
2010	21	137,689	1.5	722	216,767	33.3	−31.8	−34.3, −29.3

Abbreviations: CI, confidence interval; IRD, incidence rate difference.

[a] Assumes 100% sensitivity and specificity of the rotavirus gastroenteritis diagnostic code.

[b] Calculated using the formula $IR_1 - IR_0$.

[c] Prevaccine period, 2001–2005.

Table 6. Absolute Reduction per 10,000 Child-Years of Acute Gastroenteritis Hospitalizations Prevented by the Rotavirus Vaccination Program in Commercially Insured US Infants and Children, 2007–2010[a]

Calendar Year by Effectiveness	Observed No. of Acute Gastroenteritis Hospitalizations in Minuend	No. of Child-Years in Minuend	Rate Per 10,000 Child-Years (IR_1)	Observed No. of AGE Hospitalizations in Subtrahend	No. of Child-Years in Subtrahend	Rate Per 10,000 Child-Years (IR_0)	Observed IRD Per 10,000 Child-Years[b]	95% CI for IRD
Direct effectiveness: vaccinated versus unvaccinated in same year								
2007	142	28,209	50.3	271	37,696	71.9	−21.6	−33.5, −9.6
2008	413	85,259	48.4	317	39,319	80.6	−32.2	−42.2, −22.2
2009	512	131,096	39.1	300	32,165	93.3	−54.2	−65.3, −43.1
2010	398	118,520	33.6	109	18,932	57.6	−24.0	−35.3, −12.7
Indirect effectiveness: unvaccinated versus prevaccine period[c]								
2007	271	37,696	71.9	2,021	216,117	93.5	−21.6	−31.1, −12.1
2008	317	39,319	80.6	2,021	216,117	93.5	−12.9	−22.7, −3.1
2009	300	32,165	93.3	2,021	216,117	93.5	−0.3	−11.6, 11.1
2010	109	18,932	57.6	2,021	216,117	93.5	−35.9	−47.5, −24.4
Total effectiveness: vaccinated versus prevaccine period[c]								
2007	142	28,209	50.3	2,021	216,117	93.5	−43.2	−52.4, −34.0
2008	413	85,259	48.4	2,021	216,117	93.5	−45.1	−51.3, −38.9
2009	512	131,096	39.1	2,021	216,117	93.5	−54.5	−59.8, −49.2
2010	398	118,520	33.6	2,021	216,117	93.5	−59.9	−65.2, −54.7
Overall effectiveness: total in vaccine year versus prevaccine period[c]								
2007	413	65,905	62.7	2,021	216,117	93.5	−30.9	−38.1, −23.6
2008	730	124,578	58.6	2,021	216,117	93.5	−34.9	−40.8, −29.0
2009	812	163,261	49.7	2,021	216,117	93.5	−43.8	−49.1, −38.5
2010	507	137,452	37.0	2,021	216,117	93.5	−56.6	−61.8, −51.4

Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; IRD, incidence rate difference.

[a] Assumes 100% sensitivity and specificity of the AGE diagnostic codes.

[b] Calculated using the formula, $IR_1 - IR_0$.

[c] Prevaccine period, 2001–2005.

vaccine ICD-9-CM code is specific to RGE. Interestingly, the proportion of hospitalizations due to presumed noninfectious diarrhea declined steadily during the rotavirus vaccine period, for which reasons are currently unknown.

Our results should be interpreted with caution because of some limitations. First, the ICD-9-CM code for RGE likely had low sensitivity, and the sensitivity analyses made assumptions that may not have been entirely realistic, including that the sensitivity did not vary over time or between vaccinated and unvaccinated children, that estimates of 25% and 50% sensitivity were reasonable, and that the specificity of the RGE ICD-9-CM code was 100% (9, 10, 21). ICD-9-CM diagnostic codes for AGE were also subject to low sensitivity; a recent study conducted at 3 US children's hospitals found that only 52% of children hospitalized with AGE received a qualifying diagnostic code at discharge (22). Fortunately, low sensitivity of RGE or AGE ICD-9-CM codes would not bias VE estimates assuming 100% specificity. We can assume specificity close to 100% on the basis of a study conducted at a large US children's hospital that found the rotavirus ICD-9-CM code to be 97% specific (10), and another study showing RGE and AGE hospitalization patterns similar to those in our study (11).

Second, we limited follow-up of infants and children to 1 year (8–20 months of age) to minimize bias, because children enrolled for longer periods may differ with respect to unmeasured confounding factors from those enrolled for shorter periods of time. This restriction may have helped increase the generalizability of the results for those aged 8–20 months while decreasing the generalizability to other age groups. One modeling study and 1 study using a convenience sample of laboratories suggested that the US rotavirus vaccine program may have increased the mean age at which infants and children are first infected with rotavirus, and thus are potentially hospitalized with RGE (23, 24). Despite this potential shift, our study would still appropriately document rotavirus VE among those aged 8–20 months, and because RGE hospitalizations are generally most serious in very young children (e.g., <2 years), our study would still have captured many of the most clinically significant cases.

Third, our study considered infants receiving any number of doses of rotavirus vaccine as "vaccinated" and did not compare the direct VE of RV5 with that of RV1 because of the limited number of infants vaccinated with RV1. A few comparative effectiveness studies, as well as studies assessing partial rotavirus vaccine effectiveness, have been published, and ongoing monitoring should continue to assess these questions (17, 18, 25–28).

Fourth, our study could not confirm whether more children tested negative for rotavirus or were less frequently tested over time because we did not have access to laboratory results. Based on the US National Respiratory and Enteric Virus Surveillance System data, rotavirus testing may have decreased from July 2009 to June 2010 (29). In a study using these data, the numbers of antigen detection tests performed in 25 consistently reporting laboratories from the month of July to June of the following year during the periods 2000–2006, 2007–2008, and 2008–2009 were similar, but from July 2009 to June 2010, the number of tests declined by approximately 1 quarter to 9,909; however, the proportion of tests that were positive for rotavirus also declined by approximately half, from 9.0% and 10.7% in 2007–2008 and 2008–2009, respectively, to 4.6% in 2009–2010 (29). On the basis of these data, we assumed that, although testing may have decreased during the last rotavirus season in our study (in 2010), testing decreased because fewer children presented as inpatients with potential RGE. Thus, we do not think that changes in testing policies biased our results.

Finally, our study may have limited generalizability because it involved only US infants and children with commercial insurance and did not include those with Medicaid insurance (35% of the US population 0–18 years of age in 2012) or the uninsured population (9% of the US population 0–18 years of age in 2012) (7). Although data are limited, enrollment in Medicaid during childhood appears to have been steady over the last decade, alleviating some concern that fluctuations over time could further limit the generalizability and comparability of our cohorts (7, 30). Although direct VE is less likely to show relevant heterogeneity across US populations, all measures involving indirect VE would tend to be population specific.

If a vaccine has high direct VE, such measurements may only slightly underestimate the total VE because VE cannot exceed 100%. However, if low circulation of a pathogen is attributed to a vaccine program, failing to consider population-level VE measures on the absolute scale (e.g., indirect, total, and overall IRD) may substantially underestimate the sustained impact of the program on important public health outcomes.

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REFERENCES

1. Halloran ME, Struchiner CJ, Longini IM Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol*. 1997;146(10):789–803.
2. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further observations. *Epidemiol Rev*. 1988;10(1):212–241.
3. Schuchat A, Bell BP. Monitoring the impact of vaccines postlicensure: new challenges, new opportunities. *Expert Rev Vaccines*. 2008;7(4):437–456.
4. Charles MD, Holman RC, Curns AT, et al. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993–2002. *Pediatr Infect Dis J*. 2006;25(6):489–493.
5. Cortese MM, Parashar UD, Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58(RR-2):1–25.
6. United States Census Bureau, US Department of Commerce. The 2012 statistical abstract: births, deaths, marriages, & divorces. Updated June 27, 2012. http://www.census.gov/compendia/statab/cats/births_deaths_marriages_divorces.html. Accessed March 10, 2013.
7. The Henry J. Kaiser Family Foundation. State health facts: health insurance coverage of children 0–18. 2013. http://kff.org/other/state-indicator/children-0-18. Accessed December 12, 2013.
8. Centers for Disease Control and Prevention. Immunization information systems. CPT codes mapped to CVX codes. Updated September 11, 2013. http://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=cpt. Accessed February 5, 2014.
9. Patel MM, Tate JE, Selvarangan R, et al. Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination. *Pediatr Infect Dis J*. 2007;26(10):914–919.
10. Hsu VP, Staat MA, Roberts N, et al. Use of active surveillance to validate international classification of diseases code estimates of rotavirus hospitalizations in children. *Pediatrics*. 2005;115(1):78–82.
11. Desai R, Curns AT, Steiner CA, et al. All-cause gastroenteritis and rotavirus-coded hospitalizations among US children, 2000–2009. *Clin Infect Dis*. 2012;55(4):e28–e34.
12. Cortes JE, Curns AT, Tate JE, et al. Trends in healthcare utilization for diarrhea and rotavirus disease in privately insured US children <5 years of age, 2001–2006. *Pediatr Infect Dis J*. 2009;28(10):874–878.
13. Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. *N Engl J Med*. 2011;365(12):1108–1117.
14. United States Department of Agriculture, Economic Research Service. 2003 Rural-urban continuum codes. Updated May 10, 2013. http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx. Accessed March 10, 2013.
15. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354(1):23–33.
16. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354(1):11–22.
17. Staat MA, Payne DC, Donauer S, et al. Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics*. 2011;128(2):e267–e275.
18. Wang FT, Mast TC, Glass RJ, et al. Effectiveness of an incomplete RotaTeq (RV5) vaccination regimen in preventing rotavirus gastroenteritis in the United States. *Pediatr Infect Dis J*. 2013;32(3):278–283.
19. Patel MM, Tate J, Cortese M, et al. The impact of indirect benefits of vaccination on postlicensure vaccine effectiveness estimates: a scenario analysis. *Vaccine*. 2010;28(50):7987–7992.
20. Payne DC, Staat MA, Edwards KM, et al. Direct and indirect effects of rotavirus vaccination upon childhood hospitalizations in 3 US counties, 2006–2009. *Clin Infect Dis*. 2011;53(3):245–253.
21. Nelson EA, Tam JS, Bresee JS, et al. Estimates of rotavirus disease burden in Hong Kong: hospital-based surveillance. *J Infect Dis*. 2005;192(suppl 1):S71–S79.
22. Matson DO, Staat MA, Azimi P, et al. Burden of rotavirus hospitalisations in young children in three paediatric hospitals in the United States determined by active surveillance compared to standard indirect methods. *J Paediatr Child Health*. 2012;48(8):698–704.
23. Pitzer VE, Viboud C, Simonsen L, et al. Demographic variability, vaccination, and the spatiotemporal dynamics of rotavirus epidemics. *Science*. 2009;325(5938):290–294.
24. Hull JJ, Teel EN, Kerin TK, et al. United States rotavirus strain surveillance from 2005 to 2008: genotype prevalence before and after vaccine introduction. *Pediatr Infect Dis J*. 2011;30(1 suppl):S42–S47.
25. Patel MM, Steele D, Gentsch JR, et al. Real-world impact of rotavirus vaccination. *Pediatr Infect Dis J*. 2011;30(1 suppl):S1–S5.
26. Tate JE, Cortese MM, Payne DC, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States. *Pediatr Infect Dis J*. 2011;30(1 suppl):S56–S60.

27. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's national childhood vaccine schedule. *Pediatr Infect Dis J*. 2011; 30(1 suppl):S25–S29.
28. Martinón-Torres F, Bouzón Alejandro M, Redondo Collazo L, et al. Effectiveness of rotavirus vaccination in Spain. *Hum Vaccin*. 2011;7(7):757–761.
29. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J*. 2011;30(1 suppl):S30–S34.
30. Ma L, El Khoury AC, Itzler RF. The burden of rotavirus hospitalizations among Medicaid and non-Medicaid children younger than 5 years. *Am J Public Health*. 2009;99(suppl 2): S398–S404.