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Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine

A systematic review of the experience in industrialized countries

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Key words: rotavirus, RotaTeq, vaccine effectiveness, vaccination impact, hospitalization, laboratory

Abbreviations: AGE, acute gastroenteritis; ARI, acute respiratory infections; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis vaccine; ED, emergency department; OR, odds ratio; RR, relative risk; RV, rotavirus; RVGE, rotavirus gastroenteritis; VE, vaccine effectiveness

The pentavalent rotavirus (RV) vaccine RotaTeq™ has been available in industrialized countries since 2006. Several studies have been conducted to evaluate the benefit of RV vaccination under routine conditions of use. A systematic review of all publicly available data from RotaTeq™ vaccine-effectiveness and vaccination-impact studies in the US, Europe and Australia between 2006 and February 2010 was undertaken. Depending on the population studied, effectiveness of up to 100% (95% confidence interval 85–100%) associated with decreased hospitalizations for RV gastroenteritis (RVGE) was seen. Vaccination-impact studies demonstrated that the burden of RVGE has been reduced significantly since the introduction of RV vaccination. Evidence included reductions in healthcare utilization due to RVGE (hospitalizations and emergency-department visits reduced by up to 90%), reductions in the magnitude and duration of the RV season as assessed by laboratory testing for RV, and the possible induction of herd immunity.

Introduction

Rotavirus (RV) is the most common cause of severe acute gastroenteritis (AGE) in young children worldwide.[1-4] RV infections are most common in children aged 6–24 months,[2,5] most children will have been infected by 2–3 years of age,[6] and many are infected more than once.[7] RV gastroenteritis (RVGE) is an important cause of death due to diarrhea in children younger than 5 years of age worldwide, among whom it is estimated to cause 527,000 deaths [95% confidence interval (CI), 475,000–580,000] annually or 29% of all deaths due to diarrhea.[8] Most of the mortality is in non-industrialized countries where suboptimal access to treatment for dehydrating diarrhea can often lead to death.[2]

RV is a significant public health problem in industrialized countries mainly because of the significant burden it places on healthcare resource use. For example, RVGE has been reported to result in ~55,000–70,000 hospitalizations, 205,000–272,000 visits to the emergency department (ED) and 410,000 visits to the physician's office annually in the US.[9] During the usual RV season, RVGE has accounted for 53.8% of hospitalizations, 59.1% of ED visits and 47.4% of outpatient visits in children aged under 5 years presenting with community-acquired AGE in the US,[10] and RVGE has been estimated to account for up to half of all hospitalizations and ED visits for AGE in children less than 3 years of age in the US.[11] Similarly, in European studies, RVGE has been estimated to account for up to 52% of all AGE cases in children younger than 5 years of age in Europe,[12] and for 56.2% of hospitalizations and 32.8% of ED visits for community-acquired AGE in this age group.[13] Epidemiological studies from Australia suggest a mean of 4,260 patients are hospitalized for RVGE each year, with the highest admission rates seen in children aged 6–12 months (618.4 per 100,000).[14]

There are significant direct and indirect costs associated with RVGE. Caring for a child with RVGE also places an emotional burden on families, with parents reporting considerable levels of stress.[15-17] Direct costs associated with medical care for

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Appendix I. Search strategy for EMBASE

#	Search history	Results
1	effectiveness OR 'population surveillance'/exp OR 'population surveillance' OR 'epidemiologic studies'/exp OR 'epidemiologic studies' OR 'surveillance' OR 'case-control studies'/exp OR impact OR 'case-control studies' OR cohort*:ab,ti OR 'retrospective studies'/exp OR retrospective OR 'case-control' OR observational	2,237,378
2	'program evaluation' OR 'program effectiveness' OR 'treatment effectiveness'/exp OR 'treatment effectiveness' OR 'treatment outcome'/exp OR 'treatment outcome' OR 'outcome assessment'/exp OR 'outcome assessment'	4,759,412
3	'rotavirus' OR rota NEAR/3 virus OR 'rotavirus'/exp OR rotavirus	11,102
4	'vaccine'/exp OR 'vaccine' OR vaccine* OR 'immunization'/exp OR 'immunization' OR 'immunization'/exp OR 'immunisation'	339,345
5	'RotaTeq'/exp OR RotaTeq OR 'rotarix'/exp OR rotarix	1,909
6	#3 AND #4 OR #5	3,429
7	#6 AND (#1 OR #2)	2,585
8	review* OR 'cost of illness'/exp OR 'cost of illness' OR 'clinical trial': it OR 'randomized controlled trial': ab,ti OR placebo	2,656,254
9	'asia'/exp OR 'asia' OR 'africa'/exp OR 'africa'	628,542
10	#7 AND [2006-2010]/py NOT #8 NOT #9	526

RVGE (e.g., hospitalizations) have been estimated to account for >US$250 million each year in the US.[18,19] The estimated median direct costs per child for hospitalization and ED visits have been estimated to be US$4565 and US$867, respectively.[10] In addition, the indirect costs of caring for children affected by RVGE place a considerable burden on society and families. For example, the total cost of working days lost by parents due to their child's illness amounts to >US$700 million annually in the US.[18,19] Taken together, the indirect and direct costs associated with RV illness are substantial. A study in Europe found that the total cost per episode of RVGE requiring hospitalization ranged from €1,525 in France to €2,100 in Sweden.[15] In the US, the total costs of RVGE are estimated to be ~US$1 billion per year.[18,19]

The public health burden of RVGE made the development of RV vaccine a high priority. Two RV vaccines have been licensed for infant vaccination since 2006. RotaTeq™ is an oral, live pentavalent [G1, G2, G3, G4 and P(8)] human-bovine (WC3) reassortant RV vaccine administered as a three-dose series from 6 weeks of age with a minimum of 4 weeks between doses. It was licensed in the US and the European Union (EU) in 2006, and was the only RV vaccine licensed in the US until 2008. In large randomized, placebo-controlled, clinical trials, the three-dose vaccination schedule for RotaTeq™ was 98.0% (95% CI 88.3–100%) effective against severe RVGE over the first full RV season post-vaccination, whereas efficacy against all RVGE was 74.0% (95% CI 66.8–79.9%).[20] Furthermore, for the cohort from European countries, the combined rates of hospitalizations and ED visits due to all RVGE were reduced by 94.5% (95% CI 91.3–96.8%) over 2 years post-vaccination.[21] Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) is an oral live, monovalent [G1P(8)], attenuated, human RV vaccine that has been licensed in the EU since 2006 and in the US since 2008. It is administered as a two-dose series from 6 weeks of age, with a minimum of 4 weeks between doses. In a phase III trial, the two-dose vaccination schedule for Rotarix was 84.7% (95% CI 71.7–92.4%) effective against severe RVGE, 40.0% (95% CI 27.7–50.4%) effective against severe GE of any cause, and reduced hospitalizations for severe RVGE by 85.0% (95% CI 69.6–93.5%) from 2 weeks after the second dose until 1 year of age.[22]

After its introduction, RotaTeq™ quickly became widely used in the US, and some parts of the EU and Australia. After its licensure, several studies to evaluate the benefit of RV vaccination under routine conditions of use were conducted. The real-life benefit of a vaccine may be assessed through effectiveness studies (evaluation of the effect of the vaccine in a real-life setting) or through impact studies (evaluation of the public health benefit of a vaccination program in general). Such studies are important to evaluate how the efficacy obtained under the ideal conditions of randomized controlled trials translates to conditions of routine use. They also allow assessment of the early benefits of the vaccine as well as monitoring of those benefits over time. These studies are therefore important for future policy considerations in countries or regions that have not yet adopted the vaccine. This review summarizes recent data on the effectiveness of RotaTeq™ and the public health impact of RV vaccines in industrialized countries in which RotaTeq™ was widely used. At the time of this systematic review, many of these studies had been reported only in abstract form at scientific congresses. The review therefore encompassed all data in the public domain (abstracts or peer-reviewed publications) to gain the fullest possible understanding of the early impact of RV vaccination on public health.

Selection of Studies

All prospective or retrospective observational studies and registry data reporting the effectiveness or impact of RV vaccines in the US, Europe or Australia and published (or presented at conferences) between January 2006 and 25 February 2010 were eligible for inclusion. Review articles, editorials, randomized controlled trials and publications in a language other than English, German, Italian, French or Spanish were excluded. The EMBASE and PubMed databases were searched using the strategies summarized in **Appendices I and II**, respectively. In addition, the abstracts from relevant conferences (**Appendix III**) were hand-searched to identify studies that met the inclusion criteria.

Preliminary searches yielded 526 distinct references from EMBASE, 293 references from PubMed, and 28 references from conference proceedings. After removal of duplicates, the title and abstract for the remaining citations (n = 656) were screened. Those that did not match the eligibility criteria were excluded (**Fig. 1**). Fifty-eight references from EMBASE/PubMed and 24 abstracts from congresses that met the eligibility criteria were identified. Full-text copies of all journal publications were

obtained. An attempt was made to obtain the corresponding presentation (posters or slides) for abstracts from congresses. After detailed examination, a further 43 publications were excluded (**Fig. 1**). All excluded references were written in English.

Data from each study that met the inclusion criteria were extracted independently by two reviewers. If more than one reference was found for the same study, consistency between references was checked. If inconsistencies were identified between references reporting data on the same aspect of a study, the data from the most recent reference were included. If references reported data for different aspects of the same study, all relevant references were included. If major inconsistencies between references were identified, the entire study was excluded. Studies were further categorized according to whether they reported results for RotaTeq™ 'vaccine effectiveness' (defined as an estimate of the vaccine efficacy under routine conditions of use) or for RV 'vaccination impact' (defined as modification of baseline epidemiology of the target disease as the vaccine coverage increases). For the impact of RV vaccination, studies conducted in areas where both RV vaccines were available but where the use of RotaTeq™ was considered negligible compared with Rotarix were excluded.

Thirty-four references corresponding to 26 studies were included in the final review. Six studies considered vaccine effectiveness and 20 studies considered vaccination impact; of these, three studies considered effectiveness and impact. The data are described according to the five main themes that emerged from the publications: (1) vaccine effectiveness in controlled observational studies; (2) reductions in healthcare utilization; (3) reductions in laboratory-based rotavirus activity; (4) reductions in healthcare costs; (5) evidence for herd immunity.

Appendix II. Search strategy for PUBMED

#	Search history	Results
Disease #1	(Rotavirus OR "Rotavirus infections" OR gastroenteritis)	140,053
Vaccine #2	(Vaccination OR vaccines OR vaccine OR immunization OR immunisation OR "immunization program" OR "Rotavirus vaccines" [MESH] OR RotaTeq OR Rotarix)	274,110
Effectiveness/ impact #3	("Program evaluation" [MESH] OR "treatment outcome" [MESH] OR "outcome assessment (health care)" [MESH] OR impact OR effectiveness OR "population surveillance" [MESH] OR "epidemiologic studies" [MESH] OR surveillance OR "case-control studies" [MESH])	2,703,031
#4	("cost-effectiveness")	24,100
#5	("clinical trial" [Publication Type])	590,783
#6	("review" [All Fields])	1,784,370
#7	("africa" [MESH])	140,451
#8	("asia" [MESH])	356,441
#9	("2006" [Publication Date]: "3000" [Publication Date])	3,044,762
#1 and #2 and #3 and #9 not #4 not #5 not #6 not #7 not #8		293

Appendix III. Conference proceedings between 2006 and 2010: hand-searched for relevant abstracts

European Society for Paediatric Infectious Diseases (ESPID)
Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
International Congress for Infectious Diseases (ICID)
International Congress of Paediatrics (ICP)
Infectious Diseases Society of America (IDSA)
Pediatric Academic Societies (PAS)
Réunion Interdisciplinaire de Chimiothérapie Anti-infectieuse (RICAI)
Vaccines for Enteric Diseases (VED)
World Congress of the World Society for Pediatric Infectious Diseases (WSPID)

Results

Vaccine effectiveness in controlled observational studies. Studies on vaccine effectiveness compare the risks of disease outcomes in vaccinated or non-vaccinated populations in a real-life setting. Common study designs are comparative-cohort studies, case-control studies and case-cohort studies.

In comparative-cohort studies, vaccine effectiveness (VE) is calculated as VE = 1 - RR (RR being the relative risk of developing RVGE in the vaccinated group compared with that in the non-vaccinated group). In cohort studies, subjects with and without the exposure of interest are followed over time to assess the health outcome of interest. In case-control studies, however, study groups are defined by the health outcome and then exposure status is assessed retrospectively. Vaccine effectiveness in case-control studies is calculated as VE = 1 - OR (OR being the ratio of the odds of vaccination in cases to the odds of vaccination in disease-free controls, which approximates the relative risk).[23] In case-cohort studies, vaccination status is sampled in cases and from population controls who are at risk for disease; vaccine effectiveness can be calculated as VE = 1 - OR.[24]

Of the six studies that evaluated the vaccine effectiveness of RotaTeq™ using controlled methods, five were undertaken in the US (two case-control studies, two comparative-cohort studies and one case-cohort study) and a comparative-cohort study was carried out in France (**Table 1**). The sources for RVGE case identification in these studies were either active RV surveillance [studies VE01, VE02, VE05], databases for health-insurance claims (studies VE03, VE06) or a patient database [study VE04]. Data on vaccination status were obtained from insurance claims [studies VE03, VE06], immunization records [studies VE01, VE02], immunization registries [study VE01] and a database on pediatric practice [study VE04]. The source of data on vaccination status was not stated for one study [study VE05].

Case-control studies. Both case-control studies were done over one RV season and had control groups comprising children who were RV-negative and children with acute respiratory infections (ARI). These studies also assessed vaccine effectiveness according to the number of doses of RotaTeq™ received (**Table 2**). A study undertaken in the ED setting between February and June 2008 found that vaccine effectiveness against laboratory-confirmed

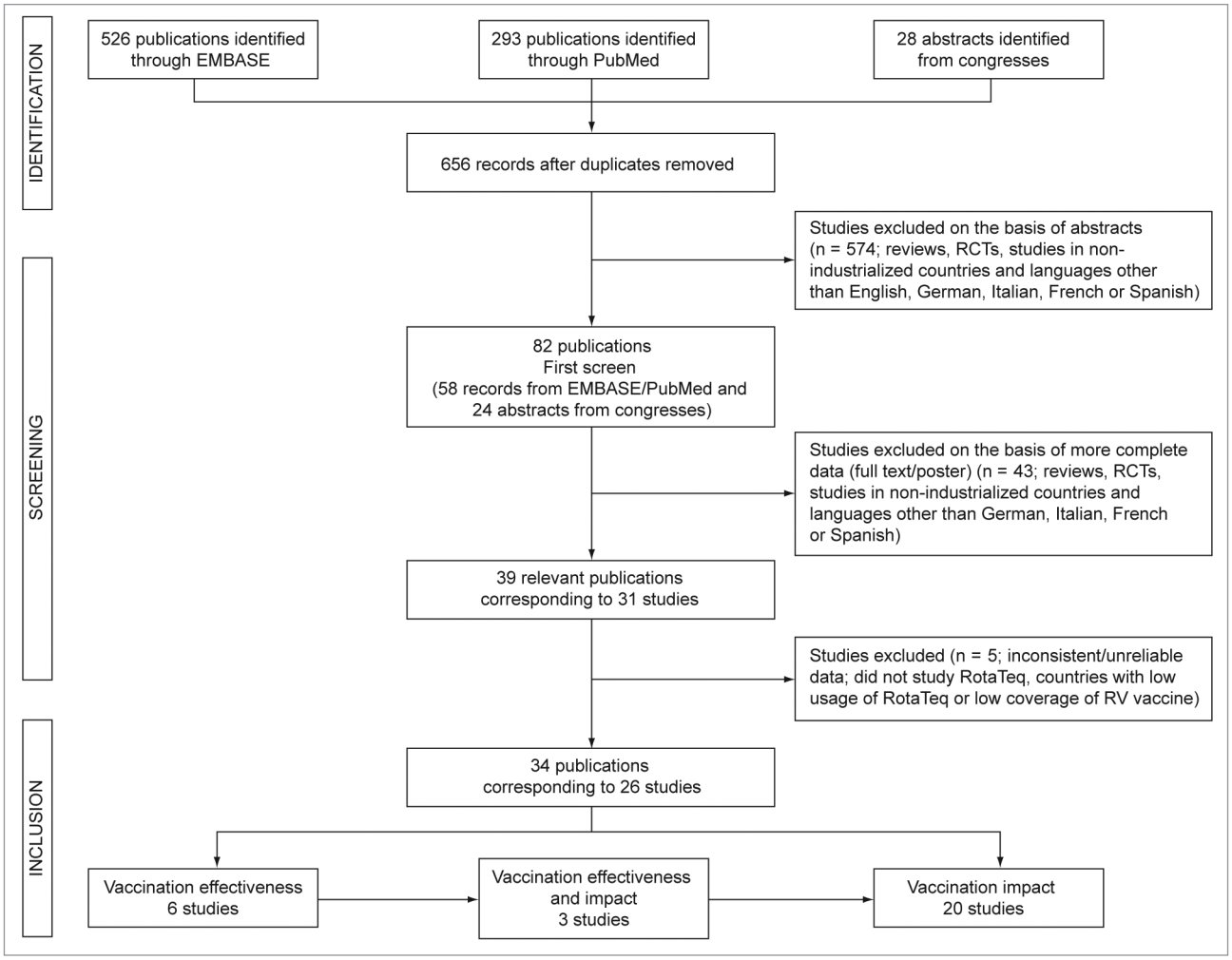

Figure 1. Summary of the study selection procedure. RCT, randomized controlled trial; RV, rotavirus.

RVGE in children aged between 15 days and 23 months increased from 69% after one dose of vaccine to 88% after all three doses versus the ARI and RV-negative control groups combined [study VE01]. A second study carried out during the 2007–2008 RV season found that vaccine effectiveness against laboratory-confirmed hospitalized cases of RVGE in children under 3 years of age after at least one dose of RotaTeq™ was 78% (range: 71% with one dose to 88% with three doses), versus RV-negative controls and 73% (range: 65% with one dose to 79% with three doses) versus ARI controls [study VE02].

Comparative-cohort studies. All three comparative-cohort studies evaluated the effectiveness of a complete course of RotaTeq™ against RVGE hospitalizations (**Table 3**). The most comprehensive study [study VE03] was based on a retrospective analysis of data from national health-insurance claims in the US for infants aged 1 year or younger during the 2007 and 2008 RV seasons who had received three doses of RotaTeq™ (n = 33,140), and controls who had received three doses of diphtheria-tetanus-acellular pertussis (DTaP) vaccine but not RotaTeq™ (n = 26,167). Strengths of this study include that the data were drawn from a large database covering the whole of the US, that it included large numbers of children in both the vaccinated and unvaccinated cohorts, and that the cohorts were compared using denominator-based incidence rates. None of the infants vaccinated with RotaTeq™ was hospitalized for RVGE (estimated effectiveness of RotaTeq™ 100%, 95% CI 85–100%), and effectiveness against all-cause AGE-related hospitalizations was 69% (95% CI 58–82%) [study VE03]. In addition, effectiveness against ED visits and outpatient visits for RVGE was 100% (95% CI <0–100%) and 96% (95% CI 76–100%), respectively. For AGE, the effectiveness was 49% (95% CI 29–63%) for ED visits and 27% (95% CI 22–33%) for outpatient visits [study VE03].

In the other comparative-cohort studies, the estimated effectiveness of RotaTeq™ against RVGE hospitalizations was 79% (95% CI 30–94%) in children under 5 years of age in New Orleans (LA) who had received at least one dose of RotaTeq™ [study VE04], and was 98% (95% CI 84–100%) in children younger than 2 years of age in the region of Brest (France) who had received a complete course of RotaTeq™ [study VE05].

Case-cohort study. The case-cohort study was based on data from a medical claims database in the US. The excess of visits for

Table 1. Summary of studies on the effectiveness of RotaTeq

Study ID	Study period	Settings	Outcome evaluated	Definition of groups		Definition of RVGE case	Method of assessment of RV vaccination status	Estimator of vaccine effectiveness
Case-control studies				**Cases**	**Controls**			
VE01[62]	February–June 2008	ED in one hospital	RVGE hospitalization and ED visits	Children aged 15 days–23 months with laboratory-confirmed RVGE	3 control groups: 1) RV-negative AGE 2) age-matched children from an immunization registry	Clinical symptoms and laboratory-confirmed RV-positive	Immunization registry and immunization records shown by parents	VE=(1– OR of vaccination)×100 for children who were age-eligible for vaccination For matched controls from registry: conditional logistic regression to calculate OR for full vaccination
VE02[31]	2007– 08 Winter–Spring season	Hospitalization or ED identified by New Vaccine Surveillance Network (NVSN)	RVGE hospitalization and ED visits	Children aged <3 years, born on/after 1 April 2006 with laboratory-confirmed RVGE ED and hospitalized children	Children aged <3 years, born on or after 1 April 2006 with 1) RV-negative AGE in ED or hospitalized 2) ARI controls in ED or hospitalized	Clinical symptoms and laboratory-confirmed RV-positive	Parental interview, medical chart and provider-verified vaccination records	VE=1–OR, adjusting for season, health-insurance status and number of age-eligible doses at enrollment
Comparative-cohort studies				**Vaccinated**	**Not vaccinated**			
VE03[33]	January 1 to May 31 2007 and 2008	National health insurance database	Claims for RVGE or AGE (hospitalization, ED visits and associated costs)	Infants enrolled in health plan within 1 week of birth who received three doses of RotaTeq	Infants who received three doses of DTaP but not RotaTeq	Presence of ICD-9 code for all-cause AGE and/or RVGE as primary diagnosis	Codes in the medical claims database	1-Rate ratio for RotaTeq vs DTaP (derived though Poisson regression).
VE04[32]	2007–08*	Inpatients	RVGE hospitalizations and ED visits	Children aged <5 years in Children's Hospital Medical Practice Corporation (CHMPC) vaccinated with RotaTeq	Children <5 years in CHMPC not vaccinated with RotaTeq	Acute GE (ICD-9 codes)	CHMPC database	1-RR
VE05[63]	June 2002 to 2009	Inpatients	RVGE hospitalization	Children aged <2 years vaccinated with RotaTeq living in the catchment area of the hospital of Brest	Children aged <2 years not vaccinated with RotaTeq living in the catchment area of the hospital of Brest	Clinical symptoms for GE with laboratory confirmed presence of RV in stools	NR	Relative reduction in risk (= 1-RR)
Case-cohort study				**Cases**	**Controls**			
VE06[64]	July 2007–June 2008	Inpatients ED, outpatients	RV-coded hospitalization, diarrhea-associated hospitalization, ED visits and outpatient visit	Children aged <5 years with codes for RVGE or GE in database	NR	Codes for RVGE or GE	Medical claims database	NR

AGE, acute gastroenteritis; ARI, acute respiratory infections; DTaP, diphtheria-tetanus-acellular pertussis vaccine; ED, emergency department; GE, gastroenteritis; NR, not reported; OR, odds ratio; RR, relative risk; RV, rotavirus; GE, gastroenteritis; VE, vaccine effectiveness.

Table 2. Effectiveness of RotaTeq against hospitalizations and/or ED visits: case-control studies

Study ID	Outcome evaluated	Definition of control group	Doses	Cases		Controls		
				Number vaccinated/ total cases	% vaccinated	Number vaccinated/ total controls	% vaccinated	Vaccine effectiveness (95% CI)
VE01	Laboratory-confirmed RVGE hospitalizations and ED visits	RV-	Unvaccinated	67/79	85	47/108	44	Reference
			1	5/79	6	16/108	15	65% (-11 to 89)
			2	2/79	3	13/108	12	82% (15–98)
			3	5/79	6	32/108	30	89% (70–96)
		ARI	Unvaccinated	67/79	85	91/206	44	Reference
			1	5/79	6	43/206	21	65% (-7 to 89)
			2	2/79	3	28/206	14	72% (-37 to 94)
			3	5/79	6	44/206	21	85% (55–95)
		Combined RV- and ARI	Unvaccinated	67/79	85	138/314	44	Reference
			1	5/79	6	59/314	19	69% (13–89)
			2	2/79	3	41/314	13	81% (13–96)
			3	5/79	6	76/314	24	88% (68–96)
VE02	Laboratory-confirmed RVGE hospitalizations	RV (overall 76/314)	1	NR	NR	NR	NR	71% (17–90)
			2	NR	NR	NR	NR	72% (1–92)
			3	NR	NR	NR	NR	88% (47–97)
			≥1	NR	NR	NR	NR	78% (53–90)
		ARI (overall 76/921)	1	NR	NR	NR	NR	65% (8–87)
			2	NR	NR	NR	NR	78% (25–93)
			3	NR	NR	NR	NR	79% (9–95)
			≥1	NR	NR	NR	NR	73% (45–87)

ARI, acute respiratory infections; ED, emergency department; NR, not reported; RV, rotavirus; RV-, rotavirus-negative; RVGE, rotavirus gastroenteritis.

Table 3. Effectiveness of RotaTeq against hospitalization and/or ED visits: comparative-cohort studies

Study ID	Dose	Outcome measured	Incidence among vaccinated cases	Incidence among unvaccinated cases	Vaccine effectiveness (unadjusted-95% CI)
VE03	3	RVGE hospitalizations (per 1,000 person/years)	0 (0–0.4)	3.5 (2.2–5.4)	100% (85–100)
		RVGE ED visits (per 1,000 person/years)	0 (0–0.4)	0.2 (0–0.9)	100% (<0–100)
		RVGE hospitalizations/ED visits (per 1,000 person/years)	0 (0–0.4)	3.7 (2.3–5.5)	100% (86–100)
		AGE hospitalizations (per 1,000 person/years)	2.7 (1.7–4.2)	8.8 (6.7–11.5)	69% (48–82)
		AGE ED visits (per 1,000 person/years)	8.6 (6.7–10.9)	16.7 (13.6–20.2)	49% (29–63)
		AGE hospitalizations/ED visits (per 1,000 person/years)	11.3 (9.1–14.0)	25.5 (21.7–29.8)	56% (42–66)
VE04	≥1	RVGE hospitalizations (per 1,000 children)	0.796	3.865	79% (30–94)
VE05	3	Total RVGE hospitalizations	1/1895	47/1985	98% (84–100)

AGE, acute gastroenteritis; ED, emergency department; RVGE, rotavirus gastroenteritis.

AGE during the 2008 RV season was compared with the mean for the three seasons before the introduction of RV vaccination. Estimated effectiveness of RotaTeq™ against RVGE in children under 5 years of age was 86% (95% CI not stated). In addition, effectiveness against diarrhea-related events was 47% against hospitalization, 43% against ED visits and 15% against outpatient visits (95% CI not stated) [study VE06].

Vaccination impact studies. To assess the benefit of a given vaccination program on public health, vaccination impact studies typically evaluate modifications to a measure of the baseline burden of the disease after widespread use of the vaccine compared to the period before the vaccine was used. For RVGE, the baseline burden measures include ED visits or outpatient/physician office visits, the number of hospitalizations due to RVGE/AGE or RVGE disease trends, and the number of laboratory tests for RV. The evidence and magnitude of modification of baseline disease burden is related to data on vaccine coverage. Access to individual patient data is not necessary; aggregated, age-specific data on disease burden and a general estimate of vaccine coverage are sufficient to evaluate the impact of vaccination.

Vaccination impact related to reductions in healthcare utilization as measured by RV hospitalizations, ED visits and physician office visits. Twenty-one studies that assessed the impact of RV vaccination on use of healthcare resources were included. Fifteen were undertaken in the US, two in Australia, and one each in Spain, France and Austria (**Table 4**). Three studies in the US [studies IM01, IM03, IM11] and the studies in France [study IM19] and Austria [study IM21] used prospective surveillance data. The remaining studies were based on retrospective analyses of data sources that included hospital records, data from laboratory reports and health-insurance claims databases.

The impact of vaccination on RVGE-related hospitalizations was the most frequently reported outcome (**Table 5**). In the US, evaluation of the pre- and post-vaccination periods demonstrated that vaccination significantly reduced the burden of RVGE-related hospitalizations; this reduction was associated with an increase in vaccine coverage between the 2007 and 2008 RV seasons. The Centers for Disease Control and Prevention (CDC; Atlanta, GA) estimated that RV vaccination coverage in the US for infants aged 3 months who had received one dose of vaccine increased from 49% in May 2007 to 56% in March 2008, whereas coverage with three doses in children aged 13 months increased from 3.4% to 33.7% during the same period.[25] As the Advisory Committee on Immunization Practices recommendations for RV vaccines were only published in August 2006, the vaccine coverage during the 2006–2007 RV season was low, and this season was considered as a transitional season.[26] The National Immunization Survey for 2009 reported that 44% of children born within 2 years of licensure had full coverage with RV vaccine.[27]

In the 2006–2007 RV season, the reduction in RVGE-associated hospitalizations varied between 24% [study IM12] and 81% [study IM15]. The reduction in hospitalizations during the 2007–2008 RV season varied between 69% [study IM06] and 90% [study IM14]. There were too few studies for a conclusive assessment of impact in the 2008–2009 RV season, but the trend appeared to be similar to the impact in 2007–2008. In addition to the impact of vaccination on hospitalization for RVGE, there were also reports of a reduction of up to 50% for hospitalizations due to all-cause AGE [study IM12] or diarrheal diseases [study IM13] during 2007–2008.

A decline in RVGE-associated hospitalizations has also been reported after the introduction of RotaTeq™ vaccination in other countries. One study, performed in South Australia, reported that hospitalizations for RVGE among children younger than 5 years of age were 79% lower in 2008 compared with 2006 (no vaccine coverage data stated) [study IM17]. A second study, performed in Brest, France, found that the rate in children below 2 years of age declined by 50% compared with expected rates from the pre-vaccination period. This was consistent with the estimated vaccine coverage of 47% with RotaTeq™, which was the only vaccine used in that region [study IM18].

Some vaccination-impact results were also obtained in countries where both RotaTeq™ and Rotarix where used. In Almeria, Spain, the annual rate of RVGE-associated hospitalizations in children younger than 2 years was reduced by 45% in 2008

Table 4. Summary of vaccination-impact studies

Study ID	Study population	Study area	Study period		Data source for RVGE cases	Definition of RVGE case	Outcomes evaluated
			before	after			
USA							
IM01[65]	All children presenting with GE and evaluable stool sample	Children's Hospital of Philadelphia	1994–2006	2007–08 2008–09	Prospective hospital-based surveillance	Clinical GE symptoms, ELISA RV+ test and PCR typing	Number of RV+/AGE Age distribution Genotypes
IM02[25,26,66,67]	Children with samples analyzed in one of the participating laboratories in the NREVSS network		1991–2006 2000–2006	2007–08 2008–09	Passive, voluntary laboratory reporting system/network	ELISA RV+ test	Number of RV+/number RV tests carried out Timing and duration of RV season
IM03[25,68]	Children aged <3 years	Monroe County, New York; Hamilton County, Ohio; Davidson County, Tennessee	01/01/2006 to 30/04/2006	01/01/2007–30/04/2007 01/01/2008–30/04/2008	Prospective surveillance study for inpatients, ED and sentinel outpatient clinics	Clinical GE symptoms and ELISA RV+ test	Number and % RV+ tests/ total number of tests overall and by setting (inpatient, ED and outpatient clinic)
IM04[69]	Patients with hospital-acquired (HA) and community-acquired (CA) RV hospitalizations	Chicago	2003–07	2007–08	Retrospective data from records	Clinical symptoms and rapid RV antigen test	CA RVGE/100 hospital admissions HA RVGE/1,000 patient days Transmission rate (HA/CA)
IM05[70,71]	Children admitted to hospital	Kansas City	January 1–May 15 2002–06	2007–09	Retrospective data from records. RV test results cross-checked with ICD-9 codes, laboratory and positive/total antigen test results	Positive RV antigen test and ICD-9 codes	RV+ tests/total tests
IM06[72,73]	Children presenting at hospital with RVGE	Philadelphia	2000–06	2007–08	Hospital laboratory database	ELISA RV+ test	Number RV+ tests/total tests Age distribution Outbreak onset and duration
IM07[74]	Patients (children and adults) at medical centre	Massachusetts	Oct–April 2003–06	Oct–April 2007–08	Retrospective analysis of laboratory-confirmed RVGE	ELISA RV+ test	Number RV+ tests (pediatric and adult) Number RV tests overall
IM08[75]	Children aged <6 years		Dec–June 2003–06	Dec–June 2006-08	Results from Quest Diagnostics Laboratories database; national reference laboratory database	ELISA RV+ test	Number RV+ tests/overall no of tests Positivity rate Age distribution
IM09[76]	Children with moderately severe/severe GE seen in primary care, ED or hospital	Texas	Oct–June 2000–06	Oct–June 2007–08	Retrospective chart review and hospital laboratory data	ELISA RV+ test	Number RVGE cases (moderate to severe) Month of occurrence of RV peak
IM10[77]	Children aged <5 years	36 states	July 2003–June 2006	July 2007–June-2008	Medical claims databases and national laboratory surveillance system	ICD-9 codes for AGE (all causes) and RVGE	Percentage reduction in GE visits/non-GE visits by region, age group and care setting
IM11[78]	Children aged <3 years hospitalized in children's hospital	Ohio	1997–2006	2007, 2008	Active surveillance system with prospective enrollment and passive laboratory system used for capture–recapture evaluation	Clinical symptoms of GE and ELISA RV+ test	Rate (/10,000) of RV hospitalization by year and age and season.
IM12[32]	Children aged <5 years with AGE	New Orleans	July 2004–June 2006	July 2007–June 2008	Children's Hospital Medical Practice Corporation Database	ICD-9 codes for GE and ELISA RV+ test	Rate of GE by care setting, RV+/RV–, and RV+ by age
IM13[64]	Children aged <5 years		2001–06	2007–08	Claims-based databases (MarketScan)	Codes for diarrhea-associated healthcare events and RV-coded diarrhea hospitalization	Diarrhea-associated healthcare events by setting and during RV season RV-coded diarrhea hospitalization
IM14[79]	Patients aged <18 years	Northeast Florida	2004–2006	2007–2009	Standard hospital records	ELISA RV+ test Hospitalization for RVGE considered as surrogate for severity	RV infections and hospitalizations before and after. Season (onset, peak and end)
IM15[80]	Hospitalized children aged 1 month – 18 years, but focus on children aged <2 years	New York State	2003–2006	2007 (intermediate season) 2008 ('after')	Hospital discharge database Electronic clinical laboratory reporting system	ICD-9 codes for GE and positive RV tests	Annual incidence of RV-associated hospitalizations Number of hospitalizations for diarrhea and RV, overall and by age
Australia							
IM16[81]	General population	Queensland	2000–2006	2007–2008	Passive routine RV notification from 2006 to 2008 and laboratory data from Queensland Health laboratories from 2000–2008	ELISA RV+ test	Percentage change in number of RV notifications/age group in 2007 and 2008, compared with 2006 Percentage change in number of RV tests and number RV+ by age in 2007 and 2008, compared with mean annual number for 2000-2006
IM17[82]	Children aged ≤5 years	South Australia	2005–06	2008–09	Retrospective routine hospital records	NR	Hospitalization for all-cause AGE Hospitalization for RVGE Peak season
Europe							
IM18[83]	Children aged <2 years	Brest, France	2002–06	2007–2008 2008–2009	Hospital-based surveillance study	NR	Number of children aged <2 years hospitalized for RVGE (observed vs. expected) Incidence rate in vaccinated, incidence rate in unvaccinated and relative incidence rate for RVGE hospitalization
IM19[83]	Hospitalized children aged <2 years	Almeria, Spain	2006–2007	2007–09	Hospital records	ELISA RV+ test	RVGE rates per 1000 children aged <2 years
IM20[84]	Children aged <15 years	Austria	2001–2006	2007–2008	Prospective surveillance study; sentinel system in11 hospitals	Clinical GE symptoms and ELISA RV+ test	RVGE hospitalization rates

RotaTeq was the only vaccine used, except in studies IM19 and IM20, where RotaTeq and Rotarix were used. AGE, acute gastroenteritis; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; GE, gastroenteritis; NREVSS, National Respiratory and Enteric Virus Surveillance System; PCR, polymerase chain reaction; RV, rotavirus; RVGE, rotavirus gastroenteritis; RV+, rotavirus-positive; RV-, rotavirus-negative.

Table 5. Impact of vaccination on hospitalizations for community-acquired RVGE

Study ID	Definition of RV season	Outcome measured	Pre-vaccination		Post-vaccination		Vaccination impact[1]
			Year	Results	Year	Results	
IM01[2]	December to June	Number of laboratory-confirmed RVGE hospitalizations	1994–06	Median: 167 (range: 92–271)	2007–2009	Mean: 54.5 (range: 36–73)	67%
IM03[2]	January to May	Incidence of RVGE hospitalization/10,000 patient-years	2006	22.5	2007*	26.8	<0%
					2008	3.7	84%
IM04[2]	September to May	Community-acquired RVGE hospitalization/ 100 admissions	2003–2007	Median: 1.61 (range: 1.21–1.87)	2007–2008	0.28	83%
IM05[2]	January to July	RVGE admissions	2002–06	Mean: 318 (range: 237–445)	2007*	323	<0%
					2008	62	81%
					2009	123	61%
IM06[2]	December to May	Number of laboratory-confirmed RVGE hospitalizations	2000–06	Mean: 128 (range: 93–178)	2007*	92	28%
					2008	40	69%
					2009	54	58%
IM10[2]	NR	Percentage reduction in RVGE hospitalizations	2004–2006	NR	2007–2008	<1 year	81%
						I year	79%
						2 years	69%
						3–4 years	78%
IM11[2]	July to June 2007–08: December to June	RVGE hospitalization/10,000 person-years (mean: 33.6)	1997	43.4 (36.6–50.1)	2007*	24.1 (18.9–28.3)	28%
			1998	48.5 (41.3–55.7)			
			1999	30.1 (24.3–35.8)			
			2000	18.4 (13.9–22.9)			
			2001	34.0 (28.5–41.0)			
			2002	19.9 (15.2–24.7)	2008	4.4 (2.3–6.9)	87%
			2005	43.9 (36.9–50.0)			
			2006	30.7 (24.8–36.5)			
IM12[2]	July to June	RVGE hospitalization	2004–05	NR	2006–07*	NR	24% (–17 to 51)
					2007–08	NR	88% (71–95)
		AGE hospitalization/1,000 children	2004–05	5.6	2006–07	4.2	25% (2–43)
					2007–08	2.8	50% (33–63)
IM13[2]	July to June	Diarrhea-associated hospitalization/10,000 children (per year)	2001–06	52	2007–08	31	40%
		RVGE hospitalization/10,000 children (per season)		NR		NR	47%
IM14[2]	January to May/June	RVGE hospitalization/1,000 admissions	2004–06	7.2	2007*	4.4	39%
					2008	0.7	90%
IM15[2]	January to May/June	RVGE hospitalization/10,000 children	2003–06	13	2008	2.5	81%
		Mean annual number of RVGE hospitalizations		1666	2006*	1379	17%
					2007*	325	81%
					2008	28	70%
IM17[4]	June to August	Number of RVGE hospitalization in one hospital	2005	60	2009	11	82%
		Number of RVGE hospitalization in state	2006	NR	2008	NR	79%
IM18[4]	June to June	Number of expected/observed RVGE hospitalizations	Expected	60	2008–09	30	50%
IM19[5]	October to March	Annual RVGE hospitalizations/1,000 children	2006	2.26	2008	1.6	45%
		Winter RVGE hospitalizations/1,000 children	2006–07	5.8	2008–09	1.7	71%
IM20[6]	October to April	Annual RVGE hospitalization/100,000 children (extrapolated to whole country from surveillance system)	2001–2006	<1 year: 2066	2008	631	70%
				1–2 years: 1822		1456	20%
				2–5 years: 436		461	<0%[7]

*July 2006–June 2007 was considered to be a transitional season [CDC, 2009]. [1]Vaccination impact expressed as the percentage reduction in hospitalizations in the post- vs. pre-vaccination period. [2]Study undertaken in the US where the CDC estimated coverage with one dose of RV vaccine in children aged <3 months as 49% in May 2007 and 56% in March 2008; estimated coverage with three doses of vaccine in children aged 13 months was 3.4% in May 2007 and 33.7% in March 2008 [CDC, 2009]. [3]Vaccine coverage not reported. [4]Vaccine coverage of 51% for ≥1 dose and 47% for all three doses of RotaTeq. [5]Vaccine coverage of 54% for ≥1 dose. [6]RotaTeq and Rotarix were used in Austria. Coverage was 59% July–December (RotaTeq) and 87% in 2008 (Rotarix). [7]Children too old to be eligible for vaccination. AGE, acute gastroenteritis; NR, not reported; RVGE, rotavirus gastroenteritis.

compared with 2006, with an estimated RV vaccine coverage of 54% (approximately equal use of both vaccines) [study IM19]. In Austria, the annual RVGE-associated hospitalization rate in children younger than 1 year of age was 70% lower in 2008 compared with the mean rate for the period 2001–2006 [study IM20]. RotaTeq™ was used exclusively in 2007 in Austria (vaccine coverage of 57%), before vaccine use changed to Rotarix in 2008.

Two studies undertaken in the US also evaluated the impact of RV vaccination on all-cause AGE- or diarrhea-related ED visits and outpatient/physician office visits (**Table 6**). A study that used excess visits for gastroenteritis during the RV season compared with visits during the rest of the year as a surrogate for RVGE activity reported that ED visits by children less than 1 year of age declined by up to 100% in 2007–2008 compared with 2004–2007. The same study found that outpatient/physician office visits also declined by up to 100% in children less than 1 year of age, and that there were substantial reductions in excess visits in non-vaccinated age groups (age 2–4 years) [study IM10]. The impact of vaccination against all-cause diarrhea-related ED visits was lower than the one against all-cause AGE-related hospitalization, with an approximate reduction of 20% in ED visits during the 2007–2008 RV season reported in one study [study IM13]. In addition, impact against all-cause diarrheal health visits was estimated at 17% for the 2007–2008 RV season [study IM13].

Vaccination impact related to delayed and diminished laboratory-assessed RV activity. These studies evaluated the impact of a vaccination program by comparing the numbers or proportions of RV-positive assay tests, and the onset and duration of the

Table 6. Impact of vaccination on emergency department and outpatient/physician office visits for AGE or diarrhea

Study ID	Study population	Outcome measured	Pre-vaccination		Post-vaccination		Vaccination impact
			Year	Results	Year	Results	
IM10	<1 year	Excess ED visits for all-cause GE/annual non-GE visits	2004–07[1]	Mean for three USA regions: NR	2007–08	Mean for three USA regions: NR	104%
	1 year						89%
	2–4 years						89%
	<1 year			USA West region: NR		USA West region: NR	93%
	1 year						64%
	2–4 years						80%
	<1 year	Excess outpatient/office visits for all-cause GE/ annual non-GE visits	2004–07[1]	Mean for three USA regions: NR	2007–08	Mean for three USA regions: NR	103%
	1 year						89%
	2–4 years						86%
	<1 year			USA West region: NR		USA West region: NR	71%
	1 year						32%
	2–4 years						33%
IM12	<5 years	ED visits for all-cause GE/1,000 children	2004–05/ 2005–06	NR	2007–08	NR	27%
		Outpatient/office visits for all-cause GE/1,000 children			2007–08	NR	18%
IM13	<5 years	RVGE-associated ED visits/10,000 children (per season)	2001–06	NR	2007–08	NR	20%
		RVGE-associated outpatient/office visits per 10,000 children (per season)		NR		NR	17%

All studies were undertaken in the USA where the CDC estimated coverage with one dose of RV vaccine in children aged <3 months as 49% in May 2007 and 56% in March 2008; estimated coverage with three doses of vaccine in children aged 13 months was 3.4% in May 2007 and 33.7% in March 2008 [CDC, 2009]. [1]Information was not provided in the reference, but assumed or provided by other source. AGE, acute gastoenteritis; ED, emergency department; GE, gastroenteritis; NR, not reported; RVGE, rotavirus gastroenteritis.

RV season, before and after introduction of the RV vaccination program.

Nine studies, all undertaken in the US, included data that demonstrated the impact of RV vaccination on the number of RV-positive tests (**Table 7**). There were substantial reductions in the numbers of RV-positive tests after the introduction of RotaTeq™ compared with the pre-vaccination era. The percentage reductions from 2008 onwards ranged from 44% [study IM12] to 95% [study IM07]. The RV vaccine coverage data for the US [25] presented previously also applied to these studies.

Eleven studies reported data relating to the impact of vaccination on the proportion of RV-positive tests (**Table 7**). In the US, the number of tests carried out varied over time, with a consequent effect on the proportions of RV-positive tests reported. Nevertheless, there were substantial reductions (between 52% [study IM14] and 94% [study IM07]) in the percentage of RV-positive AGE samples reported for the 2007–2008 RV season compared with the pre-vaccination period in the US. Reductions in RV-positive samples continued to be reported for the 2008–2009 RV season, but were smaller than those observed in the 2007–2008 season. However, the proportions of positive tests were still considerably lower compared with the pre-vaccination era [studies IM02, IM05, IM06, IM12]. In Queensland, Australia, there was an estimated 45% reduction in the proportion of RV-positive tests in 2007, and a 43% reduction in 2008 [study IM16]. Vaccine coverage with three doses of RotaTeq™ was 75% for infants born in May–July 2007 and 80% for infants born in August–September 2007 [study IM16].

In the US, there was also evidence of vaccination impact on the RV season. The CDC compared the onset, duration and magnitude of the 2007–2008 RV season with median values for the previous 15 years. In 2007–2008, onset was delayed by 2–4 months, the duration was reduced by 12 weeks (14 versus 26 weeks) and the percentage of positive RV tests during the peak week decreased from 41% to 17.8% [study IM02].

Vaccination impact related to reductions in healthcare costs. Three studies carried out in the US presented evidence of reductions in healthcare costs associated with RVGE after the introduction of RV vaccination [studies VE03, IM05, IM15]. In one of the comparative-cohort studies of effectiveness for RotaTeq™, none of the 33,140 vaccinated infants was hospitalized or visited the ED for RVGE. Hence, there were no associated costs, whereas among the control cohort of 26,167 infants who had received DTaP costs of hospitalization and ED visits amounted to ~US$75,000 (relative cost reduction 100%, 95% CI 100–100%). In addition, there was a relative reduction of 74%

Table 7. Impact of RotaTeq on laboratory-based RV activity

Study ID	Settings	Definition of RV season	Pre-vaccination				Post-vaccination				Vaccination impact	
			Year	No. of tests	No. of positive tests	% positive	Year	No. of tests	No. of positive tests	% positive	Reduction in proportion of positive tests[3]	Reduction in number of positive tests[3]
IM02[1]	Passive laboratory surveillance	2000–2006: December for 26 weeks 2007–2008: March for 14 weeks 2008–2009: January for 17 weeks	2000–06	Annual median: 14,211 (range: 11,844–17,060	Annual median: 3,551 (range 3,007–3,949)	25	2007–08	14,532	1,281	9	64%	64%
							2008–09	14,201	1,468	10	59%	60%
IM03[1]	Prospective population-based surveillance	As above	2006	405	207	51	2007*	481	259	54	(6%)	(25%)
							2008	283	18	6	88%	91%
IM05[1]	Hospital	January to July	2002–06	Annual mean: 1,375 (range: 1,056–2,003)	Annual mean: 687 (range: 476–1,023)	50	2007*	1,020	523	51	(1%)	24%
							2008	549	108	20	60%	84%
							2009	591	231	39	22%	66%
IM06[1]	Hospital	December to May	2005–06	386	155.5	40	2007*	590	92	16	60%	41%
							2008	358	40	11	73%	74%
							2009	361	54	15	63%	65%
IM07[1]	Single medical center laboratory	October to April	2005–06	170 (166–175)	65 (58–72)	38	2007*	81	37	45	(17%)	43%
							2008	118	3	3	94%	95%
IM08[1]	National reference laboratory	December to June	2004–06	27,625	7,162	26	2007–08	21,873	1,703	7.8	70%	76%
IM09[1]	Primary care, ED and hospitalized laboratory data	October to June	2000–2001	NR	60.5 (50–71)	NR	2006–07*	NR	49	NR	19%	NR
							2007–08		14		77%	
IM12[1]	Hospital	July to June	2004–05	190	55	28	2006–07*	166	47	28	0%	15%
							2007–08	139	9	7	75%	84%
							2008–09	141	31	21	25%	44%
IM14[1]	Single hospital laboratory records	January to May/June	2004–06	767	207	27	2007–2008	666	87.3	13	52%	58%
IM15[1]	Laboratory data	December to June	2005–06	672	228	34	2008	364	25	7	79%	89%
IM16[2]	State laboratory data	January to December	2001–2006	3,720	NR	(42–58)	2007*	4,511	NR	NR	45%	NA
							2008	4,113	NR	NR	43%	NA

*July 2006–June 2007 was considered to be a transitional season [CDC, 2009]. [1]Study undertaken in the USA where the CDC estimated coverage with one dose of RV vaccine in children aged <3 months as 49% in May 2007 and 56% in March 2008; estimated coverage with three doses of vaccine in children aged 13 months was 3.4% in May 2007 and 33.7% in March 2008 [CDC, 2009]. [2]Complete three-dose vaccine coverage in children aged 12 months was 75% in those born in May–July 2007 and 80% in those born August–September 2007. [3]Figures in parentheses indicate an increase in the proportion or number of positive tests. ED, emergency department; RV, rotavirus; NR, not reported; NA, not applicable.

(95% CI 74–74%) in costs of hospitalization and ED visits associated with AGE (RotaTeq™ cohort US$86,000 versus DTaP cohort US$250,000) [study VE03]. A vaccination-impact study done across New York State (NY) [study IM15], reported that the reduction in total hospital costs for RV disease among children aged 1–23 months was reduced by US$10 million from the mean of $13.7 million per year for 2003–2006 to US$3.7 million in 2008. Finally, an analysis of hospitalizations for RVGE in Kansas City (MO) [study IM05] found that, compared with estimated annual costs of US$3.6 million for 2002–2006, there were savings of US$2.6 million in 2008 due to the reduction in RVGE cases in all age groups.

Evidence for herd immunity. Herd immunity describes a type of protection against infections spread from human to human that results from interruption in the transmission of microbes when the number of susceptible individuals in the population is reduced to a critical level through vaccination, thereby providing protection to unvaccinated individuals.[28] The RV vaccination schedule should be completed by 32 weeks of age in the US and by 26 weeks in Europe,[29] so there have been no catch-up vaccination programs in older children. Evidence suggestive of herd immunity after the widespread use of RV vaccines comes, therefore, from age groups of children who were unlikely to have been vaccinated.

In the US, three vaccine-impact studies found evidence of reductions in RVGE-associated hospitalizations during 2008 in children who were too old to have received the vaccine [studies IM06, IM11, IM15] (**Table 8**). A study in New York State found that hospitalizations in 2008 decreased by 70% in children in the age groups 24–35 months and 60 months–18 years,

Table 8. Impact of vaccination on hospitalizations for community-acquired RVGE by age group/evidence of herd protection

Study ID	RV season definition	Outcome measured	Age group	Pre-vaccination		Post-vaccination		Vaccination impact
				Year	Results	Year	Results	
IM06	December to May	Number of laboratory-confirmed RVGE hospitalizations	<5 months	2000–06	30	2008	11	63%
			6–11 months		31		2	94%
			12–17 months		22		6	73%
			18–23 months		11		4	64%
			24–29 months		10		8	20%
			30–35 months		6		2	67%
			≥3 years		17		3	82%
IM11	July to June 2007–08: December to June	RVGE hospitalization/10,000 person-years	<3 months	2005–06	16	2008	18	-13%
			3–5 months		25		10	60%
			6–11 months		30		6	80%
			12–23 months		56		2	96%
			24–35 months		26		4	85%
IM15	January to May/June	Number of RVGE hospitalizations	1–11 months	2003–06	592	2008	95	84%
			12–23 months		572		95	83%
			24–35 months		245		73	70%
			36–59 months		163		34	79%
			60 months–18 years		93		28	70%

All studies were undertaken in the USA where the CDC estimated coverage with one dose of RV vaccine in children aged <3 months as 49% in May 2007 and 56% in March 2008; estimated coverage with three doses of vaccine in children aged 13 months was 3.4% in May 2007 and 33.7% in March 2008 [CDC, 2009]. RV, rotavirus; RVGE, rotavirus gastroenteritis.

and by 79% in those aged 36–59 months compared with the mean rates for 2003–2006 [study IM15]. Similar results were reported for Philadelphia (PA) [study IM06] and Ohio [study IM11]. However, there was no reduction among those infants less than 3 months of age who had been too young to be vaccinated [study IM11].

In the US, evidence of herd immunity was also seen in studies that evaluated the impact of vaccination on laboratory-assessed RV activity. Laboratory data collected across the US found that, compared with the means of the previous three seasons, in the 2007–2008 RV season there were reductions of 75%–80% and 59%–73% in the number and proportions, respectively, of RV-positive tests among children aged 2–6 years who were unlikely to have been vaccinated [study IM08]. Although most disease occurs in pediatric populations, the number of laboratory-confirmed cases of RVGE in adults was assessed at the University of Massachusetts Medical Center (Worcester, MA). A decline was noted from a mean annual number of 14 cases for the 2003–2006 RV seasons to 1 and 3 cases in the 2006–2007 and 2007–2008 seasons, respectively [study IM07]. Additional evidence of herd immunity comes from the observation that the 64% reduction in the number of RV-positive tests in the US during 2007–2008 compared with 2000–2006 was more than double the estimated vaccination coverage of 31% for children aged less than 2 years in 2007–2008 [study VE02].

Some evidence of possible herd protection has also been observed in countries other than the US. Compared with data for 2006, notifications of RV disease to the Communicable Diseases Branch of Queensland Health, Australia, decreased by 65% in 2007 and 56% in 2008 in children aged 2–4 years who were too old to have been vaccinated [study IM16]. However, herd protection was not observed consistently in all studies. The vaccination impact study undertaken in Austria found no evidence suggestive of herd protection with vaccine coverage of 57% in 2007 (RotaTeq™) and 87% in 2008 (Rotarix) [study IM20].

Discussion

The five main themes that emerged from this review of the post-licensure, real-life experience demonstrate that vaccination with RV vaccines, in countries where RotaTeq™ was widely used, has led to significant reductions in the incidence of RVGE, in RVGE-associated hospitalizations, ED visits and outpatient/physician office visits, and in RV-related laboratory activity in industrialized countries. These findings are consistent across studies and countries (US, Europe and Australia).

Overall, the estimates of comparative vaccine effectiveness from studies of RotaTeq™ in routine use were consistent with data seen in the pivotal clinical trial.[20] Thus, the estimates of the effectiveness of a complete course of RotaTeq™ in case-control studies of children who were hospitalized or visited the ED ranged from 79% to 89% against laboratory-confirmed RVGE depending on the study and selected control group.[30,31] These compare with the vaccine efficacy of 98% against severe RVGE reported in the pivotal clinical trial.[20] However, wide CIs were observed in one of these studies due to low vaccine coverage rates.[31] Estimates of effectiveness against RVGE-associated hospitalizations in comparative-cohort studies ranged between

85% (95% CI 30–94%),[32] and 100% (95% CI 85–100%),[33] compared with the 95.8% (95% CI 90.5–98.2%) reduction in the rate of hospitalization in the pivotal clinical trial.[20]

The impact of RotaTeq™ in the US became apparent within a short period after its introduction, as shown by the delayed onset and decreased magnitude of the 2007–2008 RV season compared with the 15 previous seasons.[25] Recent data from Belgium also confirm the effects reported in our Results section: vaccination with RV vaccines was followed by a 4- to 6-week delay in the onset of disease and peak incidence.[34] Similar significant reductions in disease have been noted after the introduction of other vaccines,[35,36] and provide further evidence for the significant public health benefit of vaccination. Recent research suggests that the impact of RV vaccination has been sustained for up to three seasons in the US.[26,37,38] Although these reductions could be attributed to the natural seasonal fluctuations in RV activity, they are significantly more pronounced than the historical long-term patterns typically observed for rotavirus.[39,40] It will be important, however, to continue monitoring this trend over time to confirm the long-term impact of RV vaccination. For example, in New Orleans, during the 2008–2009 season, although overall reductions in the incidence of RVGE continued to be observed compared with the pre-vaccine era, the reported incidence was increased compared with the 2007–2008 season.[41]

A potential limitation of this systematic review is that many of the included studies had been reported only in abstract form at the time of study selection. Such sources may have a number of weaknesses compared with full peer-reviewed papers, including limited details on methodology that make it difficult to assess the quality of the study, the presentation of summary statistics rather than full data sets, and the inclusion of preliminary results that may differ from the final analyses. However, a number of full peer-reviewed papers have recently been published with data that are consistent with the preliminary findings reported in the abstracts.[42-44] We therefore believe that the use of abstracts provided an accurate representation of vaccine impact at a time when they were the only source of information on this important issue.

In many of the studies, there was moderate-to-high vaccine coverage. In March 2008, the CDC estimated that 56% of infants aged 3 months in the US had received one dose of vaccine,[25] and RotaTeq™ was the only vaccine available in the US until 2008. These factors contributed to the ability of pre-/post-studies to document a significant impact of RV disease and allowed many studies to specifically evaluate the impact of RotaTeq™ in the US. Similarly, rapid attainment of high coverage may also have contributed to observation of a suggested herd immunity effect in the US.

Prospective analyses of laboratory data, such as that undertaken by the National Respiratory and Enteric Viruses Surveillance System in the US, undoubtedly represent the best method for assessing the laboratory-based impact of vaccination. However, the number of laboratories that participate in the surveillance network may decline in the post-vaccination period. This could influence the observed trends in RV disease (particularly in relation to changes in the number of positive tests) and needs to be borne in mind in future analyses of vaccination impact. A reduction in the number of reporting laboratories would have less effect on trends observed in the percentage of positive tests. Consequently, the percentage of positive tests may be regarded as a more reliable long-term measure of changes in RV activity as a result of vaccination.

In contrast to laboratory surveillance studies, vaccination-impact studies relying on healthcare resources (e.g., hospitalization, ED visits and outpatient/physician office visits) are relatively easy to conduct and provide useful markers of RV activity. However, they are vulnerable to biases due to differences in medical practice and variations in the quality of data collected. The interpretation of impact study results, as a whole, may be complicated by uncontrolled factors such as natural fluctuations in disease incidence that make it difficult to attribute the differences observed to the vaccine alone unless vaccine coverage is high and the observed reductions in disease incidence are very large.[45] Notwithstanding these limitations, the results of such studies are often considered more intuitive by healthcare providers than case-control or incidence-based cohort studies. This helps to facilitate dissemination of the data.

Several vaccination-impact studies undertaken in the US included data for RV-positive tests or RVGE-related hospitalizations that showed a reduction in RV disease in children older than 2 years of age (i.e., who were too old to have received RV vaccine). Thus, there is some evidence of herd immunity after the introduction of RV vaccination. As mentioned above, the significant rate of vaccine coverage may be a factor for the observation of herd immunity in the US. In contrast to findings in the US, there was less evidence of a decline in RV disease in unvaccinated children in Europe. This may reflect the smaller number of studies carried out there, a lower vaccine coverage rate or differences in study design. A mathematical model for the impact of vaccination in five countries in the European Union predicted that vaccination coverage rates of 70%, 90% and 95% would provide reductions in RVGE of 25%, 22% and 20%, respectively, due to herd protection 5 years after implementation of a two-dose vaccination program.[46] Indirect protection may be due to interruption of RV transmission among all children and/or exposure of unvaccinated children to vaccine virus shed in the stools of vaccinated infants.[20] However, it is theoretically possible that decreased transmission of RV during a single season may leave unvaccinated children susceptible to RVGE in future. Clearly, this area warrants further investigation as experience with RV vaccination grows.

Several additional studies have been published since the studies included in the defined literature review were retrieved. Curns et al.[47] analyzed data for hospital discharge for children <5 years of age in 18 states in the US to evaluate reductions in hospitalizations for AGE during the 2007 and 2008 RV seasons compared with the same periods in 2000–2006. The results of that study are similar to those presented here. Further data on the effectiveness and impact of RotaTeq™ in Queensland, Australia, have also been published. The effectiveness of the three-dose schedule for preventing RVGE-associated hospitalization was 93.9% (95% CI 83.1–98.1%), and immediate and sustained reductions in

RVGE-associated hospitalizations were observed in all age cohorts younger than 20 years after introduction of the vaccine in 2006.[8]

The present review focused on studies from industrialized countries due to the well-defined healthcare systems in those countries. However, "developing" countries have a greater burden of RV disease than industrialized nations that, in addition, often results in mortality.[2,49,50] Thus, vaccination can have a greater impact on public health in these countries.[51,52] Several observational studies of vaccination impact have also been done in non-industrialized countries. For example, in Nicaragua, where RotaTeq™ was introduced in 2006, a case-control study found that the effectiveness of three doses of RotaTeq™ against severe RV diarrhea was 58% between June 2007 and June 2008.[53] A second study undertaken between February 2007 and October 2009 reported vaccine effectiveness against severe RVGE of 58% (95% CI 37–72%) and 87% (95% CI 78–93%) compared with age-matched hospital controls with non-diarrheal infectious diseases, and community controls from the neighborhood of the cases, respectively.[54] In Africa, RotaTeq™ was shown to provide significant benefit during the first 2 years of life, with vaccine efficacy against severe rotavirus gastroenteritis of 39.3%.[55] Furthermore, a vaccination study performed in Malawi and South Africa reported that a greater number of severe RVGE cases were prevented in Malawi, despite lower efficacy in that country compared with South Africa.[56] No study has directly assessed the impact of RotaTeq™ vaccination on mortality, but one research group estimated that rotavirus vaccination could reduce RV mortality in children younger than 5 years of age in Nicaragua by 74% (95% CI 35–90%).[57] This estimate is similar to that from an analysis of Nicaraguan national health statistics, which suggested that 1–3 doses of RotaTeq™ were associated with a 73% reduction in mortality among children 3–11 months of age.[58] Mortality may provide the best means of measuring the impact of RV vaccination in developing countries, while in industrialized nations healthcare costs or illness rates are preferable. RV vaccination can have a significant impact on public health in both developing and industrialized nations, albeit with different manifestations.

The direct and indirect medical costs associated with RVGE are substantial.[10,15,18,19,59] The reductions in RVGE-related hospitalizations, ED and outpatient/physician office visits that have been reported in vaccination-impact studies provide evidence of a reduction in use of healthcare resources as a result of RV vaccination. This was reflected in the direct reductions in cost reported in this review. However, research has documented that indirect costs are significant and contribute ~75% of the total societal costs associated with RVGE.[18] Therefore, although it can be inferred that vaccination may contribute to an overall reduction in healthcare costs from a societal perspective, appropriate cost-effectiveness studies that also account for the costs of the vaccination program and the reduction in indirect costs using data from the post-vaccination era may contribute a better understanding of the societal value of RV vaccination campaigns.

The effect of vaccination on RV genotype distribution is another important issue to consider. To date, however, there are no robust data to determine whether RV vaccination programs have directly affected serotype prevalence. Most data come from ecologic studies, which are not able to address this question adequately due to the wide temporal and geographic variation in RV serotypes, as documented extensively before the introduction of vaccination. Thus, the emergence of specific serotypes or uncommon strains after vaccination could simply represent natural variation unrelated to vaccination. In a study that attempted to address this question, secular variation in RV serotype prevalence was noted in the post-vaccination era, even in conditions of relatively low vaccine coverage.[60] This led the authors to highlight the need for caution in assessing the impact of vaccination upon the emergence of uncommon RV serotypes. Another recent study showed increased prevalence of G2 RV strains after the introduction of vaccination, but it was unclear whether this change was related to vaccination or natural fluctuations.[61] Additional well-designed epidemiologic studies are needed to ascertain whether vaccination affects RV genotype distribution.

In summary, this systematic review confirmed the high and rapid benefit of RotaTeq™ in a real-life setting. Since its introduction in 2006, it has contributed to a significant reduction in the burden of RVGE through direct and indirect effects, thereby providing an important benefit to public health. Furthermore, the vaccine effectiveness observed under routine use is consistent with the efficacy data obtained during the clinical development of the vaccine. Moreover, these benefits were observed consistently across all industrialized countries in which it was introduced. Notwithstanding these reassuring findings, long-term follow-up of the epidemiology of RVGE will be necessary to fully understand the impact of vaccination on the natural history of RV disease.

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Conflicts of Interest

Carlo Giaquinto has served on expert groups, and has received educational grants and honoraria for conferences from Merck, sanofi pasteur MSD, GlaxoSmithKline Biologicals.

Geraldine Dominiak-Felden is an employee of Sanofi Pasteur MSD, which distributes RotaTeq™ in Europe.

Pierre Van Damme acts as chief and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers; speakers fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. P.V.D. receives no personal remuneration for this work.

Tin Tin Htar Myint was an employee of sanofi pasteur MSD, which distributes RotaTeq™ in Europe, at the time of the study

Yvonne Maldonado is a member of an advisory board on vaccines and a former member of the speakers' bureau for Merck.

Vana Spoulou is a member of the paediatric vaccines advisory board for sanofi pasteur MSD.

T. Christopher Mast is an employee of Merck, which manufactures the RotaTeq™ vaccine.

Mary Allen Staat has served on the advisory boards and speakers' bureaus and has received research funding from Merck and GlaxoSmithKline, both of which have licensed rotavirus vaccines.

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