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Review

Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014

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ABSTRACT

Prior to the introduction of rotavirus vaccines in 2006, rotavirus was the leading cause of severe gastroenteritis among European children <5 years of age. We conducted a systematic review of the published literature to examine the effectiveness and impact of rotavirus vaccines in Europe following the first eight years of routine use. Four publication databases were searched, yielding 276 unique citations from February 1st, 2006 to July 31st, 2014. Twenty four studies on effectiveness ($n = 9$) and impact ($n = 15$) met the inclusion criteria. Across Europe, vaccine effectiveness against rotavirus-related healthcare utilisation ranged from 68% to 98%, consistent with efficacy data from clinical trials. Reductions in rotavirus hospitalisations ranged from 65% to 84%, consistent with findings from post-marketing studies from the US and Latin America. We confirm the significant public health benefit of rotavirus vaccination in Europe and provide further evidence to support implementation of universal rotavirus vaccination in all European countries.

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1. Introduction

Rotavirus is the leading cause of severe gastroenteritis in children under five years of age [1]. Prior to the introduction of rotavirus vaccines in Europe in 2006, it was estimated that 3.6 million episodes of rotavirus disease occurred annually among the 23.6 million children younger than 5 years of age [2]. Every year, rotavirus accounted for 231 deaths, over 87,000 hospitalisations and almost 700,000 outpatient visits in Europe [2].

In 2006, two rotavirus vaccines, Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck and Co, Sanofi Pasteur MSD, Lyon, France) were licensed for use in Europe. Both live attenuated rotavirus vaccines given orally have shown high efficacy and good safety profiles in large clinical trials [3,4]. Rotarix (RV1), which is administered as a two-dose schedule, is a monovalent human vaccine originating from a G1P [8] strain [3]. RotaTeq (RV5), which is administered as a three-dose schedule, is a pentavalent vaccine containing five human-bovine reassortant strains (G1, G2, G3, G4, and P1A [8]) [4]. In the US, RV1 is administered at 2 and 4 months of age, and RV5 is administered at 2, 4 and 6 months of age. However, the rotavirus vaccination schedules differ slightly across Europe to better align with the timing of administration of other routine immunisations. For examples, in the United Kingdom (UK) and Belgium RV1 is administered at 2 and 3 months of age, and in Finland RV5 is administered at 2, 3 and 5 months of age.

In April 2009 the World Health Organization Strategic Advisory Group of Experts (SAGE) recommended that all national immunisation programmes include rotavirus vaccination for infants [5]. Globally a number of countries have adopted this recommendation, however, only a limited number of European countries have done so [6]. By the beginning of 2014, rotavirus vaccination had been implemented nationally in Austria, Belgium, Luxembourg, Finland, Greece, Norway, and the UK; with vaccination coverage rates ranging from over 90% in the first four countries to 23.4% in Greece and less than 10% in Norway and the UK [6]. Many European countries are at various stages of issuing national or regional recommendations or integrating rotavirus vaccination into their national immunisation programmes.

Here, we summarise published data from the past eight years on the effectiveness and impact of RV1 and RV5 in European countries to generate a transparent base of evidence for policymakers across Europe.

2. Methods

2.1. Search strategy

We developed search terms to identify articles published between 1st February 2006 and July 31st 2014 reporting (1)

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Table 1
PubMed literature search terms.

Strategy: Citations are identified that contain text in the Title/Abstract/Keywords fields using the following strategy/search term group. Case Reports, Randomised Controlled Trials, Animal Studies, Reviews and Systematic Reviews were excluded where search engines allowed. (Search Group 1) AND (Search Group 2) AND (Search Group 3) AND (Search Group 4) Date range (1st February 2006–31st July 2014)
Search Group 1: Disease Terms "rotavirus"[MeSH] OR "rotavirus"[All Fields]
Search Group 2: Vaccine Terms "rotavirus vaccines"[MeSH] OR ("rotavirus"[All Fields] AND ("vaccine"[All Fields] OR ("vaccines"[All Fields])) OR "Rotarix"[MeSH] OR "RotaTeq"[MeSH] OR "RV1"[MeSH] OR "RV5"[MeSH]
Search Group 3: Outcome Terms "impact"[MeSH] OR "effect"[MeSH] OR "effectiveness"[MeSH] OR "trends"[MeSH] OR "diarrhoea"[All Fields] OR "gastroenteritis"[All Fields] OR "rotavirus disease"[All Fields] OR "hospitalisation"[All Fields] OR "hospital admission"[All Fields] OR "outpatient"[All Fields] OR "visit"[All Fields] OR "attendance"[All Fields] OR "consultation"[All Fields] OR "general practice"[All Fields] OR "primary care"[All Fields] OR "Accident and Emergency"[All Fields] OR "emergency department"[All Fields] OR "laboratory confirmed"[All Fields] OR "positive test"[All Fields] OR "microbiologically confirmed"[All Fields] OR "laboratory confirmed"[All Fields]
Search Group 4: Setting Terms (Countries in the WHO European Region) "European Union"[MeSH] OR "European countries"[MeSH] OR "European Union"[MeSH] OR "Europe"[MeSH] OR "Austria"[All Fields] OR "Belgium"[All Fields] OR "Finland"[All Fields] OR "Luxemburg"[All Fields] OR "United Kingdom"[All Fields] OR "England"[All Fields] OR "Wales"[All Fields] OR "Scotland"[All Fields] OR "Northern Ireland"[All Fields] OR "Germany"[All Fields] OR "Armenia"[All Fields] OR "Moldova"[All Fields] OR "Georgia"[All Fields] OR "Israel"[All Fields] OR "Albania"[All Fields] OR "Andorra"[All Fields] OR "Azerbaijan"[All Fields] OR "Belarus"[All Fields] OR "Bosnia and Herzegovina"[All Fields] OR "Bulgaria"[All Fields] OR "Croatia"[All Fields] OR "Cyprus"[All Fields] OR "Czech Republic"[All Fields] OR "Denmark"[All Fields] OR "Estonia"[All Fields] OR "France"[All Fields] OR "Greece"[All Fields] OR "Hungary"[All Fields] OR "Iceland"[All Fields] OR "Ireland"[All Fields] OR "Italy"[All Fields] OR "Kazakhstan"[All Fields] OR "Kyrgyzstan"[All Fields] OR "Latvia"[All Fields] OR "Lithuania"[All Fields] OR "Malta"[All Fields] OR "Monaco"[All Fields] OR "Montenegro"[All Fields] OR "Netherlands"[All Fields] OR "Norway"[All Fields] OR "Poland"[All Fields] OR "Portugal"[All Fields] OR "Romania"[All Fields] OR "Russian Federation"[All Fields] OR "Russia"[All Fields] OR "San Marino"[All Fields] OR "Serbia"[All Fields] OR "Slovakia"[All Fields] OR "Slovenia"[All Fields] OR "Spain"[All Fields] OR "Sweden"[All Fields] OR "Switzerland"[All Fields] OR "Tajikistan"[All Fields] OR "Macedonia"[All Fields] OR "Turkey"[All Fields] OR "Turkmenistan"[All Fields] OR "Ukraine"[All Fields] OR "Uzbekistan"[All Fields]

vaccine effectiveness (VE) of rotavirus vaccines in preventing rotavirus disease and/or healthcare utilisation due to rotavirus, and/or (2) impact of rotavirus vaccination on rotavirus disease trends and/or healthcare utilisation due to rotavirus (Table 1). Studies from any country in the WHO European Region [7] and published in any European language were identified (Table 1). Case Reports, Randomised Controlled Trials, Animal Studies, Reviews and Systematic Reviews were excluded. Databases searched included PubMed, Embase and Cochrane. We also searched Google Scholar and the System for Information on Grey Literature in Europe (SIGLE) for relevant citations.

2.2. Inclusion criteria

We reviewed the title and abstract of each article identified using the search strategy to determine whether the article was potentially relevant. The review was conducted by three reviewers independently and discrepancies resolved by consensus between reviewers. Potentially relevant articles were referred for a full abstraction. Cohort, observational studies (case-control and pre- vs. post-vaccine introduction time periods) and surveillance database analyses performed under conditions of post-licensure routine rotavirus vaccine use were included, as well as before/after studies if the impact data (percentage change in crude or adjusted rates) were provided or could be calculated. Studies reporting results in both vaccine-eligible (direct effects) and/or in non-vaccine-eligible age groups (indirect effects) were included. Health economic studies were excluded, along with time-series observational studies with only post-vaccine introduction data, and studies conducted among vulnerable populations not representative of the general population.

2.3. Abstraction process

We used EndNote X5 (Thomson Reuters) to organise and track the articles, adding databases sequentially beginning with PubMed, and performing automated and manual de-duplication following the addition of each subsequent database. We double-abstracted information about the study location, design, population characteristics and size, type of vaccine, and vaccine coverage directly into a customised Microsoft Excel spreadsheet. For outcomes of interest we abstracted information on number of events in the control (or pre-introduction) and intervention (or post-introduction) groups, and effect measures (e.g. risk ratios). All included studies were independently abstracted by three reviewers and harmonised by consensus.

2.4. Data analysis

We did not perform a meta-analysis because of the substantial heterogeneity across studies. For example, studies that examined time-trends used variable pre and post-vaccine year(s), with country specific differences in vaccine introduced, introduction date and vaccine coverage rates. Among case-control studies, case definitions of rotavirus disease were based upon laboratory testing, however, control groups varied between children with rotavirus negative gastroenteritis, those admitted to hospital or attending outpatient clinics for any reason other than gastroenteritis, as well as healthy children in the community. Thus, we summarised the data in descriptive analysis. For the analysis, the studies were grouped by design based on whether they were reporting on vaccine effectiveness or impact. The results reported within each study were then summarised by outcome and country.

3. Results

The systematic literature review yielded 276 unique citations from 1st February 2006 to July 31st 2014 (Fig. 1). Of these we reviewed 31 articles. Among these, 24 studies on the effectiveness ($n = 9$) and impact ($n = 15$) of rotavirus vaccines met the inclusion criteria (Fig. 1).

3.1. Vaccine effectiveness (VE)

Nine studies evaluating VE were identified: one from Austria [8], one from Belgium [9], one from Finland [10], one from Germany [11], two from Israel [12,13] and three from Spain [14–16] (Table 2). Seven studies looked at the combined VE of RV1 and RV5, one study looked specifically at RV1 [13] and one specifically at RV5 [10].

3.1.1. VE against RVGE hospitalisations

Eight studies examined VE against rotavirus gastroenteritis (RVGE) hospitalisations. The overall VE for at least one dose of rotavirus vaccine ranged from 89.4% (95% CI 51.9–97.6%) to 95.6% (95% CI 85.6–98.6%) (Table 3). The overall VE for fully vaccinated children ranged from 80% (95% CI 77–83%) to 98.3% (95% CI 87.4–99.8) (Table 3). One study from Spain examined VE separately for RV1 and RV5 and found no significant difference in effectiveness

Table 2
Summary of vaccine effectiveness studies, Europe.

Country	Vaccine	Setting	Season	Outcome	Cases/vaccinated	Controls/not vaccinated	Ref.
Austria	RV1 + RV5	Paediatric wards	2010–2011	Hospitalisation for laboratory-confirmed RVGE	211 Vaccinated	343 Unknown vaccination status	[8]
Belgium	RV1 + RV5	Hospitals with paediatric beds	02/2008–06/2010	Hospitalisation for RVGE	215 Cases (gastroenteritis in children who were eligible for vaccination (≥1dose))	276 Controls (children admitted to/attending an outpatient clinic for any reason other than gastroenteritis (same hospital, time period, date of birth)	[9]
Finland	RV5	University hospitals	2009–2012	Hospitalisation for RVGE	7 Cases (diarrhoea testing positive for rotavirus in hospitalised children)	73 Controls (diarrhoea testing negative for rotavirus in hospitalised children)	[10]
Germany (Mecklenburg-Western Pomerania)	RV1 + RV5	Nationwide notification and hospitalisation surveillance data (from laboratories and local health authorities)	02/2009–06/2011	Laboratory-confirmed RV infections requiring medical attention or hospitalisation	114 Fully vaccinated (52 RV1, 34 RV5, 28 unknown)	901 Not vaccinated	[11]
Israel	RV1 + RV5	Hospitals	2007–2009	Hospitalisation for RVGE	111 Cases (diarrhoea testing positive for rotavirus)	216 Controls (diarrhoea testing negative for rotavirus)	[12]
Israel	RV1	Health maintenance organisation database (community-based post-marketing study)	2008–2009	Medical attention for AGE in children over 12 months	7586 AGE episodes requiring medical attention in vaccinated children (<12 mo)	18591 AGE episodes requiring medical attention in unvaccinated children (<12 mo)	[13]
Spain (Castellon)	RV1 + RV5	Microbiology Laboratory of the General Hospital	2009	Cases of RV diarrhoea	71 Cases (diarrhoea cases tested positive for rotavirus only)	261 controls (diarrhoea cases tested positive for any other microorganisms not rotavirus)	[14]
Spain (Navarre)	RV1 + RV5	Clinical records from paediatric hospitals and primary health care centres	01/2008–06/2011	Medical attention for RVGE	756 Cases (confirmed rotavirus)	6036 Controls	[15]
Spain	RV1 + RV5	Paediatric research network of primary, emergency and hospital care	10/2008–06/2009	Medical attention and hospitalisation for RVGE	163 Vaccinated	304 Unvaccinated	[16]

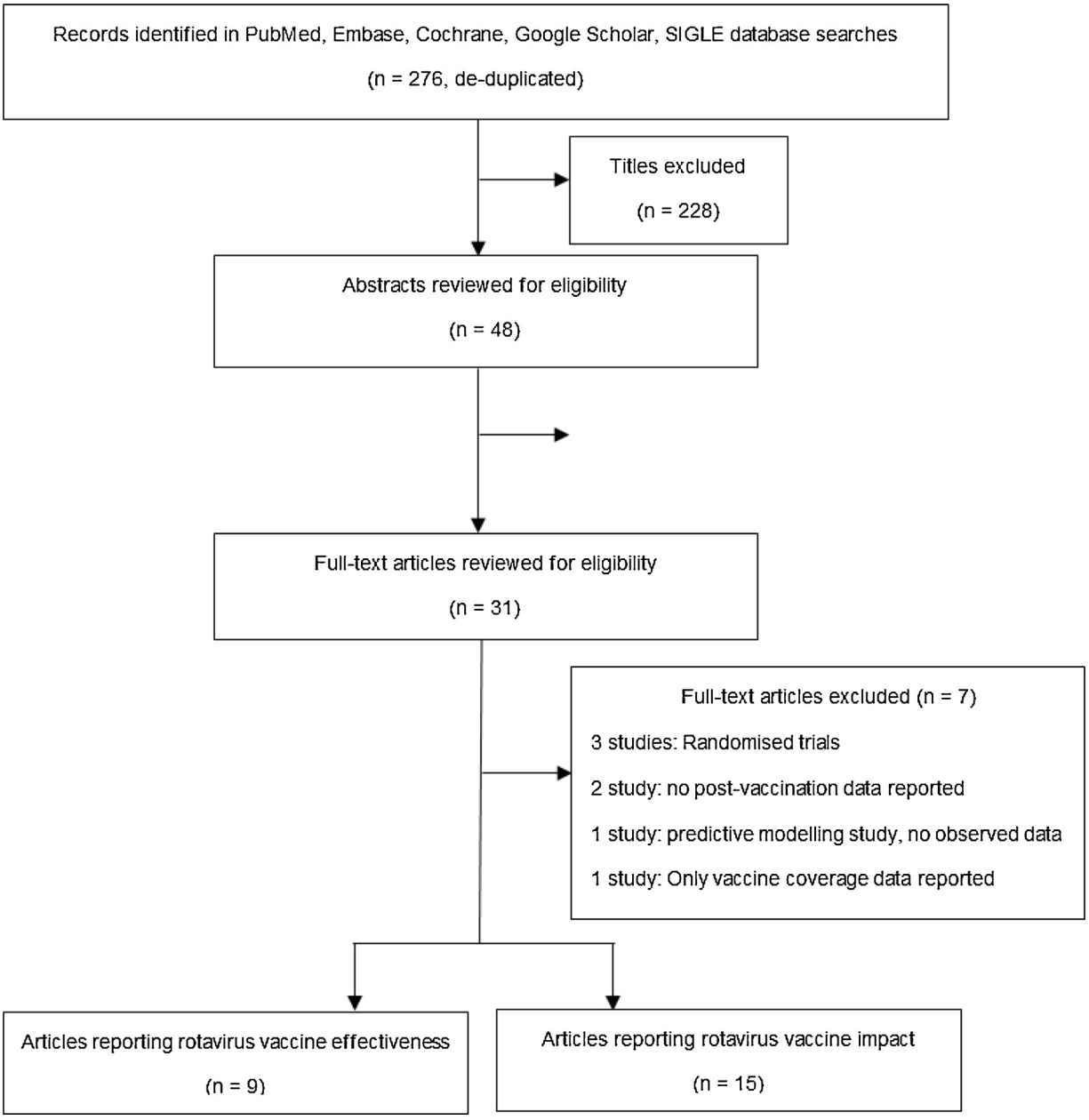

Fig. 1. Database search algorithm used for systematic literature review.

between the two vaccines [16]. VE for RV1 ranged from 90% (95% CI 81–95%) to 97.5% (95% CI 81.5–99.6%) while VE for RV5 ranged from 92.9% (95% CI 70–98.3%) to 95% (95% CI 63.1–99.3%).

In Belgium, VE was found to be very similar in younger children (3–11 months) compared to older children (over 12 months): 93% (95%CI 80–97%) vs. 89% (95% CI 75–95% for at least one dose of vaccine [9] (Table 3). In Germany VE for fully vaccinated children was also found to be similar in the two age groups: 85% (95% CI 82–88%) in children aged 18–29 months versus 80% (95% CI 77–83%) in children aged 6–17 months [11]. Although the study in Belgium showed that VE was higher for severe RVGE (91%, 95% CI 80–96%) compared to mild or moderate RVGE (66%, 95% CI 31–91%) (Table 3), this difference was not significant.

3.1.2. *VE against RVGE outpatient visits*

Four studies examined VE against RVGE outpatient visits (Table 3). VE for at least one dose of vaccine ranged from 50.1% (95% CI 47.5–52.6%) to 83.5% (95% CI 25.4–96.3) (Table 3). VE in fully vaccinated children ranged from 68% (95% CI 61–71%) to 75% (95% CI 62–83%) (Table 3). VE was lower against RVGE outpatient visits than that observed against RVGE hospitalisation [11,14,15] (Table 3).

In Germany, Adlhoch et al. found that younger children had higher VE against RVGE outpatient visits than older children (74%, 65% CI 69–78% vs. 57%, 95% CI 45–65%)[11]. In Israel children of high socioeconomic status had higher VE against RVGE outpatient visits compared to those from lower socioeconomic backgrounds (55.8%, 95% CI 52–59.5% vs 33.6%, 95% CI 27.7–39.3%) [12]. However, no information was given regarding the statistical significance of these differences.

3.1.3. *VE against laboratory-confirmed rotavirus infections*

Three studies reported VE against all laboratory-confirmed rotavirus infections (Table 3). VE ranged from 87.7% (95% CI 45.5–99.7%) to 91.5% (95% CI 83.7–95.6%) for at least one dose of vaccine, and from 78% (95% CI 68–85%) to 92.8% (95% CI 84.7–96.6%)

Table 3
Vaccine effectiveness against RVGE hospitalisations and outpatient visits, and laboratory-confirmed rotavirus infections, Europe.

Country	VE for at least 1 dose of vaccine: % (95% CI)	VE for full course of vaccine (2 doses of RV1 or 3 doses of RV5): % (95%CI)	Ref.
RVGE hospitalisation			
Austria		2010: 95 (93–97) 2011:96 (95–97)	[8]
Belgium	Overall: 91 (82–95) 3–11 mo: 93 (80–97) ≥12 mo: 89 (75–95)	Overall (RV1): 90 (81–95) 3–11 mo (RV1): 91 (75–97) ≥12 mo (RV1): 90 (76–96) Severe RVGE (RV1): 91 (80–96) Mild/Moderate RVGE (RV1): 66 (31–91)	[9]
Finland		Overall (RV5): 92.1 (50.0–98.7)	[10]
Germany (Mecklenburg-Western Pomerania)		Overall: 80 (77–83) 6–17 mo: 80 (77–83) 18–29 mo: 85 (82–88)	[11]
Israel	Overall: 89.4 (51.9–97.6)	Overall: 88.9 (6.8–98.6)	[12]
Spain (Castellon)	Overall: 93.5 (30.7–99.3)		[14]
Spain (Navarre)		Overall: 83 (65–93)	[15]
Spain	Overall: 95.6 (85.6–98.6) Overall (RV1): 97.5 (81.5–99.6) Overall (RV5):92.9 (70–98.3)	Overall: 98.3 (87.4–99.8) Overall (RV1): 97.3 (80.6–99.6) Overall (RV5): 95 (63.1–99.3)	[16]
RVGE outpatient visits			
Germany (Mecklenburg-Western Pomerania)		Overall: 68 (61–71) 6–17 mo: 74 (69–78) 18–29 mo: 57 (45–65)	[11]
Israel	Overall (RV1): 50.1 (47.5–52.6) Low SES (RV1): 33.6 (27.7–39.3) High SES (RV1): 55.8 (52–59.5)		[13]
Spain (Castellon)	Overall: 83.5 (25.4–96.3)		[14]
Spain (Navarre)		Overall: 75 (62–83)	[15]
RVGE outpatient visits			
Laboratory-confirmed rotavirus infections			
Spain (Castellon)	Overall: 87.7 (45.5–99.7)		[14]
Spain (Navarre)	Overall: 78 (70–84) Overall (RV1): 76 (63–85) Overall (RV5): 80 (69–87) <24 mo: 80 (70–86) ≥24 mo: 61 (0–84)	Overall: 78 (68–85) Overall (RV1): 75 (60–85) Overall (RV5): 81 (68–89)	[15]
Spain	Overall: 91.5 (83.7–95.6)	Overall: 92.8 (84.7–96.6)	[16]

for a full course of vaccination (Table 3). The two studies that compared number of doses of vaccine given found very similar VE in children having received at least one dose of vaccine and children having completed their vaccination course [15,16].

The study in Navarre, Spain compared VE for RV1 and RV5 and found very similar results for both vaccines: 76% (95% CI 63–85%) for RV1 and 80% (95% CI 69–87%) for RV5, for at least one dose of vaccine and 75% (95% CI 60–85%) for RV1 and 81% (95% CI 68–89%) for RV5 for full course vaccination [15]. It also found that children aged less than 24 months had significantly higher VE ($p = 0.0495$) than older children aged over 24 months (80%, 95% CI 70–86% vs 61%, 95% CI 0–84%) (Table 3).

3.2. Vaccine impact

Fifteen studies that assessed the impact of rotavirus vaccination were included (Table 4). From countries where universal rotavirus vaccination has been implemented we included four studies from Austria [8,17–19], four from Belgium [20–23] and three from Finland [10,24,25]. Studies using local or regional data from countries at various stages of integrating rotavirus vaccination into their national immunisation programmes included one from France [26], one from Germany [27] and two from Spain [28,29].

3.2.1. Impact on RVGE/AGE hospitalisations

The impact of vaccination on RVGE hospitalisations was the most commonly reported outcome (Table 5). Austria introduced universal mass rotavirus vaccination in August 2007 [17]. The programme incorporated RV5 in 2007 and 2009, and RV1 in 2008 and 2010–2012 [8]. Vaccine coverage ranged from 72% in 2008 to 84% in 2011 [8,18]. In Austria, reductions in RVGE hospitalisations in infants aged less than 1 year ranged from 70% in 2008 to 84% in 2010 compared with the pre-vaccine period (2001–2006) [8,17,18] (Table 5). RVGE hospitalisation rates remained low in children between 2 and 3.5 years of age in 2011, suggesting sustained protection of up to 3 years post-vaccination [18]. Reductions in RVGE hospitalisations were also observed in children too old to be eligible for rotavirus vaccination [8,18] suggesting indirect protection of these individuals (Table 5). However, in 2011 a distinct increase in RVGE hospitalisations was observed in children over 5 years of age compared to the pre-vaccine era [8]. Explanations for this increase included deferred exposure, and change of age distribution due to accumulation of risk of infection over time among non-immune children, and/or very high rotavirus activity in 2011 [8].

Similarly, Belgium introduced rotavirus vaccines into the infant immunisation schedule from 2006 [20]. From 2006 to 2008, 95% of children receiving a rotavirus vaccine were given RV1 and 5% received RV5 [23]. Overall vaccine coverage was estimated to be at least 90% [21] and significant reductions in RVGE hospitalisations have been observed. One study, performed across 12 hospitals, reported 65% to 80% reductions in RVGE hospitalisations in the first two years post-vaccination in the vaccine-eligible age group. Reductions of 20% to 64% were observed in age groups too old or too young to be eligible for vaccination [22] (Table 5).

In Finland, the national rotavirus immunisation programme with RV5 started in 2009 [24]. Vaccine coverage is estimated to be 95% to 97% [24]. A national hospital database study comparing RVGE and acute gastroenteritis (AGE) hospitalisations prior (1995–2005) and after (2010) the start of the programme demonstrated a 80%

Table 4
Summary of vaccine impact studies, Europe.

Country, year of vaccine introduction	Vaccine	Study population	Vaccine coverage (%)	Study period		Data source for RVGE cases	Outcomes evaluated	Ref.
				Before	After			
Austria, 2007	[a]RV1 + RV5	Children <15 years	72	2001–2006	2008	Prospective surveillance study; sentinel system in 11 hospitals	RVGE hospitalisation rates	[17]
Austria, 2007	[a]RV1 + RV5	Children <15 years	74	2001–2005	2008–2009	Prospective surveillance study; sentinel system in 11 hospitals	RVGE hospitalisation rates	[18]
Austria, 2007	[a]RV1 + RV5	Children <15 years	78–84	2001–2005	2008–2011	Prospective surveillance study; sentinel system in 11 hospitals	RVGE hospitalisation rates	[8]
Austria, 2007	[a]RV1 + RV5	Children 0–18 years	72–74	2002–2005	2008–2009	Retrospective evaluation study; 1 large tertiary care hospital	Number of RVGE hospitalisations Number of RVGE nosocomial infections	[19]
Belgium, 2006	[a]RV1 + RV5	Children <5 years	88	1986–2006	2007–2009	Prospective surveillance study; sentinel system in 1 hospital	RVGE hospitalisations as percentage of AGE hospitalisations	[20]
Belgium, 2006	[a]RV1 + RV5	All age groups	90	1999–2006	2007–2010	Prospective surveillance study; sentinel system of microbiology laboratories	Number of laboratory-confirmed rotavirus infections	[21]
Belgium, 2006	[a]RV1 + RV5	Children ≤5 years	85–90	2004–2006	2007–2009	Retrospective database study; 12 hospitals	Number of RVGE hospitalisations Number of RVGE nosocomial infections	[22]
Belgium, 2006	[a]RV1 + RV5	All age groups	90	2005–2006	2008	Prospective surveillance study; sentinel system of microbiology laboratories	Number of laboratory-confirmed rotavirus infections	[23]
Finland, 2009	RV5	Children <5 years	95–97	1999–2005	2010	Retrospective national database study; national Hospital Discharge Register	RVGE/AGE hospitalisation rates RVGE/AGE outpatient visit rates	[24]
Finland, 2009	RV5	Children <16 years	95–97	2006–2008	2009–2011	Prospective surveillance study; sentinel system in 1 hospital	Number of RVGE/AGE hospitalisations umber of RVGE/AGE outpatient visits	[25]
Finland, 2009	RV5	Children <16 years	95–97	2001–2006	2009–2012	Retrospective database study; 2 hospitals	RVGE/AGE hospitalisation rates	[10]
France, 2007	RV5	Children <2 years	47	2002–2007	2008–2009	Population-based prospective cohort study; catchment area of 1 hospital	RVGE hospitalisation rates	[26]
Germany, 2006	RV1 + RV5	All age groups	22 WFS 58 EFS	2004–2006	2008–2011	Retrospective national database study; national disease reporting system	RVGE hospitalisation rates	[27]
Spain, 2007	RV1 + RV5	Children <5 years	38	2005–2006	2009	Retrospective national database study; national Hospital Discharge database	RVGE/AGE hospitalisation rates	[28]
Spain, 2007	RV1 + RV5	Children <5 years	46	2003–2007	2008–2010	Retrospective database study; 32 hospitals	RVGE/AGE hospitalisation rates	[29]

[a] National immunisation programme has incorporated RV1 (Rotarix) and RV5 (Rotateq).

Table 5
Impact of vaccination on RVGE hospitalisations, nosocomial infections and outpatient visits, and laboratory-confirmed rotavirus infections, Europe.

Country	Vaccine	Outcome measured	Pre-vaccination		Post-vaccination		Vaccination impact % Change (95% CI)	Ref.
			Year	Result	Year	Result		
RVGE hospitalisation								
Austria	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 children (extrapolated to whole country from surveillance system)	2001–2006	<1 yr: 2066 1 yr: 1822 2–4 yrs: 436 5–14 yrs: 34	2008	<1 yr: 631 1 yr:1456 2–4 yrs: 461 5–14 yrs: 34	−70 −20 +6 0	[17]
Austria	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 children (extrapolated to whole country from surveillance system)	2001–2005	<1 yr: 2141 1 yr: 1745 2–4 yrs: 394 5–14 yrs: 31	2009	<1 yr: 441 1 yr:408 2–4 yrs: 256 5–14 yrs: 19	−79 −76 −35 −38	[18]
Austria	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 children (extrapolated to whole country from surveillance system)	2001–2005	<1 yr: 2141 1 yr: 1745 2–3.4 yrs: 611 3.5–4 yrs: 206 5–9 yrs: 53 10–14 yrs: 13	2010 2011	<1 yr: 344 1 yr: 331 2–3.4 yrs: 235 3.5–4 yrs: 188 5–9 yrs: 35 10–14 yrs: 6 <1 yr: 397 1 yr: 332 2–3.4 yrs: 216 3.5–4 yrs: 201 5–9 yrs: 78 10–14 yrs: 14	−84 −81 −62 −9 −34 −32 −81 −81 −65 −3 +48 +6	[8]
Austria	[a]RV1 + RV5	Annual number of RVGE hospitalisations	2002–2005	<1 yr: 90 0–18 yrs: 257	2008–2009	<1 yr: 11 0–18 yrs: 67	−88 −74	[19]
Belgium	[a]RV1 + RV5	Annual RVGE hospitalisations as a percentage of annual total AGE hospitalisations	1986–2006	<5 yrs:19%	2007 2008 2009	<5 yrs: 12% <5 yrs: 10% <5 yrs: 6%	−35 −49 −66	[20]
Belgium	[a]RV1 + RV5	Annual number of RVGE hospitalisations	2004–2006	<2 mo: 44 2–24 mo: 716 >24 mo: 121	2008 2009	<2 mo: 22 2–24 mo: 249 >24 mo: 97 <2 mo: 16 2–24 mo: 140 >24 mo: 43	−50 (−64 to −36) −65 (−69 to −62) −20 (−28 to −14) −64 (−76 to −49) −80 (−83 to −77) −64 (−72 to −56)	[22]
Finland	RV5	Annual RVGE hospitalisation rates/1000 person years Annual AGE hospitalisation rates/1000 person years	1999–2005 1999–2005	<1 yr: 4.9 1 yr: 5.7 2 yrs: 2.7 3 yrs: 1.3 4 yrs: 0.7 <1 yr: 20 1 yr: 21 2 yrs: 10 3 yrs: 6 4 yrs: 4	2010 2010	<1 yr: 1.0 1 yr: 1.5 2 yrs: 0.8 3 yrs: 0.4 4 yrs: 0.3 <1 yr: 9 1 yr: 9 2 yrs: 5 3 yrs: 3 4 yrs: 3	−80 (−85 to −75) −74 (−79 to −68) −70 (−77 to −60) −69 (−80 to −54) −53 (−70 to −26) −54 (−58 to −50) −55 (−59 to −51) −51 (−56 to −45) −47 (−54 to −39) −27 (−37 to −15)	[24]
Finland	RV5	Annual number of RVGE hospitalisations Annual number of AGE hospitalisations	2006–2008 2006–2008	<16 yrs: 219 <16 yrs: 434	2009–2011 2009–2011	<16 yrs: 52 <16 yrs: 186	−76 −57	[25]
Finland	RV5	Annual RVGE hospitalisation rates/1000 children Annual AGE hospitalisation rates/1000 children	2001–2006 2001–2006	<16 yrs: 0.66 <16 yrs: NR [b]	2009–2012 2009–2012	<16 yrs: 0.14 <16 yrs: NR	−78 −57	[10]
France	RV5	Annual number of RVGE hospitalisations	2002–2007	<2 yrs: 61	2008–2009	<2 yrs: 30	−51	[26]
Germany	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 population	2004–2006	WFS <2 yrs: NR EFS <2 yrs: NR	2008–2011	WFS <2 yrs: NR EFS <2 yrs: NR	−25 −36	[27]

Table 5 (*Continued*)

Country	Vaccine	Outcome measured	Pre-vaccination		Post-vaccination		Vaccination impact % Change (95% CI)	Ref.
			Year	Result	Year	Result		
Spain	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 children	2005–2006	<1 yr: 835	2009	<1 yr: 477	−43	[28]
			2005–2006	<5 yrs: 278	2009	<5 yrs: 174	−37	
		Annual AGE hospitalisation rates/100,000 children		<1 yr: 2741		<1 yr: 1584	−42	
				<5 yrs: 1156		<5 yrs: 749	−35	
Spain	[a]RV1 + RV5	Annual RVGE hospitalisation rates/100,000 children	2003–2007	<5 yrs: 298	2008–2009	<5 yrs: 254	−15	[29]
			2003–2007	<5 yrs: 600	2009–2010	<5 yrs: 165	−45	
		Annual AGE hospitalisation rates//100,000 children			2008–2009	<5 yrs: 420	−30	
					2009–2010	<5 yrs: 306	−49	
Nosocomial RVGE								
Austria	[a]RV1 + RV5	Annual number of RVGE nosocomial infections	2002–2005	<1 yr: 14	2008–2009	<1 yr: 1	−97	[19]
				0–18 yrs: 27		0–18 yrs: 2	−93	
Belgium	[a]RV1 + RV5	Annual number of RVGE nosocomial infections	2004–2006	≤5 yrs: 140	2008	≤5 yrs: 75	−46	[22]
					2009	≤5 yrs: 33	−76	
Germany	[a]RV1 + RV5	Annual RVGE nosocomial infection rates/100,000 population	2004–2006	WFS	2008–2011	WFS	−25	[27]
				<6 mo: 156		<6 mo: 117	−38	
				6–11 mo: 108		6–11 mo: 66	−4	
				12–17 mo: 59		12–17 mo: 57	+1	
				18–23 mo: 35		18–23 mo: 36	−5	
				2–4 yrs: 10		2–4 yrs: 9	+5	
				EFS		EFS	−36	
				<6 mo: 214		<6 mo: 225	−28	
				6–11 mo: 148		6–11 mo: 94	−33	
				12–17 mo: 109		12–17 mo: 79	−20	
				18–23 mo: 54		18–23 mo: 36		
				2–4 yrs: 29		2–4 yrs: 23		
RVGE outpatient visits								
Finland	RV5	Annual RVGE outpatient visit rates/1000 person years	1999–2005	<1 yr: 0.4	2010	<1 yr: 0.08	−79 (−91 to −48)	[24]
			1999–2005	1 yr: 0.4	2010	1 yr: 0.1	−73 (−88 to −39)	
		Annual AGE outpatient visit rates/1000 person years		2 yrs: 0.3		2 yrs: 0.15	−43 (−71 to 13)	
				3 yrs: 0.09		3 yrs:0.07	−30 (−75 to 97)	
				4 yrs: 0.08		4 yrs: 0.02	−79 (−97 to 55)	
				<1 yr: 22		<1 yr: 19	−13 (−18 to −7)	
				1 yr: 19		1 yr: 17	−11 (−16 to −5)	
				2 yrs: 10		2 yrs: 8	−22 (−29 to −14)	
				3 yrs: 6		3 yrs: 6	−1 (−11 to 10)	
				4 yrs: 4		4 yrs: 5	+27 (−12 to 43)	
Finland	RV5	Annual number of RVGE outpatient visits	2006–2008	<16 yrs: 177	2009–2011	<16 yrs: 34	−81	[25]
		Annual number of AGE outpatient visits	2006–2008	<16 yrs: 375	2009–2011	<16 yrs: 144	−62	
Laboratory-confirmed rotavirus infections								
Belgium	[a]RV1 + RV5	Annual number of laboratory-confirmed rotavirus infections	1999–2006	NR (monthly counts shown on graph)	2007–2010	NR (monthly counts shown on graph)	−50	[21]
Belgium	[a]RV1 + RV5	Annual number of laboratory-confirmed rotavirus infections	2005–2006	6383	2008	2464	−61% (−63 to −60)	[23]

[a] National immunisation programme has incorporated RV1 (Rotarix) and RV5 (Rotateq).

[b] NR: data not reported.

reduction in RVGE hospitalisations among infants aged less than 1 year of age and 54% when the total inpatient AGE burden was considered in the same age group [24] (Table 5). Reductions of 53% to 74% and 27% to 55% in RVGE and AGE hospitalisations, respectively, were observed in age groups too old to be eligible for rotavirus vaccination [24] (Table 5). Further studies conducted in individual hospitals reported similar reductions in childhood RVGE and AGE hospitalisations compared with the pre-vaccine period [10,25] (Table 5).

In the absence of a national rotavirus vaccination programme in France a study performed in the city of Brest found that RVGE hospitalisations in children less than 2 years of age declined by 51% compared with the pre-vaccination period. This was consistent with the estimated vaccine coverage of 47% with RV5, which was the only vaccine used in the region [26] (Table 5). No reduction was observed in age groups over 2 years of age [26].

In Germany, rotavirus vaccines have been available on the market since 2006. However, rotavirus vaccination (RV1 and RV5) has been included in the routine vaccination scheme in only five of the 16 federal states since 2008 [27]. In 2010 a moderate (58%) and low (22%) vaccine uptake was observed in the five eastern federal states (EFS) and the 11 western federal states (WFS), respectively [27]. A study using the national mandatory disease reporting system found that RVGE hospitalisations in children less than 2 years of age were reduced by 36% and 25% in EFS and WFS, respectively, in post-vaccine seasons (2008–2011) compared to pre-vaccine seasons (2004–2006) [27] (Table 5). No significant reduction was observed in age groups over 2 years of age [27].

In Spain, rotavirus vaccines have been available since 2006 (RV1) and 2007 (RV5) but they are neither funded nor reimbursed by the National Health System [29]. Overall vaccine coverage in 2009 was 38% [28]. A national hospital database study comparing RVGE and AGE hospitalisations prior (2005–2006) and after (2009) vaccine introduction demonstrated a 43% reduction in RVGE hospitalisations among infants less than 1 year of age and a 42% reduction in total AGE hospitalisations in the same age group [28] (Table 5). Hospitalisation rates for RVGE and AGE in children less than 5 years of age were 37% and 35% lower [28] (Table 5). A regional study performed in Galicia (North-western Spain), where vaccine coverage was estimated to be 49%, reported similar reductions in childhood RVGE and AGE hospitalisations compared with the pre-vaccine period. Hospitalisation rates for RVGE and AGE in children less than 5 years of age were 45% and 49% lower, respectively [29] (Table 5). In 2010, the Spanish Drugs and Health Products Agency did not authorise the release of new batches of the two vaccines onto the Spanish market for five months (June to November 2010) due to the detection of circovirus in both vaccines [30]. The withdrawal of RV1 in Spain still remains, so currently only RV5 is available. The impact of this temporary withdrawal was evaluated in Galicia [31] as an extension of the previous study [29]. A sudden drop in vaccine coverage was observed from 49% to 22% [31]. A rebound 260% increase in RVGE hospitalisations in children less than 12 months of age was observed in 2010–2011 compared to the previous season [31]. In 2011–2012, once rotavirus vaccination was resumed, rates decreased by 30% compared to 2010–2011 [31].

3.2.2. Impact on nosocomial RVGE infections

In Austria, a 93% reduction in hospital-acquired rotavirus infections in 0–18 year olds was reported from one large tertiary hospital during 2008–2009 compared to the pre-vaccine period (2002–2005) (Table 5) [19]. The largest decrease in nosocomial cases was in infants aged less than 1 year (97%) [19]. Similarly in Belgium, hospital-acquired rotavirus infections in children less than 5 years of age declined by 46% to 76% post-vaccination [22] (Table 5). In Germany, the largest reductions in nosocomial rotavirus infections were in infants 6–11 months of age (36% and 38% in EFS and WFS, respectively) [27] (Table 5).

3.2.3. Impact on RVGE/AGE outpatient visits

In Finland a national hospital database study comparing RVGE and AGE outpatient visits prior (1995–2005) and after (2010) the start of vaccination demonstrated a 79% reduction in RVGE outpatient visits among infants less than 1 year of age and 13% when the total AGE outpatient visits burden was considered in the same age group [24] (Table 5). Reductions of 30% to 79% in RVGE outpatient visits were observed in age groups too old to be eligible for rotavirus vaccination [24] (Table 5). A further study conducted in a single hospital in Finland reported similar reductions in childhood RVGE and AGE outpatient visits compared with the pre-vaccine period [25] (Table 5).

3.2.4. Impact on laboratory-confirmed rotavirus infections

In Belgium, vaccine impact measured through national sentinel-based surveillance systems have reported a 50% to 61% decline in the number of laboratory-confirmed rotavirus infections in all age groups in post-vaccination years compared to the pre-vaccine era [21,23] (Table 5). The greatest reductions were observed in infants aged less than 1 year (80%) [23].

4. Discussion

Eight years after their initial introduction in Europe, rotavirus vaccines have shown to be highly effective with substantial impact against RVGE-related healthcare utilisation, including hospitalisations, nosocomial infections and outpatient visits. These findings are consistent across studies and countries in Europe and comparable to observations from Australia [32] and the US [33].

Overall, the estimates of vaccine effectiveness from studies of rotavirus vaccines in routine use in Europe were consistent with data from clinical trials [3,34]. Estimates of effectiveness for a complete course of RV1 or RV5 in case-control studies in Europe against RVGE hospitalisation or RVGE outpatient visits ranged from 68% to 98% depending on the study and selected control group [8–16]. These compare with vaccine efficacy of 90% and 98% against severe RVGE, and 79% and 68% against RVGE of any severity reported in European clinical trials for RV1 and RV5, respectively [3,34]. Additional years of experience will provide more complete estimates of effectiveness, and enable documentation of any potential waning immunity. Future VE studies in Europe will need to demonstrate whether or not effectiveness is sustained in older children, and whether these vaccines provide protection against a range of heterotypic circulating rotavirus strains in Europe. This will provide further evidence that rotavirus vaccines perform well even against non-vaccine genotypes, which would be consistent with findings from clinical efficacy trials [3,34] as well as from post-licensure studies from the US [33] and Latin America [35].

The impact of RV1 and RV5 in Europe is evident not only in the changing epidemiology of rotavirus activity, but also in the reduction of healthcare utilisation due to diarrhoeal disease. From countries in Europe where universal rotavirus vaccination has been implemented, studies summarised in this review have estimated 65% to 84% reductions in rotavirus hospitalisations in vaccine eligible children following vaccine introduction [8,10,17–25]. Additionally, despite the fact that the greatest impact was observed in infants, significant reductions were also seen in older children and adults, suggesting herd immunity. The reduction in RVGE/AGE hospitalisations and outpatient visits could represent large healthcare cost savings attributable to rotavirus vaccination and should be accounted for in subsequent European cost-effectiveness studies for rotavirus vaccines, which have so far only considered cost benefits afforded by direct protection of infants [36–38].

Reductions have also been observed among unvaccinated individuals, providing evidence of indirect impact of rotavirus vaccines. Although these reductions could be attributed to the natural seasonal fluctuations in rotavirus activity, they are significantly more pronounced than the historical long-term patterns typically observed for rotavirus. Recent research in Austria and Finland suggests these reductions have been sustained for up to four seasons [8,10]. It will be important, however, to continue monitoring these trends over time to confirm the long-term impact of rotavirus vaccination in Europe. In addition, continued monitoring will allow characterisation of the evolving epidemiology of rotavirus genotypes. Reductions in rotavirus hospitalisations in Europe are consistent with the estimated 50% to 90% reduction reported in the US [33]. These substantial benefits have been observed with only rare adverse events, such as intussusception, reported in post-marketing studies in the US, Australia and Latin America [39]. In these countries the morbidity and mortality averted by vaccination has been shown to outweigh even the most liberal estimates of increased risk [39]. Further quantification of this risk in Europe is necessary.

Having said, that it's important to note that studies looking at vaccine impact have similar limitations. Their designs are descriptive and ecological and, therefore, the effects measured may be due to other factors not related to immunisation. First, rotavirus testing practices could have changed in the post-vaccination period. Second, the accuracy of hospital diagnoses codes depends on clinical diagnoses recorded in patients' medical records. Coding practices could have changed over time. Last, there is natural year-to-year variability in the size of the rotavirus season. It remains a possibility that at least some of the observed decrease may be due to a less active rotavirus year, independent of vaccination effect.

In summary, this systematic review confirmed the significant public health benefit of rotavirus vaccination in Europe as an important tool for protecting children against severe acute gastroenteritis. Since its introduction in 2006, it has contributed to a significant reduction in burden of RVGE through direct and indirect effects. Furthermore, the vaccine effectiveness observed under routine use is consistent with efficacy data from clinical trials. These benefits were observed consistently across all European countries in which it has been introduced as part of the routine childhood immunisation schedule. Thus, we provide further evidence to support the implementation of universal rotavirus vaccination in all European countries.

Authors' contribution to the manuscript

The manuscript has been read and approved by all named authors, who have worked collaboratively on the study design, data collection, data analysis, data interpretation and on the writing up of the review.

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Conflict of interest statement

None.

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