DRAFT SCIENTIFIC ADVICE FOR PUBLIC CONSULTATION

ECDC PRELIMINARY SCIENTIFIC ADVICE

Expert opinion on rotavirus vaccination in infancy

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THIS DRAFT SCIENTIFIC ADVICE WILL BE SUBJECT TO PUBLIC CONSULTATION. COMMENTS PROVIDED DURING THE CONSULTATION PROCESS MAY LEAD TO CHANGES IN THE FINAL REPORT.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, USA
ADR	adverse drug reaction
AGE	acute gastroenteritis
CHMP	EMA Committee for Medicinal Products for Human Use
CI	confidence interval
DNA	deoxyribonucleic acid
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ED	emergency department
EEA	European Economic Area
ELISA	enzyme-linked immuno-sorbent assay
EMA	European Medicines Agency
EU	European Union
EV	Eudravigilance database, European Medicines Agency
FDA	Food and Drug Administration, USA
GMT	geometric mean titers
GSK	GlaxoSmithKline
IgA	immunoglobulin A
IgG	immunoglobulin G
IS	intussusception
NICUS	neonatal intensive care unit
NITAG	national immunisation technical advisory group
OR	odds ratio
PCV	porcine circovirus
QALY	quality-adjusted life year
RCT	randomised placebo-controlled clinical trial
RR	relative risk
RV	rotavirus
RV1	monovalent rotavirus vaccine (Rotarix™)
RV5	pentavalent rotavirus vaccine (RotaTeq™)
RV GE	group A rotavirus-induced gastroenteritis
SCID	severe combined immunodeficiency
SMR	standardised morbidity ratio
SPC	Summary of Product Characteristics
SPMSD	Sanofi Pasteur Merck Sharp Dome
STIKO	German Standing Committee on Vaccination
TGA	Therapeutic Goods Administration, Australia
US CDC	United States Centers for Disease Control and Prevention
US NIAID	United States National Institute of Allergy and Infectious diseases
VAERS	Vaccine Adverse Event Reporting System
VLP	virus-like particle
VP	viral protein
WHO	World Health Organization
WHO SAGE	World Health Organization Strategic Advisory Group of Experts

Executive summary

Aim

Since 2006, two oral live attenuated vaccines (RV1 and RV5) have been available in the European Union/European Economic Area (EU/EEA) for prevention of group A rotavirus-induced gastroenteritis (RV GE). The main objective of rotavirus vaccination is to provide protection against moderate-to-severe disease and thereby prevent hospitalisation and death.

The aim of this expert opinion is to provide EU/EEA Member States with relevant scientific information and expert opinion to support the decision-making process on the possible introduction and monitoring of routine vaccination of infants against rotavirus-induced gastroenteritis. The opinion provided in this document is based on evidence collected from the scientific literature and an analysis of the EMA Eudravigilance database which was then evaluated by a group of independent EU/EEA public health experts. The opinion highlights issues to be considered before and after introduction of rotavirus vaccines.

It also identifies knowledge gaps and areas in need of further research.

Methods

The data presented in this document are based on reviews of the literature published in scientific journals, grey literature and a search in the EMA Eudravigilance database for reported cases of intussusception following rotavirus vaccination. The information collected summarises:

- burden of severe rotavirus disease in the EU/EEA
- rotavirus vaccine efficacy in countries with low mortality due to rotavirus infections (hereafter referred to as 'low-mortality rotavirus countries')
- rotavirus vaccine effectiveness in low-mortality rotavirus countries
- herd protection provided by infant rotavirus vaccination in low-mortality rotavirus countries
- rotavirus vaccine safety
- cost-effectiveness of using rotavirus vaccines in EU/EEA immunisation programmes
- attitudes to rotavirus vaccination among parents and healthcare workers.

Results

Burden of severe rotavirus disease in the EU/EEA

A literature review identified 46 studies conducted in eighteen EU/EEA Member States, suggesting that approximately 300−600 children per 100 000 under the age of five years are hospitalised due to rotavirus disease annually. However, significant variation occurs over time and between countries. Extrapolating these data to the whole EU/EEA with a birth cohort of approximately five million infants suggests that ~75 000−150 000 hospitalisations in children under five years occur on an annual basis. Mortality rates reported in two studies were low (one study found death rates of less than 0.1/100 000 and the other less than 0.2/100 000 children under five years of age). A few risk factors for development of severe rotavirus disease have been identified, but severe disease may develop in any child. The risk factors identified are low-birth-weight (<2 500 g) (OR 2.8; 95% CI 1.6−5.0), day-care attendance (OR 3.0; 95% CI 1.8−5.3) and having another child aged under 24 months in the same household (OR 1.6; 95% CI 1.1−2.3).

Children seeking medical attention in emergency departments/out-patient clinics or those hospitalised with rotavirus disease have the potential to be sources of nosocomial infection in other children attending medical services. In a recent meta-analysis of studies of nosocomial rotavirus disease, an adjusted year-round incidence of 0.7 (95% CI 0.0−1.8) per 100 hospitalisations was estimated for children under five years.

Vaccine efficacy

A Cochrane review published in 2012 evaluated vaccine efficacy in 41 randomised controlled trials with 186 263 participants. The trials compared one of the rotavirus vaccines with placebo, no intervention or another vaccine. The RV1 vaccine was evaluated in 29 trials involving 101 671 participants and the RV5 vaccine in 12 trials involving 84 592 participants. The large trials were conducted in low- and high-mortality settings throughout the world. The Cochrane analysis showed that in the first two years of life, RV1 and RV5 prevent more than 80% of severe cases of rotavirus diarrhoea in low-mortality developed country settings. Furthermore, a German systematic review and meta-analysis of randomised placebo-controlled clinical trials (RCTs) conducted in Europe, Australia, Canada, USA, Latin America and Asia and published in 2013 suggest a vaccine efficacy against rotavirus-induced hospitalisation during the first two years following vaccination of 92% (95% CI 82−96%).

Vaccine effectiveness

Rotavirus vaccine effectiveness was assessed in observational studies using either case-control or cohort study designs in the following rotavirus low-mortality and developed countries that recommend rotavirus vaccines in their routine programmes: Australia (RV1 and RV5), Austria (RV1 and RV5), Finland (RV5), France (RV5), Germany (RV1 and RV5), Spain (RV5), and the US (RV1 and RV5). After at least two doses of rotavirus vaccine, pooled vaccine effectiveness, to prevent severe rotavirus-induced gastroenteritis leading to hospitalisation was estimated at 84% (95%CI 75−89%) in case-control studies (based on 15 studies) and at 91% (95%CI 88−94%) in cohort studies (based on four studies).

Herd immunity

A meta-analysis of studies conducted to estimate herd immunity in children <1 year of age in low-mortality rotavirus countries (n=5) reporting on rotavirus-specific gastroenteritis outcomes suggest a median herd effect on rotavirus disease morbidity of 22% (19−25%) across 12 study years.

Vaccine safety

An earlier first generation, US-licensed oral live attenuated rotavirus vaccine RRV-TV (Rotashield, authorised 1998) was withdrawn because of an associated estimated excess of one additional case of intussusception (IS) per 4 670 to 9 474 infants vaccinated (beyond the natural background incidence of IS).

In pre-authorisation trials, which served as the basis for authorisation of the second generation of rotavirus vaccines in the EU, no increased risk of IS was observed in recipients of either rotavirus vaccine (RV1 or RV5), compared to the placebo groups. This was also the conclusion of the 2012 Cochrane systematic review assessing vaccine safety in randomised placebo-controlled clinical trials. However, a risk of IS lower than one additional case in 10 000 vaccinated infants could not be excluded in the conducted trials. Formal pharmacoepidemiological studies in Australia, Brazil, Mexico and the US assessing the second generation of rotavirus vaccines used in routine vaccination programmes indicate that rotavirus vaccines carry an increased risk of intussusception during the first seven days following dose 1, ranging between 1 per 20 000 to 1 per 69 000 for RV1 vaccinated infants and 1 per 14 000 to 1 per 67 000 for RV5 vaccinated infants in the different studies. The exception to this was the first studies conducted by Belongia et al, Shui et al and Haber et al, using VAERS or VSD data where no increased risk of intussusception following RV5 was observed, possibly due to small sample size. The EU summaries of product characteristics (SPCs) for both rotavirus vaccines were updated in May 2014:

> 'Data from observational safety studies performed in several countries indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively. There is limited evidence of a smaller increased risk following the second dose. It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow up'.

Risk minimisation strategies to reduce incidence of intussusception following rotavirus vaccination have been recommended by a few European public health agencies/NITAGs in three countries (Germany, Norway and two regions in Sweden). The impact of these strategies needs to be carefully studied.

Other identified adverse events include severe gastroenteritis and long-term excretion of rotavirus by severely immunocompromised vaccinated infants (SCID), for whom RV vaccines now are contraindicated. Furthermore, any vaccinated infant may transmit vaccine virus to severely immunocompromised contacts of any age and therefore contact between a newly vaccinated child and such individuals should be avoided.

Cost-effectiveness in EU/EEA Member States

There is no clear consensus among the identified studies on cost-effectiveness for universal rotavirus vaccination in the EU/EEA. A recent survey in EU/EEA Member States found that eight out of eleven countries having undertaken economic assessments have introduced rotavirus vaccines into their programmes. The inclusion of societal costs significantly affects the estimated cost-saving threshold, and the majority of studies, particularly those that do not take into account societal costs, conclude that the vaccines would have to be priced more competitively to make this intervention cost-effective. A meta-analysis of data from five EU Member States (Belgium, the UK - England & Wales, Finland, France and the Netherlands) calculated an estimated threshold price for rotavirus vaccination to be cost-effective in these countries ranging between EUR 28−52 per vaccine course.

Attitudes to rotavirus vaccination among parents and healthcare workers

No studies are available in the EU/EEA on attitudes to rotavirus vaccination among parents and healthcare workers. In countries that report vaccination coverage for rotavirus vaccines used in national immunisation programmes, the coverage ranges between 61 and 93%, suggesting good acceptance among parents, care providers and healthcare workers.

Conclusions and possible implications for public health practice and research

Burden of disease studies assessing severe rotavirus disease leading to hospitalisation conducted in eighteen EU/EEA countries suggest that ~75 000–150 000 hospitalisations occur annually in children aged under five years, while mortality is low. Two rotavirus vaccines for use in routine immunisation programmes have been authorised for prevention of rotavirus-induced gastroenteritis and shown, in a series of studies, to be effective in preventing severe rotavirus-induced gastroenteritis leading to hospitalisation. Vaccine effectiveness against rotavirus-related hospitalisation ranges from 85–90% in countries with low mortality due to rotavirus disease (all EU/EEA countries are categorised as low-mortality countries). Furthermore, herd immunity contributes to the overall impact of vaccination programmes. A risk of up to six additional intussusception cases per 100 000 infants has been identified for both rotavirus vaccines, as specified in respective EU/EEA SPC. Benefit-risk has been assessed by many regulatory agencies throughout the world including EMA, FDA, TGA and found to be positive, given the severity of rotavirus disease and availability of treatment for cases of intussusception. However, in accordance with the recommendations of several public health agencies, options for risk minimisation with the current vaccines should be explored and vigilance among parents, care-providers and healthcare workers is essential to ensure that affected infants are promptly treated.

The expert panel suggests the following set of data collection and monitoring to be considered at the EU-level and in EU/EEA Member States before and after introduction of rotavirus vaccines into a routine immunisation programme:

- case-based routine or sentinel surveillance of severe rotavirus disease leading to hospitalisation and/or death
- investigation and reporting of hospitalised breakthrough rotavirus disease in vaccinated individuals (including genotyping)
- estimation of country-specific background rates of intussusception (by month of age during the first year of life);
- collection of data on individual vaccine exposure (including batch number) in manual or electronic registries and overall vaccine coverage.

Furthermore, EU/EEA countries could consider measuring the impact of rotavirus vaccines in formal epidemiological studies for clinically-relevant disease endpoints that may include surveillance of reduction in hospitalisation of children due to rotavirus disease, reduction in emergency room visits due to rotavirus disease and reduction in the number of stool samples referred to laboratories for rotavirus diagnostics. Three generic study protocols for vaccine effectiveness and impact studies using different methodologies are available for use on the ECDC website. Further studies assessing the frequency, extent of complications (e.g. need for surgery and anaesthesia and resection of intestine) and possible underlying medical conditions predisposing to development of IS are needed in the European setting. In addition, EU/EEA countries that have implemented risk reduction strategies with early vaccination should consider conducting pharmacoepidemiological studies to inform others of the potential impact of such interventions.

Finally, sharing available health economic models of rotavirus vaccination cost-effectiveness should be encouraged so that they could be used in various settings by those EU/EEA countries interested and the new option for EU-level joint procurement for Member States could also be explored.

1. Background

In 2006, two live attenuated rotavirus vaccines for oral use in infants were authorised by the European Commission for prevention of rotavirus-induced gastroenteritis; Rotarix™ (RV1), and RotaTeq™ (RV5) [1, 2]. Uptake of rotavirus vaccines into EU/EEA routine immunisation programmes has been limited. As of March 2016, twelve EU/EEA Member States were recommending vaccination against rotavirus-induced gastroenteritis in their national paediatric immunisation programmes and had initiated or were about to initiate the programme.

Rotaviruses are classified serologically into serogroups (A-G) (see Figure 2 in the Section 'Overview of human rotaviruses'). Rotaviruses in group A are the most common cause of gastroenteritis in young children worldwide and the new rotavirus vaccines offer protection against these infections.

Estimates suggest that by the age of five years, every child in the world will have been infected with group A rotaviruses at least once. While infected, many of these children will suffer severe disease and be in need of medical attention due to extensive fluid loss [3]. Furthermore, group A rotaviruses are a frequent cause of diarrhoea-associated deaths in developing countries, estimated in the pre-vaccine era to represent approximately 527 000 deaths (95% CI 475 000−580,000) worldwide annually [4] while in developed countries mortality is low, thanks to medical supportive healthcare being readily available [5].

Already in 2007, WHO SAGE recommended the inclusion of rotavirus vaccines into national immunisation programmes in regions where efficacy data from randomised clinical trials suggested that rotavirus vaccines would provide significant protection against severe disease, mainly in the Americas and Europe [6].

In 2009, the WHO SAGE recommendation was extended, after clinical trials had been performed in more deprived settings, to include infants throughout the world [7].

Finally, in 2013 WHO SAGE recommended an extension of the age restriction for completion of the vaccine series to 24 months, to enable children with delayed immunisations to be fully vaccinated [8].

The aim of this expert opinion on rotavirus vaccination in infancy is to provide EU/EEA countries with relevant scientific information to support the decision-making process on the possible introduction and monitoring of routine vaccination to prevent rotavirus-induced gastroenteritis.

Rotavirus disease

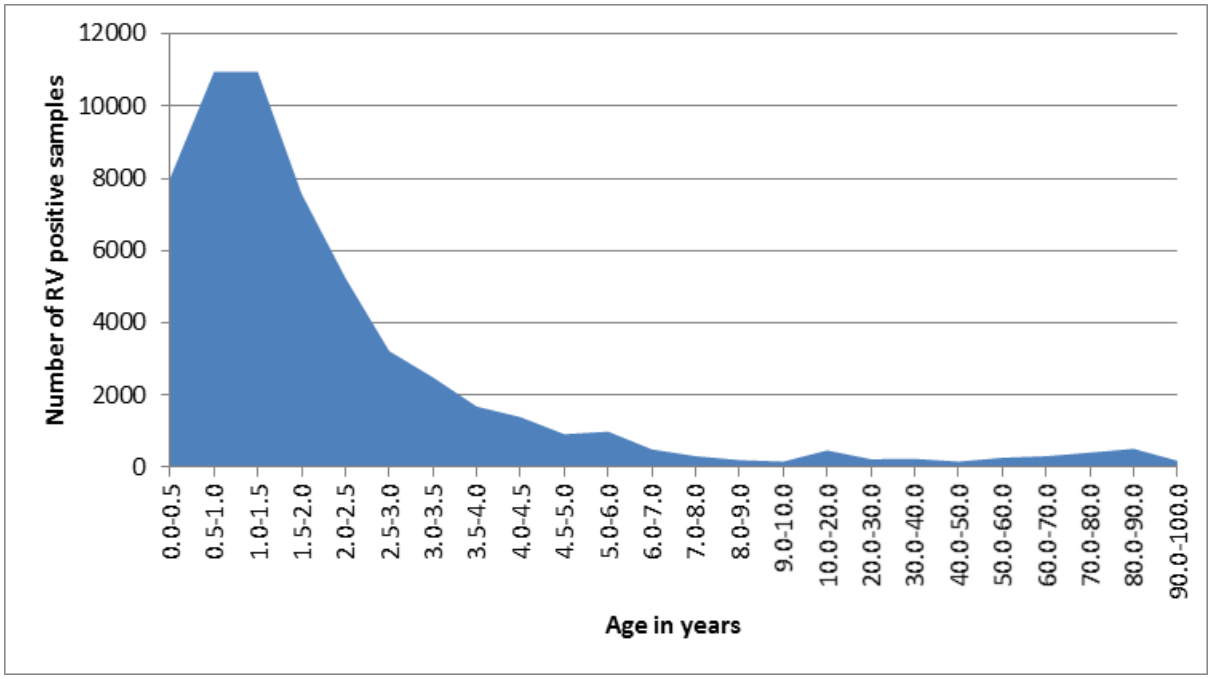
Symptoms

The clinical spectrum of group A rotavirus-induced gastroenteritis (RV GE) is wide in young children, ranging from transient mild diarrhoea to severe gastroenteritis with concomitant fever. Primary infections frequently result in a symptomatic episode of acute gastroenteritis (AGE), while reinfections are often asymptomatic or mild and only rarely lead to hospitalisation [9, 10]. Symptoms such as diarrhoea, vomiting and fever may all contribute to the significant dehydration observed in some children [11].

The vast majority of rotavirus disease episodes are mild or moderate, however, severe rotavirus disease leading to hospitalisation is often observed in the age group 0–36 months (see Figure 1), an age group when children are particularly vulnerable to dehydration. This is also the age when most children acquire their first rotavirus infection [12, 13].

The incubation period for rotavirus disease is 1–2 days. Symptoms are commonly relieved within three to eight days, but may last up to two or occasionally even three weeks in healthy, well-nourished children.

Figure 1. Number of rotavirus samples per age group (years) submitted to 16 EU/EEA countries' rotavirus reference laboratories for genotyping 2006–2013 and reported to EuroRotaNet, showing that the major burden of disease is in the 0–3 year age group [14]



Further information available at www.eurorota.net

Complications

In some children extensive nausea and vomiting results in difficulties providing oral rehydration in home settings, and may lead to severe fluid loss with or without accompanying electrolyte disturbances (hypo-, iso- or hypertonic dehydration that may require prolonged rehydration treatment). Further complications may include seizures due to high fever or the electrolyte disturbances, encephalitis/meningitis, shock and possibly death. Long-term, some children develop chronic diarrhoea and in more deprived settings malnutrition. In an observational retrospective cohort study conducted in Sweden (n=987), complications requiring additional medical attention, other than general dehydration, were observed in >15% of hospitalised children with laboratory-confirmed rotavirus disease [15]. Younger children (<12 months) were particularly prone to more severe dehydration (>10% of body weight).

Extraintestinal spread of rotaviruses to blood, cerebrospinal fluid, heart and liver has been reported and is suggestive of rotaviruses causing an invasive viral infection, rather than one confined to the intestinal mucosa [16-21]. In previously healthy well-nourished children, treated for rehydration before development of shock, no residual sequelae develop following an acute rotavirus infection. However, access to good clinical supportive care is crucial. Natural rotavirus disease has only rarely been identified as a cause of intussusception [22].

Infections in immunocompromised children

In general, rotaviruses do not cause more severe clinical symptoms in moderately immunocompromised patients, however, prolonged shedding of rotaviruses may occur in these individuals [23, 24]. Severe, prolonged and even fatal rotavirus disease may develop in those with severe immunodeficiency conditions such as severe congenital immunodeficiency, solid organ transplantation or bone marrow transplantation [25].The severity of rotavirus disease among children infected with HIV may be similar to that of non-HIV infected children [24], however whether the incidence rate of severe rotavirus disease among HIV-infected children is similar to or greater than that among non-HIV infected children is unknown.

Nosocomial infections

Children seeking medical attention in emergency departments/out-patient clinics or hospitalised with rotavirus disease have the potential to become sources of nosocomially-acquired infections [26-29].

Infections in family and household members

Household transmission of rotavirus disease is common. Adults and older siblings in contact with young children experiencing their primary rotavirus disease are at particularly high risk of developing a rotavirus disease. In a Canadian study it was shown that in 47% of hospitalised rotavirus cases at least one other family member experienced AGE in association with an index case infection [30]. Among these household contacts experiencing diarrhoea, 44% were < 2 years of age, 37% were 2–5 years of age, 12% were 6–18 years of age and 22% were adults. Only occasionally did household members need medical attention, but symptoms prevented some from attending school or work.

Asymptomatic infections

Asymptomatic rotavirus infections are common among neonates [31-33], older children and adults [34, 35], including healthcare workers [36]. All these groups are likely to be protected against symptomatic disease due to an immune response acquired during one or more previous rotavirus infections earlier in life or, in the case of neonates, through maternal antibodies providing protection during the first 3–4 months of life. Viral load in stool samples from individuals with symptomatic infection is significantly higher than in individuals with asymptomatic infection [37]. Nonetheless, asymptomatic carriers are likely to play a role in sustained transmission of rotaviruses in the human population as well as boosting the initial acquired primary immune response.

Risk factors for severe disease

Severe rotavirus disease may develop in any child, however a limited number of risk factors for development of severe disease were identified in three studies [38-40]. In these studies low-birth-weight infants (<2 500 g) were shown to be at increased risk of hospitalisation even beyond the first few months of life (OR 2.8; 95% CI 1.6–5.0) and children in day-care were more likely to be hospitalised than those cared for at home (OR 3.0; 95% CI 1.8–5.3). In addition, another child <24 months of age in the household was also shown to be a risk factor (OR 1.6; 95% CI 1.1–2.3). In contrast, breast-feeding was shown to protect against hospitalisation for rotavirus disease, with an increased risk for infants <6 months of age if not breastfed in the month before hospitalisation (OR 5.1; 95% CI 1.2–13.2).

Pathogenesis

Rotaviruses, first discovered in 1973 [41, 42], primarily infect mature intestinal epithelial cells on the tips of the small intestinal villi. Destruction of infected cells and subsequent development of villous atrophy reduces digestion and absorption of fluid and nutrients, resulting in secretory diarrhoea with loss of fluids and electrolytes into the intestinal lumen. In addition, one of the viral non-structural proteins, NSP4, which can be detected early during a rotavirus infection has been reported to function as a viral enterotoxin, and is thought to play a role in the development of symptoms [43]. Further, spread of rotaviruses systemically may be more common than previously understood, since antigenemia/viraemia and subsequently elevated transaminases (S-AST and S-ALT) have been reported [17-21,44,45].

Mode of transmission

Rotaviruses are mainly transmitted from person-to-person through the faecal-oral route, but transmission may also occur through contaminated objects (e.g. door-handles, water-taps, toilet-seats and toys), airborne droplets or contaminated water or food [46, 47]. Animal rotaviruses from infected animals are also occasionally transmitted to humans and may result in co-infections with human rotaviruses and development of new emerging serotypes/genotypes through the reassortment mechanism [48]. Rotaviruses may persist on dry surfaces for up to two months [46].

Infectious dose and virus shedding

The infectious dose is small, an inoculum of as few as 10–100 particles is sufficient to produce illness in susceptible individuals. The typical excreted virus load is between 10^8–10^{10} particles per mL faecal sample in children with their first rotavirus infection. Virus shedding has been described for up to three weeks in healthy individuals (personal communication, K-O Hedlund, Public Health Agency of Sweden). Moreover, cases of chronic rotavirus shedding have been reported among severely immunodeficient children [23].

Routine diagnostics

As mentioned earlier, there are several serogroups of rotaviruses that may infect humans: A, B and C. Serogroup A is the most common and therefore most laboratory assays only detect serogroup A rotaviruses. Excretion of rotaviruses may be confirmed by using antigen-detecting assays (enzyme immunoassays, immunochromatographic rapid tests), genome-detecting assays (PCR) or electron microscopy.

Clinical management

Clinical management is directed towards early replacement of fluid losses using oral rehydration at home. However, with more extensive fluid losses there may be a need for nasogastric or intravenous rehydration, alone or in combination, provided in hospital settings. Apart from fluid replacement, no other therapy is required in previously healthy individuals and the condition is self-limiting. No antiviral drugs are available. In the rare instances when immunodeficient children develop chronic excretion of rotaviruses, treatment with intravenous or oral immunoglobulin may be indicated [49]. However, oral immunoglobulin administered for prevention of rotavirus disease, although safe, did not provide protection against rotavirus disease in hospitalised low birth-weight infants (birth-weight <2500 g) according to a 2011 Cochrane review [50].

Protective efficacy induced by natural disease against subsequent clinical infections

The protective efficacy of an episode of natural infection in a young child against subsequent symptomatic re-infections is estimated to be 58–75% [9,10,51]. However, it is important to distinguish between symptomatic and asymptomatic infections. Re-infections occur throughout life. In a prospective cohort study performed in Mexico, a single rotavirus infection early in life was shown to provide protection against a subsequent laboratory-confirmed infection with rotavirus in 38% of all children, while 77% were protected against a subsequent symptomatic laboratory-confirmed rotavirus infection and 87% against a subsequent severe symptomatic laboratory-confirmed rotavirus-induced gastroenteritis [9]. In a large observational retrospective study in a northern European setting (n=987) spanning 11 years, it was shown that children are rarely hospitalised more than once (<0.2% of hospitalised children with rotavirus disease) for an acute rotavirus infection [15].

Serological correlates for protection including cross-immunity

Serological correlates of protection against rotavirus infections are poorly understood, but are likely to involve neutralising antibodies to the rotavirus outer surface viral proteins (VP4 and VP7). Rotavirus-specific IgA and IgG antibodies, neutralising antibodies directed to VP4 and VP7 (see Figure 2 ‘Human rotavirus particle’) and cell-mediated immunity all develop after a primary rotavirus disease infection [52]. In addition, a humoral immune response is known to develop to other internal viral proteins such as VP6 and the non-structural protein 4 (NSP4) known to have toxic effects [53, 54].

Immune response after a primary infection with group A rotaviruses is thought to be mostly against the infecting serotype/genotype. A broader heterotypic response is elicited following further re-infections (symptomatic or asymptomatic), possibly explaining why immunity is cumulative. Since natural rotavirus infections do not provide sterilising immunity, it is not expected that the vaccines will provide sterilising immunity in vaccinated individuals. Reinfections are also expected in vaccinated individuals, which will likely induce and maintain heterotypic protection.

Rotavirus vaccines available in EU/EEA countries

Two live attenuated vaccines for oral use providing prevention against rotavirus disease were authorised in the European Union in 2006; Rotarix, a monovalent vaccine (RV1) developed from a human rotavirus strain attenuated through serial passage in cell culture (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq, a human-bovine rotavirus reassortant pentavalent vaccine (RV5) derived from several cell-culture-adapted human rotavirus strains and a bovine rotavirus strain (Sanofi Pasteur MSD, Lyon, France) (1, 2). The indication for these vaccines is active immunisation of infants for prevention of gastroenteritis due to rotavirus disease (see Table 1).

EU dose recommendations

The dose recommendations, as mentioned in respective EU/EEA SPC, vary for the two rotavirus vaccines:

RV1 should be administered in two doses any time from the age of six weeks, with an interval of at least four weeks between the doses. The full vaccination course of two doses should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks. RV1 should not be used in infants >24 weeks of age (see Table 1).

RV5 should be administered in three doses any time from the age of six weeks, with an interval of at least four weeks between each of the three doses. The first dose should be provided at no later than 12 weeks of age, and it is preferable that all three doses should be administered before the age of 20–22 weeks. If necessary, the third dose may be given up to the age of 32 weeks (see Table 1).

The reason for the narrow age window for dose 1 in particular, but also for completion of the whole series, is the experience with an earlier first generation oral live attenuated rotavirus vaccine, Rotashield®, licensed in 1998 in the US. Following the introduction of this rotavirus vaccine into the US national immunisation programme it was found to be effective in providing protection against hospitalisation due to rotavirus-induced gastroenteritis [55], but an adverse event was reported – development of intussusception (IS). IS was later found to be epidemiologically associated with this vaccine and the vaccine was therefore withdrawn from the US market [56, 57]. An estimated risk of one additional case of intussusception per 4 670 to 9 474 infants vaccinated was identified. In further follow-up studies it was also shown that infants vaccinated before day 60 of life had no increased risk (>70 000 doses administered) and infants vaccinated day 61–90 of life were significantly less prone to develop intussusception [58].

EU/EEA countries may recommend immunisation schedules within the span of the EU/EEA SPC recommendations (see Table 4 for choices made by countries that have introduced rotavirus vaccines.)

Concomitant administration of other paediatric vaccines

Both rotavirus vaccines can be administered concomitantly with other monovalent and/or combination infant vaccines containing one or more of the following antigens: D, T, aP, Hib, IPV or OPV, HBV, PCV and MenC.

Vaccination of premature infants

The recommendations for vaccination of premature children differ between the two vaccines.

RV1 may be given to preterm infants born after at least 27 complete weeks of gestational age. Apnoea has been reported in younger infants.

RV5 may be given to infants born prematurely provided that the period of gestation was at least 25 weeks.

Due to excretion of vaccine virus in stool from vaccinated infants that may cause symptoms in the youngest and most vulnerable premature infants, most neonatal intensive care units (NICUs) do not offer vaccination until the infants are discharged from hospital. This results in a number of unvaccinated premature children caused by prolonged treatment period in NICUs which is unfortunate since they have been shown to be vulnerable to severe rotavirus disease. Therefore, a retrospective cohort study using electronic records and assessing clinical symptoms in RV5 vaccinated (n=96, born at gestational age 32.6 weeks ±5.0) and unvaccinated patients (n=801, born at gestational age 34.8 weeks ±5.0) treated in a neonatal intensive care unit was conducted to evaluate safety. Results suggest that RV5 vaccination was well tolerated, with no indication of symptomatic transmission to neighbouring unvaccinated infants, but diarrhoea was observed in 18/96 (19%) vaccinated infants compared to 1/801 control infants [59]. Authors conclude that a larger prospective study is needed to assess severity of observed diarrhoea, virus shedding and transmissibility.

Table 1. Rotavirus vaccine contents, indications, contraindications, route of administration, dose regimens and frequency of reported undesirable effects according to EU/EEA SPCs

	RV1	RV5
Rotavirus genotypes included in vaccine	Human rotavirus strain P1A[8]G1	Five reassortant strains with a bovine rotavirus strain WC3, P7 [5] G6 expressing viral surface proteins corresponding to the human rotavirus genotypes G1, G2, G3 and G4, and P [8]
Formulations	Live attenuated	Live attenuated
Vaccine production	Vero cells	Vero cells
Excipients	9 mg sucrose per dose, 13.5 mg sorbitol	1080 mg sucrose per dose
Indications	Prevention of GE due to rotavirus disease	Prevention of GE due to rotavirus disease
Contraindications	- Hypersensitivity to the active substance or to any of the excipients. - Hypersensitivity after previous administration of rotavirus vaccines - Previous history of intussusception. - Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception. - Diarrhoea and vomiting. - Febrile illness. - Severe combined immunodeficiency (SCID)	- Hypersensitivity to the active substance or to any of the excipients. - Hypersensitivity after previous administration of rotavirus vaccines - Previous history of intussusception. - Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception. - Known or suspected immunodeficiency including HIV. - Diarrhoea and vomiting - Febrile illness. - Severe combined immunodeficiency (SCID)
Route of administration	Oral	Oral
Dose regimens‡	- Two doses from the age of 6 weeks. Interval of at least four weeks between doses. - The vaccination course should preferably be given before 16 weeks of age, but all doses must be completed by the age of 24 weeks. - RV1 should NOT be used in the paediatric population over 24 weeks of age.	- Three doses from the age of 6 weeks. Interval of at least four weeks between doses. - The first dose should not be given later than the age of 12 weeks. - It is preferable that all three doses should be administered before age of 20–22 weeks. If necessary, the third (last) dose may be given up to the age of 32 weeks. - RV5 is NOT indicated in the paediatric population from 33 weeks to 18 years.
Undesirable effects	Diarrhoea and vomiting < 1:10* Irritability < 1:10 Abdominal pain, flatulence < 1:100 Dermatitis < 1:100 Intussusception <10 000** Apnoea in very premature infants (≤ 28 weeks of gestation)*** Haematochezia*** Gastroenteritis with vaccine viral shedding in infants with Severe Combined Immuno-deficiency (SCID)***	Fever > 1:10 Diarrhoea and vomiting > 1:10* Upper respiratory tract infection < 1:10 Rash < 1:100 Nasopharyngitis <1:100 Otitis media <1:100 Abdominal pain upper <1:100 Bronchospasm < 1 000 Urticaria < 1 000 Intussusception < 10 000** Apnoea in very premature infants (born ≤28 weeks of gestation)*** Haematochezia*** Anaphylaxis*** Irritability*** Angioedema***

‡ US ACIP recommends that the first dose of rotavirus vaccine, irrespective of product, is administered from 6 weeks through 14 weeks, six days of age.

* In the event of an infant spitting out or regurgitating most of the vaccine dose, a single replacement dose may be given.

** Updated 14 May 2014: Up to six additional cases of intussusception per 100 000 infants within seven days of vaccination observed in observational studies conducted in Australia and the US. See Chapter 6.3 for further details.

*** Frequency cannot be estimated based on available data.

Vaccination of infants with immunodeficiency and immunodeficient close contacts

Excretion of live attenuated vaccine virus has been shown to occur after vaccination of healthy infants with both rotavirus vaccines [60]. Approximately 50% of RV1 vaccine recipients were shown to excrete vaccine virus after the first dose of RV1 and 4% after the second dose [1] while approximately 9% of RV5 vaccine recipients excreted vaccine virus after dose 1 [2] and 0.3% after dose 3 [61]. Peak viral shedding generally occurs ~7 days after the first dose. Transmission of vaccine virus to healthy individuals has been observed with limited or no clinical symptoms [62].

Live attenuated rotavirus vaccines should always be administered with caution in individuals with congenital or acquired immunodeficiency, as well as to infants in close contacts with immunodeficient patients [63]. Safety and efficacy have not been established for use of RV1 and RV5 in immunocompromised infants, including those with blood dyscrasias, leukaemia, lymphoma, malignant neoplasms affecting bone marrow or the lymphatic system, infants on immunosuppressants including high-dose corticosteroids, or infants with primary and acquired immunodeficiencies, including cellular immune deficiencies, hypogammaglobulinemic and dysgammaglobulinemic states. However, in general, live vaccines should be administered ≥4 weeks prior to planned immunosuppression and avoided within two weeks of immunosuppression, where feasible. Specific recommendations for use of rotavirus vaccines in immunocompromised patients with asplenia, cancer, HIV infection, cerebrospinal fluid leaks, cochlear implants, hematopoietic stem cell transplant (prior to or after), sickle cell disease, solid organ transplant (prior to or after), those receiving immunosuppressive therapy for chronic conditions and contacts of immunocompromised patients are available from the Infectious Diseases Society of America (IDSA). They are based on international consensus, however, often with limited evidence [64]. An individual benefit-risk assessment taking into account the risk of natural infection vs vaccination could guide clinical decisions.

Children with asymptomatic and mildly symptomatic human immunodeficiency virus (HIV) infection can be offered rotavirus vaccines [65], while for children with severe combined immunodeficiency (SCID) vaccination is not recommended since they may develop chronic excretion of vaccine viruses. However, there are differing indications in the EU/EEA SPCs of RV1 and RV5 and vaccinators should consult their respective SPC before considering administration of rotavirus vaccines to infants diagnosed with HIV or SCID.

Vaccination of infants with other underlying medical disorders

With the exception of vaccination of premature infants, no experience has been obtained from clinical trials to vaccinate infants with underlying medical disorders including gastrointestinal disease, growth retardation, or having received blood transfusion, plasma or immunoglobulins within 42 days since they were all excluded from the trials.

In one retrospective review of nine infants with functional short gut syndrome secondary to an ileostomy who had received RV5, vaccination in eight out of the nine infants did not alter expected weight gain or body temperature [66]. However, one of the infants developed significant stomal losses, resulting in weight loss after vaccination. No other reports on vaccination of infants with other underlying medical disorders are available in the scientific literature.

Vaccination of infants exposed to biological therapy in utero

Women with inflammatory bowel disease (IBD) increasingly receive biological therapy (e.g. antibodies against tumour necrosis factor, such as infliximab, or certolizumab), influencing their immune response. During pregnancy this treatment will also impact the immune response of their new-born infants. A position statement by the World Congress of Gastroenterology on biological therapy for IBD notes that infants exposed to biological therapy in utero should be given routine vaccinations at standard schedules during the first six months of life, except for live-virus vaccines such as rotavirus [67].

Interchangeability

Interchangeability between the two vaccines has not formally been evaluated until now and vaccination clinics retaining both vaccines are recommended to complete the vaccination series with the vaccine used for the primary dose in EU/EEA SPCs.

However, a clinical trial initiated in 2014 by the National Institute of Pediatrics, Mexico[1] will assess as the primary objective the immunological behaviour of children from two months of age that receive one out of seven anti-rotavirus vaccination schedules: Group 1 (routine schedule with two doses of RV1 - Rotarix), Group 2 (routine schedule with three doses of RV5 - RotaTeq), Group 3 (one dose of monovalent vaccine followed by two doses of pentavalent vaccine), Group 4 (one dose of pentavalent vaccine followed by two doses of monovalent vaccine), Group 5 (two doses of pentavalent vaccine followed by one dose of monovalent vaccine), Group 6 (one dose of

[1] Clinical trials registration NCT02193061

pentavalent vaccine followed by one dose of monovalent vaccine and one dose of pentavalent vaccine), and Group 7 (one dose of monovalent vaccine followed by one dose of pentavalent vaccine and one dose of monovalent vaccine) in children from Mexico City.

The secondary objectives of this trial are

- to describe number and features of acute diarrheal disease (ADD) episodes due to rotavirus in the seven vaccination schedules
- to describe adverse events temporarily associated with the seven vaccination schedules.

The hypotheses to be tested in this trial are that the seroconversion percentages and geometric mean titers (GMT) of anti-rotavirus antibodies from Groups 3, 4, 5, 6 and 7 are not inferior to the seroconversion percentages and the GMTs induced in subjects that received the routine vaccination schedules, with two doses of the monovalent vaccine or three doses of the pentavalent vaccine (Groups 1 and 2). It is unknown when results will become available.

Vaccine-induced immunity

The immunological mechanisms by which rotavirus infection with either wild-type or vaccine strains protect against subsequent rotavirus disease are not completely understood. Humoral and mucosal immunity is believed to play an important role. Since no serological correlate of protection has been identified, serum IgA has been used as a surrogate marker by both vaccine manufacturers in the clinical trials. A high level of serum IgA antibody has been shown to correlate with clinical protection against rotavirus disease [68, 69]. However, the IgA assays used by the two manufacturers are different and not comparable.

Table 2. Percentage of seropositive RV1-vaccinated subjects developing serum rotavirus-specific IgA antibodies antibody titers > 20 U/mL post-immunisation, using different EU immunisation schedules [70]

Immunisation schedules evaluated	Studies conducted in	Vaccine-recipients		Placebo-recipients	
		n	% seropositive [95% CI]	n	% seropositive [95% CI]
2, 3 months	Germany	240	82.1 [75.1-87.7]	127	8.7 [4.4-15.0]
2, 3 months	France	126	84.3 [74.7-91.4]		
2, 4 months	Spain	275	85.5 [79.6-90.2]	89	12.4 [6.3-21.0]
3, 5 months	Finland	272	94.6 [90.0-97.5]	114	3.5 [1.0-8.7]
3, 5 months	Italy	22	92.3 [64.0-99.8]		
3, 4 months	Czech Republic	272	84.6 [78.5-89.5]	90	2.2 [0.3-7.8]

Immunogenicity has been evaluated in many of the European childhood immunisation schedules. Both rotavirus vaccines induce a high percentage of seropositive individuals after a complete vaccination course. The percentages of seropositive infants following vaccination with the two available rotavirus vaccines used in different EU immunisation schedules are presented in Tables 2 and 3.

Table 3. Percentage of seropositive RV5-vaccinated subjects developing at least a threefold rise in serum rotavirus-specific IgA antibodies from baseline 42 days post-immunisation, using different EU immunisation schedules [71], [72]

Immunisation schedules evaluated	Studies conducted in	Vaccine-recipients		Placebo-recipients	
		n	% seropositive [95% CI]	n	% seropositive [95% CI]
2, 4 and 6 months	11 countries	189	95.2 [91.2-97.8]	161	14.3 [9.3-20.7]
2, 4 and 6 months	US, Finland*	67	95.5	73	12.3

*Study performed at end of shelf life

Storage of vaccines

Storage of RV1 is recommended at 2–8ºC, but immunogenicity after seven days storage at 37ºC was similar to vaccine stored at the recommended temperature [73]. No similar study of RV5 has been identified.

Contamination of RV1 and RV5 vaccines with porcine circovirus

In 2010, the presence of porcine circovirus (PCV) genome fragments was identified in both rotavirus vaccines. PCV are animal viruses infecting pigs. Human exposure to PCV is common due to its presence in meat and other food products of pig origin. The origin of PCV contamination of the two rotavirus vaccines was attributed to porcine trypsin, used during the manufacturing process to facilitate infection of the cell line to propagate the rotaviruses. The EMA Committee for Medicinal Products for Human Use (CHMP) reviewed the contamination and, based upon the fact that PCV does not cause human disease, concluded that the benefit-risk balance was not changed[2]. However, manufacturers were instructed to develop PCV-free vaccines which will become available shortly. A similar recommendation was issued in 2010 by WHO[3].

Rotavirus vaccines authorised in non-EU/EEA countries and vaccine candidates

Two additional rotavirus vaccines are authorised in China and India respectively and several vaccine candidates are at various developmental stages.

An oral, live attenuated lamb rotavirus vaccine, containing monovalent group A genotype P[12]G[10] is being produced by Lanzhou Institute of Biological Products, Lanzhou, China. The vaccine was approved in 1998 for prevention of rotavirus disease in children aged 2 to 59 months in China. A case-control study conducted in Chinese children 9–11 months old showed that one dose of the Lanzhou rotavirus vaccine provided 44.3% (95% CI, 28.4–56.7%) protection against laboratory-confirmed rotavirus infection in an area where rotavirus is a notifiable disease; 52.8% (95% CI, 40.8–62.3%) in children 12–17 months old, and 51.8% (95% CI, 11.6–73.8%) in children 18–35 months old [74]. Uptake of this vaccine in the routine programme has been limited [75].

Furthermore, an oral, live attenuated monovalent human-bovine reassortant rotavirus vaccine, derived from a neonatal group A rotavirus strain isolated from an Indian infant (116E, genotype G9 [P11]), has been developed and is now being produced under the trade name ROTAVAC by Bharat Biotech, Hyderabad, India [76-78]. ROTAVAC was licensed in India in 2014 and is currently being introduced into the Indian national immunisation programme. The vaccine was developed in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID), the US Center for Disease Prevention and Control and PATH (formerly Program for Appropriate Technology in Health) and the Indian vaccine producer. NIAID sponsored early clinical trials in healthy adults and children and initial studies were conducted in the US. Overall vaccine efficacy against severe rotavirus disease in Indian children up to two years was shown to be 55.1% (95% CI 39.9–66.4; p<0.0001); vaccine efficacy in the second year of life, 48.9% (95% CI 17.4–68.4; p=0.0056), was only marginally less than in the first year of life [56.3% (95% CI 36.7–69.9; p<0.0001).

In total, five rotavirus vaccine candidates currently in human clinical trials can be identified on the website ClinicalTrials.gov. Among them several candidate vaccines are being developed under non-exclusive licences for technology transfer and production of the NIH human-bovine (UK) reassortant vaccine granted to the Chengdu Institute of Biological Products (China), Instituto Butantan (Brazil), and Serum Institute of India Ltd. (India):

- a randomised, double blind, placebo-controlled phase I clinical trial assessing safety and immunogenicity of a new 5-valent rotavirus vaccine candidate for oral use, produced by Instituto Butantan in Brazil, has been conducted in healthy adults (n=80)[4] [79]. This vaccine candidate is receiving financial support from PATH and the Bill & Melinda Gates Foundation;
- randomised, double blind, placebo-controlled phase I & II clinical trials assessing safety and immunogenicity in adults, toddlers and infants of a new 5-valent rotavirus vaccine candidate (BRV-PV)[5] for oral use produced by the Serum Institute of India Ltd have been conducted [80]. This vaccine candidate will now undergo a large Phase III study to assess efficacy against severe rotavirus disease;
- a randomised, double-blind, placebo-controlled phase 2b trial evaluating safety and immunogenicity of Rotavin-M1, a live attenuated G1P[8] strain[6] isolated, developed and produced for oral use by the Center for Research and Production of Vaccines and Biologicals, Vietnam, in healthy Vietnamese infants and sponsored by the National Institute of Hygiene and Epidemiology, Vietnam. First study results from a phase 1 study were published in 2012 [81];

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001059.jsp&mid=WC0b01ac058004d5c1 and http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001121.jsp&mid=WC0b01ac058004d5c1

[3] http://www.who.int/immunization_standards/vaccine_quality/PCV1_Q_and_As_rotavirus_vaccines_3Jun10.pdf

[4] Clinical trials registration NTC 00981669

[5] Clinical trials registration NCT02133690

[6] Clinical trials registration NCT01502969

- a randomised, double-blind, placebo-controlled dose-escalation phase 1/2 descending age clinical trial, assessing safety and immunogenicity of a VP8 subunit vaccine[7] (a truncated VP8 subunit protein from the Wa strain G1P8 fused to tetanus toxin P2 and adsorbed on aluminium hydroxide for intramuscular administration in three concentrations 10, 30 or 60 µg), sponsored by the Bill and Melinda Gates Foundation/PATH non-replicating rotavirus vaccine project. The study is being conducted in the US. First study results from healthy adults were published in June 2015 [82];
- a randomised, double-blind, placebo-controlled phase 3 trial assessing efficacy of RRV-TV for the prevention of rotavirus disease in Ghana, West Africa, with infants receiving the first dose of two during the neonatal period, the second before they are 60 days old, and with follow-up to age 12 months. RRV-TV was, as mentioned previously, licensed in the US in 1998 but withdrawn in 1999 due to a rare association with intussusception, which occurred disproportionately in infants receiving their first dose at ≥90 days of age [83]. A vaccine efficacy of 63.1% against rotavirus disease of any severity was observed, which is similar to the obtained efficacy acquired by RV1 and RV5 in similar African settings [84]. Funding for this trial was made available through the International Medica Foundation, a non-profit foundation.

In addition to the clinical trials listed on the ClinTrials.gov website data, a neonatal rotavirus strain (RV3-BB isolated from an Australian infant) candidate has been tested in a randomised placebo-controlled Phase I study that evaluated safety and tolerability of a single oral dose of the RV3-BB rotavirus vaccine candidate in 20 adults, 20 children and 20 infants (10 vaccine recipients and 10 placebo recipients per age cohort) [85]. Most infants (8/9) who received RV3-BB demonstrated vaccine take following a single dose. These data support progression of the RV3-BB candidate to Phase II immunogenicity, safety and efficacy trials that will be conducted by academic groups in New Zealand and Indonesia with funding from the Australian National Health and Medical Research Council, New Zealand Health Research Council, the Bill and Melinda Gates Foundation and the vaccine producer, Bio Farma in Indonesia. Neonatal and infant schedules will be evaluated.

Finally, in animal models both rotavirus whole virion and virus-like particles (VLPs) have been shown to provide protective immunity. No human clinical trials appear to have been initiated for any of these technologies.

[7] Clinical trials registration NCT01764256

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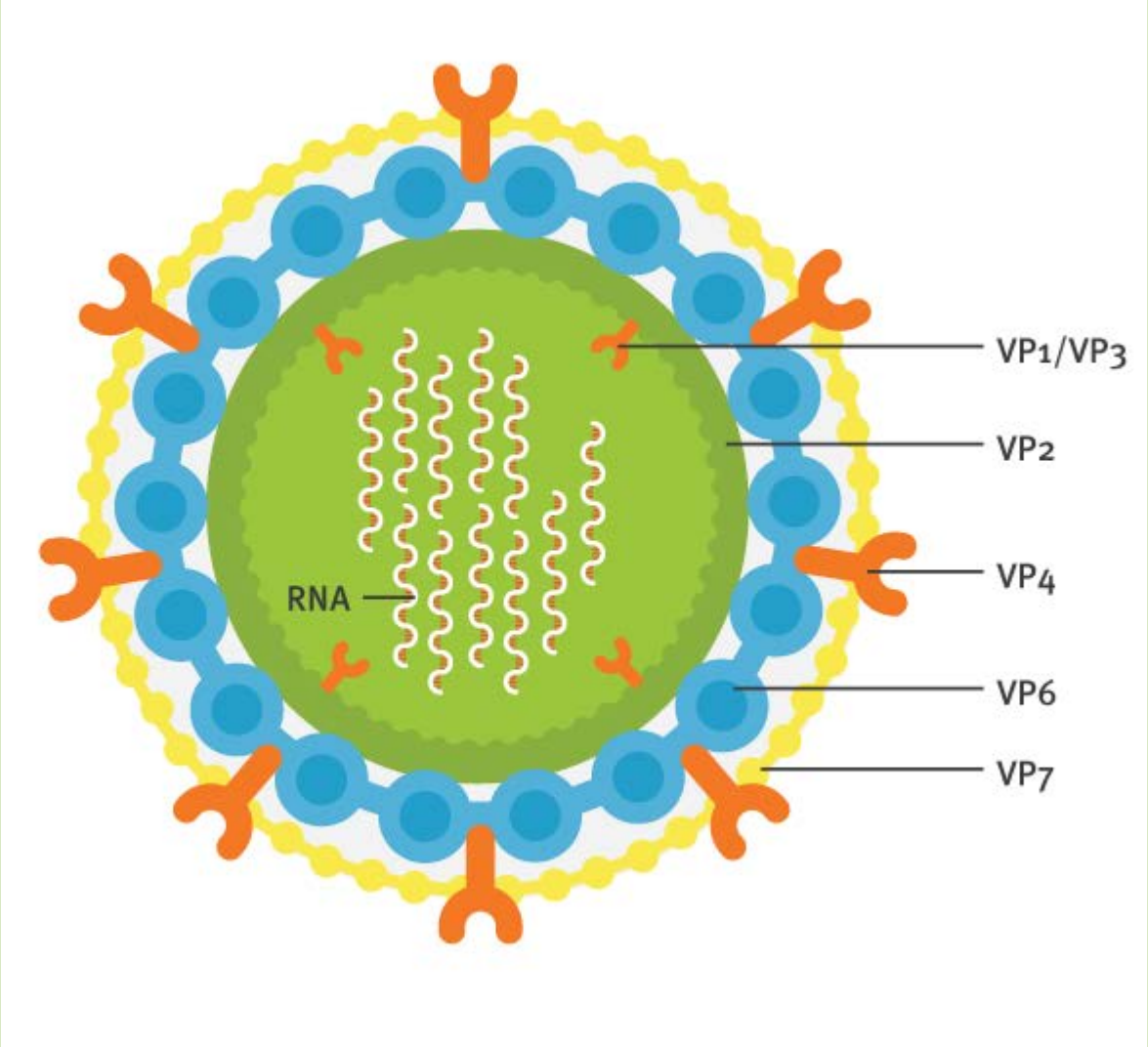
Overview of human rotaviruses[8]

Figure 2. Human rotavirus particle



- The virus particle consists of a triple-layered icosahedral protein capsid, composed of an outer protein (VP7 in yellow), an intermediate protein (VP6 in blue) and an inner core (VP2 in green) layer.
- From the smooth surface of the outer layer, sixty spikes extend ~12 nm (VP4 in red).
- Mature and infectious virus particles are approximately 70–75 nm in diameter. The infectivity of rotavirus particles depends on the presence of the outer protein layer.
- Rotaviruses are relatively stable when inactivated. Infectivity is retained within pH range 3 to 9 and virus samples are stable for months to years at + 4ºC. Viral particles present on objects may be infectious for months.
- The virus genome contains eleven segments of double-stranded RNA, providing a possibility for reassortment.
- Rotaviruses are classified serologically into serogroups. A serogroup comprises viruses that share cross-reacting antigens detectable by a number of immunological tests. Seven distinct serogroups have been identified (A–G). Serogroups A, B and C cause disease in humans, while the others have only been identified in animals. Domestic animals commonly excrete rotavirus of different types, which occasionally can be transmitted to humans as a zoonosis. Cross-immunity between serotypes has been shown.
- Rotaviruses may also be genotyped. Generally, genotyping is currently used for classification of circulating rotavirus strains but must be correlated to the knowledge of serotypes/serogroups. Determination of the potential development of protective immunity after vaccination to current and emerging new rotavirus

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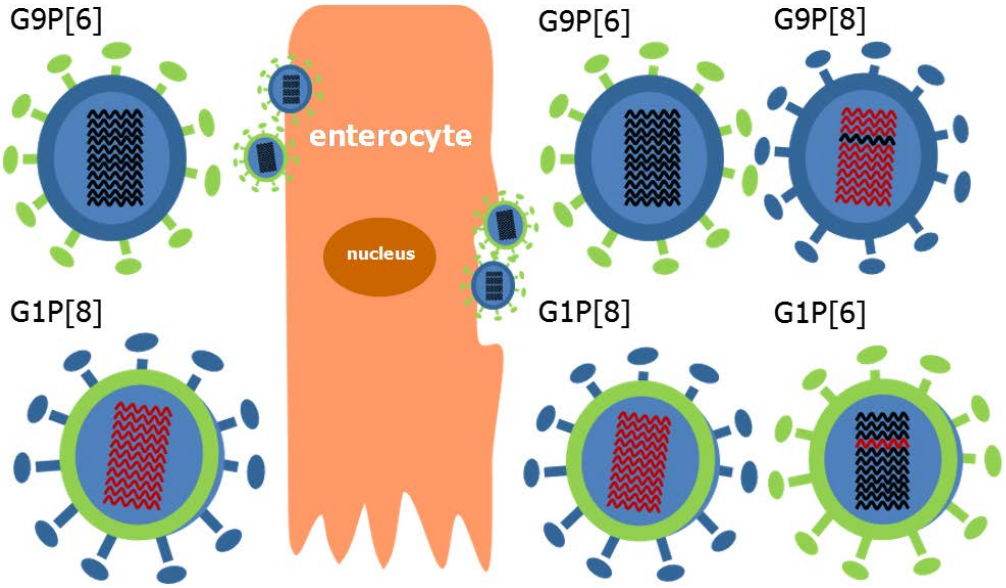
[8] Knipe D, Howley P Rotaviruses Fields Virology 6th Edition 2012

Post-authorisation monitoring of circulating rotavirus strains in EU/EEA countries

The segmented genome of rotaviruses facilitates genetic reassortment when intestinal epithelial cells are infected with more than one rotavirus sero-/genotype and co-infections do occur. This property has the potential to generate many combinations of outer surface viral G- and P proteins (theoretically > 2^{11} different combinations). However, the number of G and P combinations commonly detected is significantly less than the theoretical number of possible reassortant combinations, although reassortant group A rotaviruses develop regularly (see Figure 3).

Figure 3. Schematic overview of rotavirus reassortment (the two parenteral rotaviruses above infect an enterocyte, simultaneously providing the possibility for reassortment of genes resulting in expression of different surface proteins [G- and P-types])



Reassortments may occur between human rotaviruses or human and animal rotaviruses co-infecting one individual [48].

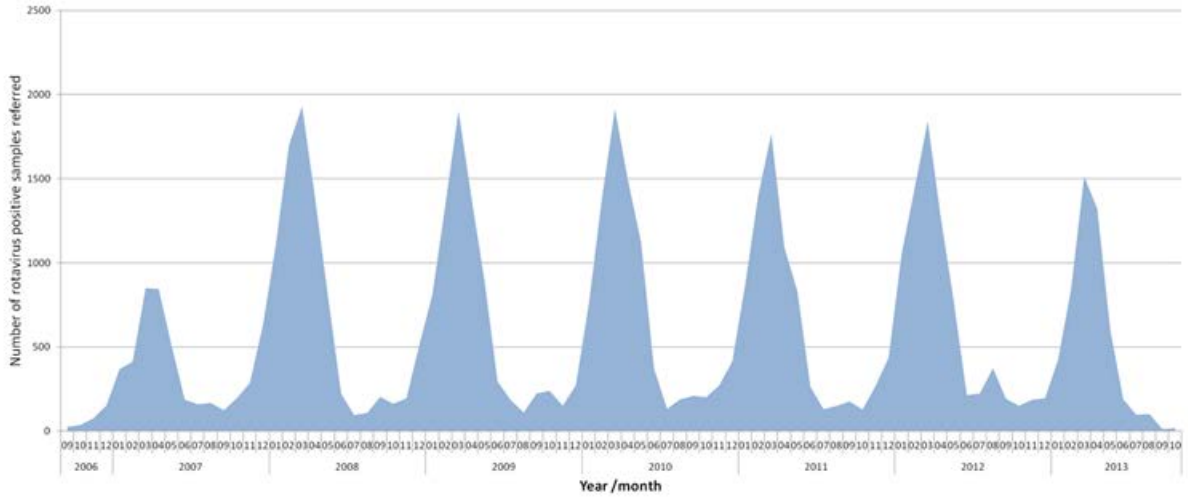
Rotavirus strain surveillance in the EU/EEA

Rotaviruses cause winter seasonal peaks of gastroenteritis in EU/EEA between December and May. However, sustained transmission is identified all year round (see Figure 4) [86]. Establishing the viral cause for a hospitalised case of diarrhoea is rare, since patient management of dehydration is not influenced by the identified pathogen. Therefore, to ensure genotyping of a statistically sound and geographically representative sample within the EU the European Rotavirus Surveillance Network (EuroRotaNet) [86] was formed to collect and genotype faecal samples from European children seeking medical advice for rotavirus disease. This network was established by both vaccine producers of the RV1 and RV5 vaccines, to fulfil requirements in the EMA Risk Management Plan to monitor possible strain replacement induced by immunological pressure following the use of rotavirus vaccines. Participants in the network have mainly been public health institutes and academia in eighteen EU/EEA Member States. The requirements from EMA subsided in 2015 and it is unknown whether the vaccine producers will continue to fund the network.

Rotavirus strain diversity

Results from the EuroRotaNet network on genotyping of rotavirus strains from seven consecutive seasons are now available [87, 88] (EuroRotaNet 7th year report) (see Figure 5). Genotyping is performed in a standardised manner across the sixteen countries by multiplex PCR and/or sequencing. Annual quality assurance programmes are conducted.

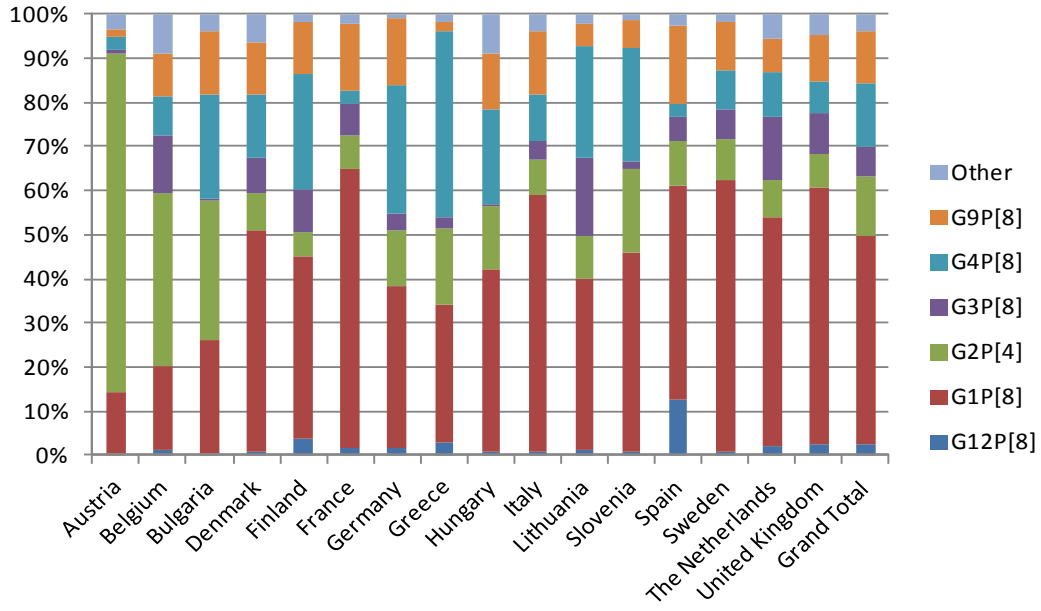
Figure 4. Temporal distribution of rotavirus positive samples submitted to the EuroRotaNet database in consecutive seasons between September 2006 and August 2013, numbers by month and year



Source: Eurorotanet 7th annual report, www.eurorota.net

The vast majority of human cases within EU/EEA and worldwide are caused by six genotypes within serogroup A rotaviruses and are responsible for > 90% of all human rotavirus disease, namely G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8]. Results obtained within the EuroRotaNet network confirm that G1P[8] was the most prevalent rotavirus strain, but all six genotypes circulated in all countries (see Figure 5). However, for two seasons G1P[8] was identified in < 50% of infected children. A new emerging genotype G12P[8] was identified in most participating EU/EEA countries and seasons in 0.5–0.8% of all stool samples and other new emerging G8- and G12-containing strains were also identified, but with lower incidence. Vaccine efficacy has been evaluated against G1P[8], G2P[4], G3P[8] and G4P[8] and G9P[8] in the clinical trials performed in the Americas and Europe [1, 2].

Figure 5. Overall distribution of the six most frequent rotavirus genotypes by country across the EuroRotaNet between 2006 and 2013 (N=47 549)



Source: Eurorotanet 7th annual report, www.eurorota.net

Significant cross-protection is expected, also for new emerging genotypes, as suggested by clinical trials performed in Malawi (RV1) and South Africa (RV1) and Ghana (RV5), which are countries with a more diverse picture of co-circulating genotypes [89, 90]. Vaccine efficacy in these studies ranged between 49.4% and 76.9%, where only 12.9% of the rotavirus strains were G1P[8]. However, the circulating genotypes may not be the only reason for a lower efficacy observed in these countries. In a recent study genetics involving the histo-blood group antigens appeared to play a role in susceptibility and vaccine take [91].

In the seven-year EU/EEA surveillance, 1.5% of the rotavirus strains were reassortments among common human strains, while 1.2% were likely to have emerged through zoonotic transmission or by reassortment between human and animal rotavirus strains. Mixed infections were detected in 5.7% of cases and 3.8% of strains were only partially characterised.

However, until 2013 no novel emerging group A rotavirus strains causing larger outbreaks had been detected in any of the countries under surveillance, although the time period surveyed is short for virus evolution. The number of rotavirus positive cases available for typing has diminished in all the countries that have introduced rotavirus vaccination, as a consequence of the reduction in rotavirus disease. There is no evidence to date that rotavirus vaccination programmes are driving the emergence of vaccine escape strains, and shifts in strain distribution and predominant type in the post-vaccine era need to be interpreted with caution and in the context of differences in distribution of genotypes according to age.

Rotavirus immunisation programmes in EU/EEA countries

As of March 2016[9], a positive decision had been taken by the national health authorities in twelve EU/EEA countries regarding the introduction of rotavirus vaccination into routine paediatric immunisation programmes and implementation had already occurred or was underway (Austria, Belgium, Estonia, Finland, Germany, Greece, Latvia, Luxembourg, Norway and the United Kingdom introduced rotavirus vaccination in the whole country while Italy and Sweden have introduced vaccination in some regions). Among the nineteen Member States that have not included rotavirus vaccination in the routine paediatric immunisation schedule, a positive decision had been taken but not yet implemented in two (Ireland and Poland). A negative decision had been taken by national health authorities in four countries (Cyprus, Denmark, France and Spain), while in the remaining countries no decision (either positive or negative) had been made by national health authorities on the question of whether to introduce rotavirus vaccination. Details on decisions made, year of introduction in countries with a positive decision, recommended age groups, vaccine coverage obtained and the proportion of cost covered by public or insurance funding are presented in Table 4.

Austria
Rotavirus vaccination was initiated in 2006. Both RV1 and RV5 are being used in the country according to routine procurement practices. Reporting of breakthrough infections is mandatory and isolated rotavirus strains from these children are genotyped.

Belgium
Rotavirus vaccination was recommended at national level in 2006 but is not included in the vaccination programmes at regional level. However, it is systematically offered (but not free of charge, unlike other childhood vaccines) during preventive consultations organised by the government agency 'well-baby clinics' at regional level. Both RV1 and RV5 are used in the country. A network of laboratories is monitoring the number of stool samples sent for rotavirus diagnostics. Stool sampling for rotavirus diagnosis in children <2 years of age is reimbursed by the Public Health Institute, therefore sampling has historically been generous.

Estonia
Rotavirus vaccination was initiated in 2014. RV5 is currently used in the country.

Finland
Rotavirus vaccination was initiated in 2009. RV5 is currently used in the country.

Germany
Rotavirus vaccination was initiated in 2013. Both RV1 and RV5 are being used in the country. Rotavirus disease is notifiable in Germany.

Greece
Rotavirus vaccination was initiated in 2015. Rotavirus vaccination is only partially reimbursed. Both RV1 and RV5 are available in the country.

Latvia
Rotavirus vaccination was initiated in 2015. Both RV1 and RV5 are available in the country.

Luxembourg
Rotavirus vaccination was initiated in 2006. RV1 is currently used in the country.

Norway
Rotavirus vaccination was initiated in 2014. RV1 is currently used in the country.

[9] VENICE III report on the current status of introduction of rotavirus vaccination into national immunisation programmes in Europe, submitted to ECDC May 2016. Publication pending. Available upon written request.

Sweden

Two regions covering ~30% of the infant population. Rotavirus vaccination was initiated in these regions in 2014. Both RV1 and RV5 are being used in the country according to routine procurement practices.

United Kingdom

Rotavirus vaccination was initiated in 2013. RV1 is currently used in the country.

Furthermore, it should be noted that rotavirus vaccine is being provided to additional European children through the private sector, this being more common in southern Europe than in other parts of Europe, based on vaccine distribution statistics.

The main reasons for not including the rotavirus vaccine into the national routine paediatric programme investigated in the recent VENICE III survey (see footnote 9 above) were cost/cost-effectiveness ratio, insufficient anticipated epidemiological impact, and other competing health priorities. Other reasons mentioned included risk of emergence of serotypes not covered by the vaccine, improved clinical management preferred to vaccination, and concerns regarding safety (intussusception).

842 **Table 4. Current status of rotavirus immunisation programmes in EU/EEA countries**

Member State	Stage of decision-making Positive/negative decision/not started	Year of introduction into national immunisation programme	Age group recommended	Vaccine coverage reported (%)	Proportion of cost covered by public or insurance funding
Austria	Positive decision by national health authorities	2006	D1-D3 7 weeks - 6 months	61	100%
Belgium	Positive decision by national health authorities (partly reimbursed)	2006	D1 8 weeks D2 12 weeks D3 (16 weeks)	86	75%
Bulgaria	No decision by national health authorities	-	-	-	-
Croatia	Recommended for risk groups only	-	-	-	-
Cyprus	Negative decision by national health authorities	-	-	-	-
Czech republic	No decision by national health authorities	-	-	-	-
Denmark	No decision by national health authorities	-	-	-	-
Estonia	Positive decision by national health authorities	2014	D1 2 months D2 3 months D3 4.5 months	No data available	100%
Finland	Positive decision by national health authorities	2009	D1 2 months D2 3 months D3 5 months	93	100%
France	Negative decision by national health authorities	-	-	-	-
Germany	Positive decision by national health authorities	2013	D1 6 weeks D2 10 weeks D3 14 weeks	No data available	100%
Greece	Positive decision by national health authorities	2015	D1 8 weeks D2 12 weeks D3 (16 weeks)	No data available	100%
Hungary	No decision by national health authorities	-	-	-	-
Iceland	No decision by national health authorities	-	-	-	-
Ireland	Positive decision by national health authorities but no implementation yet	-	-	-	-
Italy	No decision by national health authorities Several regions – positive decision	Varies by region	-	No data available	-
Latvia	Positive decision by national health authorities	2015	D1 8 weeks D2 12 weeks D3 (16 weeks)	No data available	-
Lichtenstein	No decision by national health authorities	-	-	-	-
Lithuania	No decision by national health authorities	-	-	-	-
Luxembourg	Positive decision by national health authorities	2006	D1 2 months D2 3 months	No data available	-
Malta	No decision by national health authorities	-	-	-	-
Netherlands	Negative decision by national health authorities	-	-	-	-
Norway	Positive decision by national health authorities	2014	D1 1.5 months D2 3 months D3 (5) months*	No data available	100%

Member State	Stage of decision-making Positive/negative decision/not started	Year of introduction into national immunisation programme	Age group recommended	Vaccine coverage reported (%)	Proportion of cost covered by public or insurance funding
Poland	Positive decision by national health authorities but no implementation yet	-	-	-	-
Portugal	No decision by national health authorities	-	-	-	-
Romania	No decision by national health authorities	-	-	-	-
Slovakia	No decision by national health authorities	-	-	-	-
Slovenia	No decision by national health authorities	-	-	-	-
Spain	Negative decision by national health authorities	-	-	-	-
Sweden (two regions with ~30% of the paediatric population)	No decision by national health authorities Two regions – positive decision	2014	D1 1.5 months D2 3 months D3 (5) months	Stockholm region 82%	100% in these two regions. Partly reimbursed in other regions, dependent on overall medicinal product consumption in children of a family
UK	Positive decision by national health authorities	2013	D1 2 months D2 3 months	No data available	100%

Source: data adapted from national official websites and 2016 VENICE III survey, submitted to ECDC according to contract and available upon written request (publication pending).

2. Methods

The aim of this expert opinion is to provide EU/EEA Member States with relevant scientific information to support the decision-making process on possible introduction and monitoring of routine vaccination to prevent against rotavirus-induced gastroenteritis. The opinion provided in this document is based on the evidence collected from the scientific literature and an analysis of the EMA Eudravigilance database which was then evaluated by a group of independent EU/EEA public health experts.

The data presented in this document are based on reviews of the published literature in scientific journals, grey literature and a search in the EMA Eudravigilance database for reported cases of intussusception following rotavirus vaccination. The information collected summarises:

- burden of severe rotavirus disease in EU/EEA in children under five years
- rotavirus vaccine efficacy
- rotavirus vaccine effectiveness
- herd protection provided by infant rotavirus vaccination
- rotavirus vaccine safety
- cost-effectiveness of using rotavirus vaccine in routine programmes in the EU/EEA
- attitudes to rotavirus vaccination among parents and healthcare workers in EU/EEA.

The literature searches were conducted by ECDC library staff in PubMed, Embase and Cochrane databases to collect relevant articles published in English between 1 January 1995 and 14 February 2014. Search strategies and results are available in Annex 4 and 5. The systematic searches were complemented by manual searches that included websites of public health institutes in the EU/EEA for current immunisation schedules. An Endnote database was created and completed with references identified in all search strategies. Identified article titles with abstracts were reviewed by ECDC experts. Based on inclusion and exclusion criteria taking into account the different search queries mentioned above, a second screening of selected full text articles was performed. A decision on study inclusion was made jointly by ECDC staff. For each study included, information on study design, number of participants, sampling and group allocation, intervention if relevant, outcomes, and study results was extracted and summarised. All outcomes were dichotomous (occurrence of the event or not).

Methodology used for evaluating burden of severe rotavirus disease in EU/EEA

Burden of severe rotavirus disease was defined as rotavirus disease leading to hospitalisation. The search terms 'rotavirus', 'rotavirus infection', 'disease outbreaks', 'epidemics', 'communicable disease', 'epidemiology', 'all EU/EEA countries by name, e.g. Austria, Belgium, etc.' and 'hospitalisation' were used to identify studies assessing burden of severe rotavirus vaccines in infants. Results of the burden of disease studies were not appropriate for a meta-analysis since no uniform effect estimator was reported. Therefore, a descriptive summary of identified data is presented.

Methodology used for evaluating rotavirus vaccine efficacy

Since two recently published systematic reviews with meta-analyses were available and provided high-quality and sufficient information on all relevant efficacy outcomes, results from these reviews were used. The review published by the Cochrane Collaboration in 2012 and the German Standing Committee on Vaccination (STIKO) in 2013 have both assessed relevant outcomes in randomised controlled trials (RCTs) conducted until 2011. No further RCTs have been conducted in rotavirus low-mortality countries. Results from the systematic review and meta-analysis, conducted by STIKO, are presented in this expert opinion with permission.

Methodology used for evaluating rotavirus vaccine effectiveness

Rotavirus vaccine effectiveness was defined as the relative reduction in rotavirus disease risk for a specified end point: hospitalisation with regard to the rotavirus vaccination status of study subjects, based on odds ratio in case-control studies and relative risk in cohort studies. Search terms such as 'rotavirus', 'rotavirus vaccine', 'immunisation' and 'vaccine effectiveness' were used to identify studies that assessed effectiveness of rotavirus vaccines. Each study that was included in the final analysis was assigned an acronym consisting of the author of the primary publication, year of publication and vaccine brand tested.

Case-control or cohort studies were included if effectiveness of either RV1 or RV2 on at least one of the pre-defined patient-relevant outcomes was reported for healthy children <5 years of age from developed countries (Europe, Australia, Canada, USA, Latin America and Asia). Observational studies were excluded if a vaccine formulation was used that was different from the vaccines licensed in the EU/EEA and if there was concomitant

administration with OPV since this is not current practice in the EU/EEA. Data for both vaccines were pooled, as the objective of this expert opinion was to evaluate the effectiveness of rotavirus vaccination and not individual products. The final analysis presents pooled data for both vaccines.

Meta-analyses of effectiveness data from included case-control and cohort studies were performed in relation to rotavirus vaccine status (at least two doses). Extracted data were entered into the computer software Review Manager (version 5.3, Nordic Cochrane Centre, Copenhagen, Denmark). Pooled estimates were calculated using random effects models. The dichotomous data were analysed by calculating Mantel-Haensel random effects risk ratios (RR) or odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for rotavirus vaccine recipients versus placebo recipients in the RCTs, or no vaccine in the observational studies. The pooled RR or were used to calculate pooled vaccine effectiveness using the following formula: (1-[Relative Risk or Odds Ratio]) x 100 [92]. Judgement of the extent of heterogeneity was based on similarity of point estimates, extent of confidence interval overlap, and statistical criteria including tests of heterogeneity and I^2 [93].

Methodology used for evaluating rotavirus vaccine-induced herd protection

Herd protection was defined as indirect protection of unvaccinated individuals in a population where rotavirus vaccination is recommended and used. The search terms ‘rotavirus’, ‘vaccine’, ‘immunisation’, ‘herd-immunity’ were used to identify studies assessing herd-immunity-induced by rotavirus vaccination in infants. Results of the herd immunity studies were not appropriate for a meta-analysis since no uniform effect estimator was reported. Therefore a descriptive summary of identified data is presented.

Methodology used for evaluating rotavirus vaccine safety

Rotavirus vaccine safety was assessed by estimation of risk for development of specified end points in relation to the rotavirus vaccination status of study subjects. The relevant outcomes assessed were vaccine-induced intussusception and Kawasaki disease, for which EMA had requested surveillance in their risk management plans. The risk window used in the RCTs varied but most post-marketing observational studies of intussusception utilised the Brighton Collaboration case definition levels 1–4, i.e. a risk window within 21 days of vaccination (see Annex 2) [94]. No similar generally agreed case definition exists for Kawasaki’s disease.

Since a recently published systematic review with meta-analysis was available and provided sufficient, high-quality information on all relevant safety outcomes in RCTs, results from this review were used. The review published by Cochrane Collaboration in 2012 assessed relevant outcomes in randomised controlled trials (RCTs) conducted until 2011. No further RCTs have been conducted in rotavirus low-mortality countries.

Following introduction of rotavirus vaccines into routine immunisation programmes and the first vaccine safety signals, observational studies assessing safety have been conducted in rotavirus low-mortality countries (mainly non EU/EEA countries). Results based on odds ratios in case-control studies, relative risk in cohort studies, relative incidence in self-control case series and standardised morbidity ratio in one observed versus expected analysis have been published.

The search terms ‘rotavirus’, ‘rotavirus vaccine’, ‘immunisation’, ‘intussusception’, ‘Kawasaki disease’ were used to identify studies that assessed safety of rotavirus vaccines.

Observational studies were included if safety of either RV1 or RV2 in relation to at least one of the pre-defined patient-relevant outcomes was reported for healthy children <5 years of age from rotavirus low-mortality countries (Europe, Australia, Canada, USA, Latin America and Asia). Only one smaller observational study from the EU/EEA using the observed versus expected methodology was identified. Observational studies were excluded if a vaccine formulation was used that was different from the vaccines licensed in the EU/EEA and if there was concomitant administration with OPV since this is not current practice in the EU/EEA. Results of the observational studies concerning the risk for developing intussusception did not permit a meta-analysis due to different study designs and different baseline risks. Therefore a descriptive summary of identified data is presented.

In addition, since only one smaller observational study assessing intussusception in the EU/EEA was available, information on intussusception cases spontaneously reported from EU/EEA Member States to the Eudravigilance (EV) database was made available to the ECDC[10] in accordance with EV access policy. The request was handled by EMA in accordance with the ‘Rules for the implementation of Regulation (EC) No 1049/2001 on access to European Medicines Agency (EMA) documents’ and ‘EudraVigilance access policy for medicines for human use’ EMA/759287/2009). EMA provided line listings for case reports of intussusception submitted during the time period from authorisation of the two rotavirus vaccines in 2006 until 1 July 2014. Data were partially redacted in accordance with Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000

[10] N.B. The analysis and interpretation of Eudravigilance data presented in this expert opinion may not be understood or quoted as being made on behalf of the European Medicines Agency or any of its working parties.

on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. The information provided in the line listings was based on a query performed in EV using the following search criteria: all reports submitted as spontaneous to EV up to 1 July 2014, where Rotarix or Rotateq were reported as a suspect or interacting medicinal product. Line listings of IS cases were analysed for number of cases by product, gender, age at vaccination, dose number in vaccine series, time to onset of IS from vaccination and clinical outcome. Chart review of reported cases of IS to validate the diagnosis against a common case definition was not possible due to data protection laws. Number of vaccinated infants during the same time period is unknown but 9.7 million doses of RV1 and 7.9 million doses of RV5 were distributed from the manufacturer.

Methodology used for evaluating vaccine cost-effectiveness

Rotavirus vaccine cost-effectiveness studies were defined as evaluation of cost-effectiveness for introduction of these vaccines into national immunisation programmes. The search terms 'rotavirus', 'rotavirus vaccine', 'immunisation', 'cost', 'cost analysis', 'economics', 'costs', 'price', 'pricing', 'pharmacoeconomics', 'cost-effective', 'cost-effectiveness', 'value for money', 'budget' and 'all EU/EEA countries by name' were used to identify studies assessing cost-effectiveness for rotavirus vaccination in infants. Results obtained in the cost-effectiveness studies were not appropriate for a meta-analysis due to diversity in assumptions and model structures. Therefore a descriptive summary of identified data is presented.

Methodology used for evaluating attitudes to rotavirus vaccination

Attitude was defined as parents' and healthcare workers' attitudes to rotavirus vaccination. The search terms 'rotavirus', 'rotavirus vaccine', 'attitude, 'health behaviour', 'health promotion', 'health personnel attitude', 'family attitude', 'parent attitude', 'patient non-adherence', 'patient noncompliance', 'refusal', 'compliance', 'wellness programs', and 'health campaign' were used to identify studies assessing attitudes to rotavirus vaccination in infants. Results of the attitude studies were not appropriate for meta-analysis since no uniform effect estimator was reported. Therefore a descriptive summary of identified data is presented.

Expert panel opinion

The opinion provided in this document is based on the identified evidence which was then evaluated by a group of independent EU/EEA experts. Scientific articles were summarised and discussed in two meetings and a series of telephone conferences. Experts were also able to provide additional relevant literature.

Furthermore, based on the literature review, the experts suggested options for relevant data which could be obtained by Member States before including rotavirus vaccination in a routine paediatric immunisation programme. They also suggested indicators which could be followed after implementation to facilitate evaluation of impact.

Finally, integration with other medical interventions such as rehydration, current use of rotavirus vaccines in Member States, impact evaluation of vaccination programmes and knowledge gaps are discussed.

The EU experts were selected based on the following criteria:

- experience in running and evaluating national routine immunisation programmes for children;
- experience in evaluating scientific evidence addressing vaccine safety, efficacy, effectiveness, and cost-effectiveness;
- experience in issuing national recommendations for new vaccines to be included in routine immunisation programmes.

Panel members' declarations of interest were reviewed by ECDC and no potential conflicts of interest were found that could influence the work of the panel.

3. Results

Burden of severe rotavirus disease in EU/EEA countries

A number of prospective and retrospective epidemiological studies published between 1995 and 2014 described country-specific burden of rotavirus disease in eighteen EU/EEA Member States [12, 95-125]. Most studies focus on describing severe rotavirus disease and address the burden of hospitalisation including nosocomial infections due to rotavirus disease (see Table 5). Only a limited number of European studies address deaths caused by rotavirus disease and burden in out-patient facilities.

Deaths

Five studies were identified addressing rotavirus-disease-associated deaths in the EU/EEA [5,97,126-128].

Using an adaptation of the CDC mortality model for Europe, an estimate was made of the number of RV-associated deaths in children <5 years of approximately 200 deaths per annum [128]. This study has been criticised for over-estimating the mortality rate, as indicated by country-specific data presented below.

A study from the UK using national statistical reports from two different sources indicates 3.3 and 3.8 deaths per year in children <5 years due to rotavirus disease, suggesting a mortality rate of <0.1 per 100 000 children <5 years and a hospital case-fatality rate of ~0.2% [126].

A study from Germany, suggests a hospital case-fatality rate of 0.1% during a 10-year period of surveillance [127]. Additional data from Germany reveal that 1–2 deaths due to rotavirus disease are reported each year in children <5 years of age[11].

Czech Republic reported three deaths in children <2 years over a nine-year period of surveillance but interestingly also reported three deaths in elderly people related to rotavirus disease outbreaks in retirement homes [97].

In a review of the WHO European Region of 49/52 countries, using published literature or WHO data sources, rotavirus disease caused an estimated 6 550 deaths (range 5 671–8 989) and 146 287 (range 38 374–1 039 843) hospital admissions each year in children aged <5 years [5]. Seven countries, mostly in the low- and lower-middle-income groups, accounted for 93% of estimated deaths. In total, three EU Member States - Slovakia, Bulgaria and Slovenia - reported mortality data as part of this review. Bulgaria and Slovenia did not report any deaths, while Slovakia reported a mortality rate of 0.1 per 100 000 children.

By way of international comparison, researchers from US CDC estimated in a study that one in 200 000 children would die each year in the US from rotavirus disease[3].

Hospital admissions

In the EU/EEA, all 46 studies identified from eighteen Member States reported that rotavirus is the most common pathogen isolated from children hospitalised with AGE. The contribution of rotavirus as a cause of acute gastroenteritis in hospitalised children < 5 years varied between years and between countries, ranging from 26 to 69% (see Table 5). The reasons for this wide range is not entirely clear, however there are probably some seasonal fluctuations. Methods used for diagnostics (antigen-detection and more recently PCR) and differences in surveillance in Member States may also influence results.

The number of children hospitalised per year also differs significantly; from 100 in Spain to 1 190 in Ireland per 100 000 < 5 years. However, in a majority of countries around 300–600 cases per 100 000 children <5 years are hospitalised per year (see Table 5).

In a review performed by WHO Regional Office for Europe hospital admission rates were similar across country income groups (medians 200, 280, 420 and 190/100 000 per year in low-, lower-middle-, upper-middle- and high-income countries in 49/52 WHO European Region countries, respectively) [5].

The median duration of hospitalisation for rotavirus disease varied in the EU/EEA studies, ranging from 1.3 days in one study conducted in nation-wide registries in Norway [115] to 9.5 days in one study hospital in Poland [116]. The duration of hospitalisation may also vary within countries, as observed in Italy and Spain (see Table 5).

By way of international comparison, studies among US children aged <5 years have shown that rotaviruses accounted for 30–50% of all hospitalisations for acute gastroenteritis and approximately 70% of hospitalisations for gastroenteritis during the seasonal peaks [129, 130]. The US CDC researchers further estimated that in the first

[11] http://www.rki.de/

five years of life, four out of five children in the United States will develop a symptomatic rotavirus disease, one in seven will require a clinic or emergency department visit, and one in 70 will be hospitalised [3].

The need for intensive care in the EU/EEA setting has been evaluated in several studies. One study conducted in Sweden suggests 1–2% of hospitalised children with rotavirus disease appear to be in need of intensive care, often due to severe dehydration (>10% of body weight) [15]. While in a prospective study by the German Paediatric Surveillance Unit, assessing children with very severe rotavirus disease (defined as in need of intensive care treatment, or hyper- or hyponatremia (>155 mmol/L or <125 mmol/L), or clinical signs of encephalopathy (somnolence, seizures or apnoea) or RV-associated deaths), 101 cases were identified during a two-year period [131]. Using these estimates the annual incidence of very severe rotavirus disease was estimated at 1.2 per 100 000 (95% CI 0.9–1.4/100 000). Among the 101 children, 48 of the children were in need of intensive care, 12 suffered from necrotising enterocolitis, and 58 had signs of encephalopathy.

Nosocomial infections

Evaluating the burden of intra-healthcare-acquired rotavirus disease suggests that up to ~25–30% of rotavirus infections diagnosed in hospitalised children may be due to rotavirus infections acquired within the healthcare system [27, 29, 132-140]. Nosocomial rotavirus infections often occur in younger children than the community-acquired rotavirus infections, and fewer complications develop [124, 141]. Furthermore, nosocomial infections often develop in children with underlying chronic diseases spending time in hospital settings where rotavirus is easily transmitted.

In a German study assessing hospitalised cases 2002–2008, 14% of reported cases were nosocomial [142], a four-year (2006–2010) Polish study suggested that the mean proportion of nosocomial rotavirus disease among all hospitalised rotavirus infected cases was 24% [143)] and a Spanish study 1998–2007 reported an incidence of 59.0 nosocomial cases per 100 000 children <5 years of age [141]. Another German longitudinal prospective study in paediatric in-patients 0–48 months in Austria, Germany and Switzerland suggested that almost one third of cases occurred in infants aged two months or younger [136].

In a review of nosocomial rotavirus disease in European countries (France, Germany, Italy, Poland, Spain and the United Kingdom) rotaviruses were found to be the major cause of paediatric nosocomial diarrhoea (ranging from 31 to 87%) [27] and in a recent meta-analysis of twenty surveillance studies of nosocomial rotavirus disease, an adjusted year-round incidence of 0.7 (95% CI 0.0–1.8) per 100 hospitalisations was calculated for children under five years [144]. Highest nosocomial rotavirus infection incidence rate was found in children <2 years of age, hospitalised during the epidemic months (8.1/100 hospitalisations 95% CI 6.4–9.9). The authors conclude that nosocomial rotavirus infections are an important problem for those children affected and for the quality of the healthcare systems.

Table 5. Overview of studies evaluating percentage of children < 5 years hospitalised due to AGE in whom rotavirus excretion was identified, number of hospitalised children < 5 years per 1 000/year due to rotavirus disease and median duration of hospitalisation

Country	Authors	Study year	% hospitalised AGE with laboratory-verified rotavirus disease <5 years	Number of children hospitalised <5 years per 100 000/year	Median duration of hospitalisation (days)
Austria	Rendi-Wagner et al [95]	1997-2003	-	770	4.7
Belgium	Van Damme et al, REVEAL [12]	2004-2006	58	990	-
	Zeller et al [96]	1986-2006	19	-	-
	Bilcke et al [145]	2004-2006	-	676	-
Czech Republic	Pazdiora et al [97]	1998-2006	-	698	-
Denmark	Fischer et al [98]	1995-1999	-	280	-
	Fischer et al [146]	2009-2010	39	380	-
England/Wales	Ryan et al [99]	1993-1994	43	520	2
	Harris et al [100]	1995-2003	45	450	-
Finland	Vesikari et al [101]	1985-1995	54	600	2.3 for all AGE
	Rasanen [147]	2006-2007	38	-	-
	Rasanen [147]	2007-2008	63	-	-
France	Fourquet et al [102]	1997	51	210	-
	Van Damme et al, REVEAL [12]	2004-2006	56	870	-
	Forster et al, SHRIK [103]	2005-2006	64	-	-
Germany*	Berner et al [127]	1987-1996	25	-	4
	Poppe et al [104]		41	770	4.9
	Van Damme et al, REVEAL [12]	2004-2006	66	500	-
	Koch et al [105]	2001-2008	-	~1000	-
	Forster et al, SHRIK [103]	2005-2006	61	-	-
Greece	Kavaliotis et al [106]	2006	49	-	-
	Konstantopoulus et al* [107]	2008-2010	24	-	4
Ireland	Lynch et al [108]	1997-1998	50	1190	4.1
Italy	Ruggeri et al [109]		27	-	-
	Van Damme et al, REVEAL [12]	2004-2006	69	520	-
	Gabutti et al [110]	2001-2005	36	-	5.7
	Mattei et al [111]	2002-2005	-	157-204	-
	Marsella et al [148]	2003-2005	-	154‡	5
	Panatto et al [149]	2006	33	550	4.2
	Forster et al SHRIK [103]	2005-2006	33	-	-
	Saia et al [150]	200-2007	-	196	3.5
Hungary*	Szúcs et al [113]	1993-1996	21	840	-
Netherlands	de Wit et al [114]	1997-1998	32-58	90-340	3-4
	Bruijning-Verhagen et al [151]		-	510	-
Norway	Flem et al [115]	2006-2008	63	300	1.3
Poland	Mrukowicz JZ [116]	1994-1996	41	310	9.5
Romania	Lesanu et al [152]	2011	58	-	6.4
Spain	Visser et al [117]	1999-2000	25	100	4.8
	Luquero Alcade et al [118]	2000-2004	32	480	-
	Cilla et al [119]	2002-2005	~40	-	6.3
	Cilla et al [153]	1996-2008	39	136	4.7
	Garcia-Basteiro et al [120]	2003-2008	22	104	3.2
	Forster et al, SHRIK [103]	2005-2006	52	-	-
	Van Damme et al, REVEAL [12]	2004-2006	53	650	-
	Sanchez-Fauquier et al [154]	2006-2008	40	-	-
Sweden	Johansen et al [124]*	1993-1996	36-45	370	2.4
	Van Damme et al, REVEAL [12]	2004-2006	62	770	-
	Rinder et al [125]	2007-2008	41	388	-
United Kingdom	Van Damme et al, REVEAL [12]	2004-2006	61	290	-
	Forster et al, SHRIK [103]	2005-2006	51	-	-

‡up to 14 years of age

*up to 4 years of age

Outpatient visits

Few European studies have focused on evaluating the burden of rotavirus disease handled within the healthcare system in out-patient clinics/emergency departments. The large number of children being assessed in outpatient settings (emergency departments or primary care) do contribute to the significant burden of rotavirus disease on the healthcare systems and societal costs [100, 123, 155-157]. The burden of rotavirus disease in the outpatient setting was estimated in the REVEAL study and was observed to be 2–4 times higher than the incidence of hospitalised children with rotavirus disease [12].

Conclusions

- Epidemiological studies conducted in eighteen EU/EEA Member States suggest that acute rotavirus disease results in ~300–600/100 000 children under five years being hospitalised annually, however significant variation occurs within and between countries. Extrapolating these data to the whole EU/EEA with a birth cohort of ~5 million infants suggests that ~75 000–150 000 hospitalisations in children <5 years occur yearly.
- Further epidemiological studies in ten EU/EEA Member States suggest that around two to four times more children seek medical evaluation for dehydration in outpatient settings, leading to significant burden on healthcare systems.
- Finally, limited mortality due to rotavirus disease is reported in studies conducted in eight EU/EEA Member States. An estimated mortality rate of <0.1 per 100 000 children <5 years and a hospital case-fatality rate of ~0.1–0.2% is reported.

Identified knowledge gaps and needs for capacity building

- No case definition for disease surveillance of rotavirus disease exists in most EU/EEA countries and at the EU level. Development and adoption of a suitable case definition would facilitate impact assessment of implemented rotavirus immunisation programmes.
- Rotavirus disease is not a notifiable disease in most EU/EEA Member States, with the exception of Germany. Initiation of EU/EEA Member State and EU-level routine or sentinel reporting of severe rotavirus disease leading to hospitalisation and/or death would facilitate impact assessment of implemented rotavirus immunisation programmes.

Rotavirus vaccine efficacy

The first randomised placebo-controlled clinical trials that served as the basis for licensure in the EU/EAA are briefly described below [71,158,159]. Subsequently 41 randomised placebo-controlled clinical trials were reviewed by the Cochrane Collaboration [160].

RV1. A large randomised placebo-controlled clinical trial to evaluate efficacy of RV1 was conducted in Finland and 11 Latin American countries [158]. The study was designed to evaluate safety with respect to intussusception (n=63 225), and to evaluate efficacy of the vaccine in reducing the need for hospitalisation related to rotavirus disease. The efficacy evaluated in 17 867 infants (n=9 009 in the rotavirus vaccine recipient group) against severe rotavirus disease during the first year of life was 84.7% [95% CI: 71.7–92.4], and 79% [95% CI: 66.4–87.4] during the second year of life. Serotype-specific rate reductions against severe rotavirus disease were for G1[P8] 90.8% [95% CI 70.5–98.2], for G3[P8], G4[P8] and G9[P8] 86.9% [95% CI 62.8–96.6] and for G2[P4] 45.4% [95% CI -81.5–85.6]. In addition, studies involving 3 994 infants (n=2 572 in the rotavirus vaccine group) were conducted in six European countries and showed that after two doses of Rotarix, the vaccine efficacy obtained from two weeks post-second dose to the end of two consecutive rotavirus seasons (combined efficacy follow-up period; mean duration 17 months) was 83.8% [95% CI: 76.8–88.9] against rotavirus disease requiring medical attention and 96.0% [95% CI: 83.8–99.5] against hospitalisation due to rotavirus disease.

RV5. A large randomised placebo-controlled was carried out to assess efficacy of RV5 with subjects < 8 weeks of age from 11 countries (including USA, several Latin American countries, Taiwan and Europe (Finland, Belgium, Germany, Italy and Sweden) [71]. The study was designed to evaluate safety with respect to intussusception, and efficacy of the vaccine in reducing the need for hospitalisation and emergency department visits related to rotavirus disease. Sub-studies nested within the large-scale study were designed to evaluate safety with respect to all adverse events, as well as immunogenicity and efficacy against rotavirus disease of any severity. Efficacy was evaluated in 68 038 infants (n=34 035 in the rotavirus vaccine group) and serotype-specific reduction in rotavirus disease was evaluated in a subset of 5 673 infants (n=2 834 in the rotavirus vaccine group).

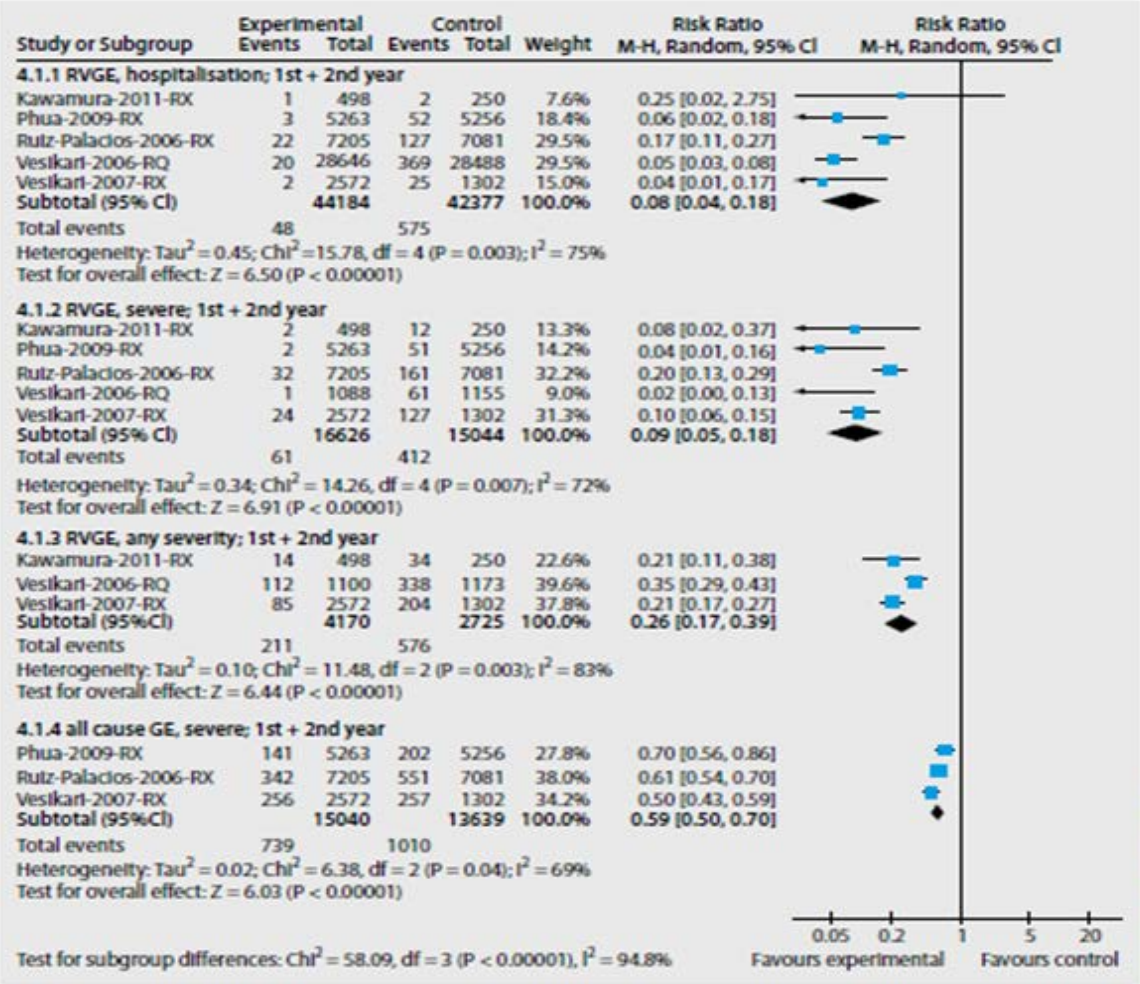
The RV5 vaccine reduced hospitalisations and emergency department visits related to G1–G4 rotavirus disease by 94.5% [95% CI 91.2–96.6]. The overall efficacy through the first rotavirus season after vaccination against any G1–G4 rotavirus disease was 74% [95% CI: 66.8–79.9]; and against severe gastroenteritis 98% [95% CI: 88.3–100]. The reduction in incidence of rotavirus disease caused by G1–G4 during the second rotavirus season after vaccination was 88% [95% CI: 49.9–98.7] for severe disease and 62.6% [95% CI: 44.3–75.4] for disease of any severity.

The duration of protection after a complete vaccination series has not been studied beyond the third season after vaccination and, according to manufacturers, it will not be since studies have been closed [161,162]. In an extension study conducted in Finland, 21 941 children were followed for up to 3.1 years after the third vaccine dose of RV5 revealed rate reductions in hospitalisations and emergency room visits during the first, second and third years of life by 94.0% (95% CI 90.0–96.5), 94.7% (95% CI 90.7–97.2) and 85.9% (95% CI 51.6–97.2) [201]. In this study the serotype-specific rate reductions in rotavirus disease healthcare encounters (ED-visits and hospitalisations) in the per protocol population were: G1[P8] 95.3% (95% CI 92.5–97.2), G2[P4] 66.8% (95% CI <0–75.8), G3[P8] 91.7% (95% CI 43.5–99.8), G4[P8] 66.8% (95% CI <0–94.2) and G9[P8] 92.3% (95% CI 48.5–99.8). It is expected that reinfection with naturally circulating wild-type rotavirus will boost the immune response in vaccinated individuals since vaccination will not induce sterilising immunity. It is therefore essential that effectiveness and possible breakthrough infections are monitored.

A systematic Cochrane review published in 2012 evaluated 41 randomised controlled trials assessing efficacy of rotavirus vaccines with 186 263 participants [160]. The trials compared a rotavirus vaccine with placebo, no intervention or another vaccine. The vaccines tested were RV1 (29 trials involving 101 671 participants) and RV5 (12 trials involving 84 592 participants). The large trials were conducted in low and high rotavirus-mortality settings throughout the world. They showed that in the first two years of life, RV1 and RV5 prevented more than 80% of severe cases of rotavirus diarrhoea in low-mortality developed countries.

Further systematic reviews were performed in support of the vaccine recommendation in Germany by STIKO (Ständige Impfkommission) with a focus on efficacy, effectiveness, impact and safety of rotavirus vaccines [163, 164]. Figure 6 presents the results obtained in the review of efficacy studies conducted in Europe, Australia, Canada, USA, Latin America and Asia, indicating a vaccine efficacy of 92% (95% CI 82–96%) against rotavirus-induced hospitalisation during the first and second year following vaccination.

Figure 6. Rotavirus vaccine efficacy compared with placebo against different outcomes over a follow-up period of two years in randomised controlled trials reported as risk ratio (Mantel-Haentzel random effects model)



X-axis in log scale

Adapted from: Background paper to the recommendation for routine rotavirus vaccination of infants in Germany [163,164] (Permission received from Dr Koch to use the figure)

Cross-protection against other genotypes

Cross-protection has been shown for both vaccines against the five common genotypes (see above), which is expected since antibodies to the common antigen VP6 have been shown in animal experiments to provide protection.

However, the number of cases with G2P4 has been very limited and the confidence intervals are wide. Furthermore, there are no data available on new emerging genotypes such as G8, G10 and G12. None of them have so far been able to induce larger outbreaks in Europe or the US to enable the evaluation of cross-protective immunity. However, studies performed in Africa and South East Asia indicate statistically significant cross-protection for at least one of the genotypes G8 [90,165].

Conclusions

- A Cochrane review published in 2012, evaluating 41 randomised controlled trials with 186 263 participants, showed that in the first two years of life, the second generation rotavirus vaccines RV1 and RV5 prevented more than 80% of severe cases of rotavirus diarrhoea in low-mortality developed countries.
- A German systematic review and meta-analysis of RCTs conducted (published in 2013) suggests a vaccine efficacy of 92% against rotavirus-induced hospitalisation during the first two years following vaccination (95% CI 82–96%).

Identified knowledge gaps and needs for capacity building

- Efficacy data for G2P4-induced infections is limited and is entirely missing for cases induced by new emerging rotavirus genotypes such as G10 and G12. Observational studies should be conducted for G10, G12 or any other new emerging genotype that begins causing larger outbreaks.
- Efficacy data are missing in chronically ill individuals and those with gastrointestinal malformations. Observational studies can fill these gaps.

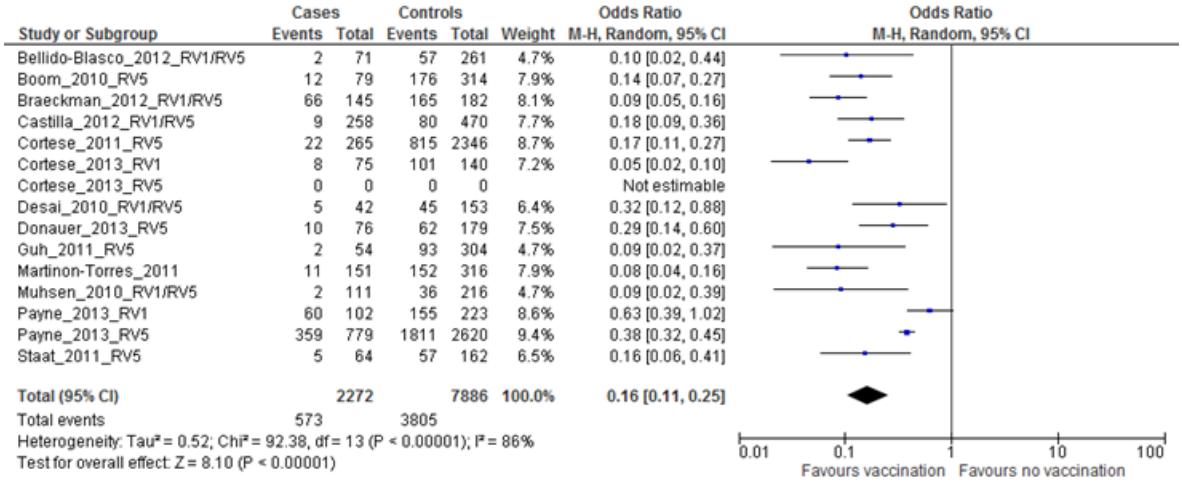
Rotavirus vaccine effectiveness

As of mid-2015, 60 countries worldwide had introduced rotavirus vaccines into their routine immunisation programme. Vaccine effectiveness has been assessed for the two rotavirus vaccines in observational studies conducted in rotavirus low-mortality settings in Australia, Belgium, Finland, France, Germany, Israel, Spain and the USA. In contrast to efficacy assessed in randomised controlled trials by administering vaccines and observing outcomes under controlled conditions in a cohort of healthy participants, vaccine effectiveness is assessed in the general population after the vaccine went into widespread use. Despite the inherent weaknesses of their study design, observational studies can provide important additional evidence on the effects of the vaccine including population-effects (such as herd immunity); outcomes in population groups not included in the randomised clinical trials (e.g. chronically ill), and rare outcomes such as rotavirus-induced deaths. We identified a total of 19 articles reporting results from either case-control (n=15) or cohort studies (n=4) conducted in low rotavirus-mortality countries [166-181]. Studies were conducted between 2010 and 2013 and assessed effectiveness over 2–3 winter seasons.

Case-control studies

Pooled odds ratios (ORs) from the 15 case-control studies showed that rotavirus vaccination is effective in preventing rotavirus-induced gastroenteritis requiring hospitalisation, based on both crude and adjusted data. A forest plot with adjusted results is presented in Figure 7. After at least two doses of rotavirus vaccine, pooled vaccine effectiveness to prevent severe rotavirus-induced gastroenteritis leading to hospitalisation was estimated at 84% (95% CI 75–89%) [166-177, 182]. Pooled ORs were homogenous and consistent. This analysis suggests that rotavirus-vaccination is also effective in the general paediatric population.

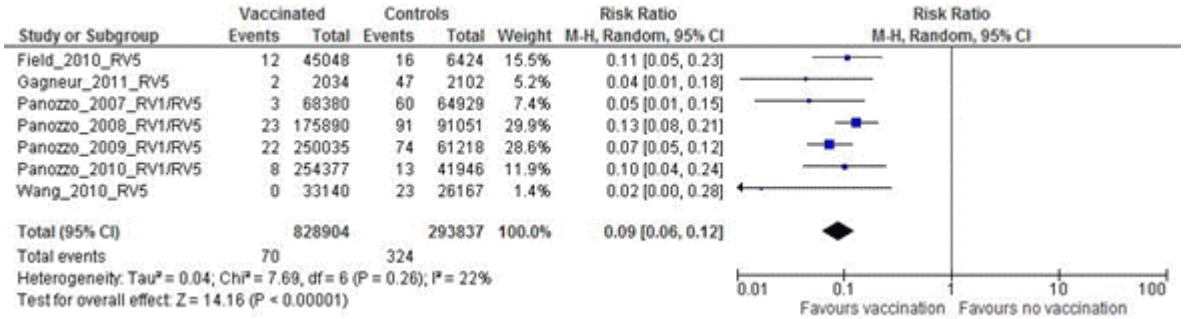
Figure 7. Forest plot of pooled odds ratios for the occurrence of hospitalisation due to rotavirus disease in fully rotavirus-vaccinated children, as observed in case-control studies published between 2010 and 2013 (X-axis in log scale)



Cohort studies

Pooled risk ratios (RRs) from the four cohort studies (one study by Panozzo et al. reports results for four seasons) confirmed that rotavirus vaccination is effective in preventing rotavirus-induced gastroenteritis requiring hospitalisation [178-181]. Pooled effectiveness was estimated at 91% (95% CI 88–94%) (see Figure 8). It should be noted that there was greater heterogeneity among the cohort studies than the case-control studies.

Figure 8. Forest plot of pooled risk ratios for the occurrence of hospitalisation due to rotavirus disease in fully rotavirus-vaccination children, as observed in cohort studies published between 2007 and 2010 (X-axis in log scale)



Effectiveness against non-vaccine genotypes

Effectiveness reported from high rotavirus-mortality countries is somewhat lower, but still significant, taking into account effects on both mortality and morbidity [90,165,183,184]. This may largely be related to circulation of a broader range of rotavirus genotypes (see Figure 2 in Section 'Overview of rotaviruses' above). Whether rotavirus vaccines will provide protection against severe rotavirus disease caused by rotavirus strains that did not circulate during the clinical trials conducted in Europe, Australia and North America is addressed in studies from Brazil (RV1), Nicaragua (RV5) South Africa (RV1), Malawi and Ghana [90, 183-185]. Populations included in these studies in impoverished settings suggest waning immunity with lower vaccine effectiveness in the second year of life compared with the first year. The study from Brazil [183] also demonstrates high vaccine effectiveness of RV1 against fully heterotypic circulating strains, but the authors discuss the possibility of a more rapid decline of protective immunity against heterotypic strains.

The first effectiveness study conducted in South Africa with broader range of circulating rotavirus strains has been published and this also includes some children who are HIV-positive [186]. South Africa introduced rotavirus vaccine into its routine immunisation programme in August 2009 and it is administered at six and 14 weeks of age. Figures for rotavirus-associated diarrhoeal hospitalisations among children <5 years at three sentinel sites were 54% and 58% lower in 2010 and 2011 than in 2009.

Extrapolation of these studies to the European paediatric population may not be valid and effectiveness studies, including less frequently circulating rotavirus strains in European vaccinated settings, are warranted. In order to

obtain statistically-testable estimates, large paediatric populations need to be followed up, which suggests that cross-country border collaborations may be more valuable than country-specific studies.

Other studies of interest

Initial effectiveness data assessing reduction in mortality, available from Mexico after introduction of rotavirus vaccine in their routine programme, suggest a 66% relative reduction in overall diarrhoea-related deaths in children <1 year of age compared with baseline years (2003–2006) [187].

An observational cohort study conducted in the US investigated whether rotavirus vaccination prevent against a known complication associated with rotavirus disease (seizures) [188]. A full-course of rotavirus vaccination was statistically associated with an 18–21% reduction in the risk of seizure requiring hospitalisation or emergency room attention (RR 0.79 95% CI 71–88) in the year following vaccination.

Long-term vaccine effectiveness beyond the first three years of life in vaccinated individuals after introduction of rotavirus vaccines in paediatric routine immunisation programmes and in vaccinated populations is unknown. However, it is expected that rotaviruses will continue to circulate in Europe and provide a natural immunity boost to vaccinated individuals. Therefore the ultimate outcome of introducing rotavirus vaccines is containment and not elimination/eradication.

Conclusions

Protection by the two rotavirus vaccines, RV1 and RV5, against severe rotavirus disease leading to hospitalisation, was assessed in observational studies conducted in rotavirus low-mortality and developed countries as follows: Australia (RV1 and RV5), Austria (RV1 and RV5), Finland (RV5), France (RV5), Germany (RV1 and RV5), Spain (RV5), and the US (RV1 and RV5). A meta-analysis of identified case control studies suggests a vaccine effectiveness against severe rotavirus disease leading to hospitalisation of 84% (95% CI 75–89%) and a meta-analysis of identified cohort studies suggests a vaccine effectiveness of 91% (95% CI 88–94%).

Identified knowledge gaps and needs for capacity building

- Whether current rotavirus vaccines provide protection against mild-to-moderate rotavirus disease leading to AGE but not hospitalisation which, although it has not been studied, is very likely.
- Whether current rotavirus vaccines administered during the first six months of life will provide life-long protection against severe rotavirus disease is unknown and needs to be monitored. Routine surveillance for fully immunised and hospitalised children with breakthrough, laboratory-confirmed rotavirus disease infections is a possible strategy. No known serological surrogate marker for correlates of protective immunity is available, although serum IgA has been used in the RCTs and could possibly be explored as another tool for monitoring the long-term response in seroepidemiological studies.
- Whether current rotavirus vaccines will provide protective immunity to new emerging rotavirus strains is unknown and needs to be monitored through routine or sentinel rotavirus strain surveillance in the EU/EEA, and through observational studies should outbreaks occur.

Herd immunity provided by infant rotavirus vaccination

The main aim for vaccines is to provide direct protection to immunised individuals. In addition, indirect protection of unvaccinated individuals may be observed and may add to the impact achieved through population-wide vaccination programmes. Possible mechanisms behind indirect effects may include transmission of vaccine virus to unimmunised individuals inducing protective immunity, or reduced virus circulation/number of asymptomatic carriers in a defined population through high vaccination coverage with vaccines that induce sterile immunity or significantly lower virus excretion. Such indirect effects are often called herd, population or community immunity/protection and are beneficial to individuals unable to be vaccinated due to contraindications. Herd immunity may be demonstrated through detection of a level of protection higher than expected from vaccine coverage achieved, or by observing any level of protection in unimmunised subjects [188-190]. The level of immunisation coverage required in a defined population for indirect protection to become evident varies with disease and its corresponding vaccine.

One important factor for consideration when looking at the possibility of rotavirus vaccine-induced herd immunity is that catch-up campaigns of older age groups have not been possible due to the narrow age window for vaccination recommended by regulatory agencies to minimise risk of intussusception [1,2]. Hence, population immunity to rotaviruses is either acquired through natural infection or vaccination of young infants.

Rotavirus vaccine viruses are known to be shed after vaccination with both RV1 and RV5. A randomised placebo-controlled clinical trial evaluating transmission of RV1 vaccine virus among twins living in the Dominican Republic showed that transmission of the vaccine strain occurred, from a vaccinated to an unvaccinated twin living in close contact, but whether transmission leads to indirect protection is still unknown [62]. Seroconversion occurred in the vaccinated twin in

62.5% (95% CI 51.0–73.1) and in 21.3% (12.9–31.8) of the unvaccinated twins. Transmission of vaccine virus to siblings of RV5 vaccinated infants has also been described and resulted in limited clinical symptoms [68, 191].

A mathematical transmission model to project the impact of a rotavirus vaccination programme at the population level was developed by Van Effelterre et al [192]. The model was applied to five European countries using different expected vaccination coverage rates; 70%, 90% and 95%. Using the model, herd immunity would induce a reduction of any severity of rotavirus disease incidence by 25%, 22% and 20%, respectively, for the different levels of vaccine coverage and for moderate-to-severe rotavirus disease by 19%, 15% and 13% five years after implementation of a vaccine programme.

In addition to the observed direct effect, a number of effectiveness studies conducted in Australia, Austria, Belgium, Brazil, El Salvador, Mexico, Panama and the United States also suggest an indirect effect of the second generation rotavirus vaccines, implying that herd immunity may occur [96, 178, 182, 187, 193-214].

Furthermore, Pollard et al. recently conducted a meta-analysis to estimate the herd immunity effect in children aged under one year in studies published between 2008 and 2014 [96, 178, 182, 187, 193-215]. The meta-analysis of studies conducted in low-mortality rotavirus countries reporting on rotavirus-specific gastroenteritis outcomes suggested a median herd effect on rotavirus-specific gastroenteritis morbidity/mortality of 22% (19–25%) for 12 study years presented in five studies [180, 182, 201, 213, 214].

Conclusions

Observational effectiveness studies suggest that herd immunity in children of the same age group, and possibly older age groups, evolve after vaccination. Herd immunity may contribute significantly to the overall impact of rotavirus vaccination programmes.

Identified knowledge gaps and needs for capacity building

- Whether rotavirus vaccine virus excreted by newly vaccinated infants and transmitted to older populations will have any clinical impact for induction or maintenance of immunity, as natural disease has done, is unknown and needs to be investigated further.
- Whether reduced circulation of rotavirus disease in the community will reduce burden of disease in other age groups, particularly in the elderly, is unknown and needs to be monitored.

Rotavirus vaccine safety

Severe gastroenteritis with vaccine viral shedding in patients with severe combined immunodeficiency

Post-authorisation spontaneous adverse event reports of severe gastroenteritis and chronic viral shedding in infants later diagnosed with severe combined immunodeficiency (SCID) were received in countries that first introduced rotavirus vaccines. Immunodeficiencies have often not been diagnosed at the time in life when rotavirus vaccines are administered. Rotavirus vaccines are the only live vaccines recommended for infants. A review conducted in VAERS using MedDRA terms such as ‘combined immunodeficiency’ or ‘SCID’ or ‘combined immunodeficiency’ from 3 February 2006 to 15 January 2010 following rotavirus vaccination (RV1 and RV5) identified nine reports of SCID and rotavirus vaccination [63]. All infants but one presented to the healthcare system with symptoms including diarrhoea and were hospitalised. Subsequent investigations led to a diagnosis of SCID. Rotavirus diagnostics of stool samples were positive in all nine cases and the virus was identified as the vaccine strain in six cases. Prolonged viral shedding was documented in five cases. No deaths were reported.

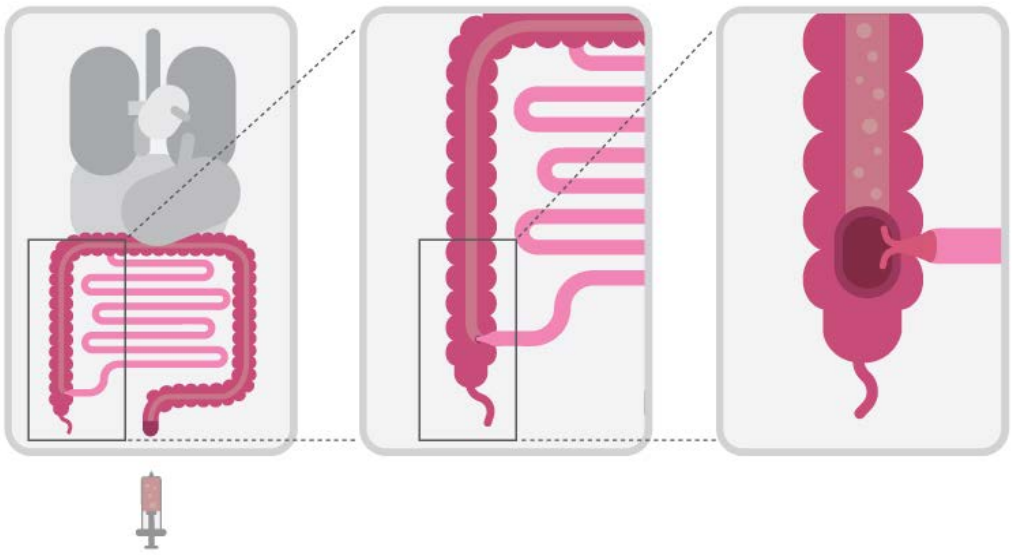
Subsequently, EMA and other global regulatory agencies approved a labelling change in the SPC for the two (RV1 and RV5) vaccines contraindicating administration to individuals with a history of SCID (see Table 1 ‘Rotavirus vaccine contents, indications, contraindications, route of administration, dose regimens and frequency of reported undesirable effects’ and Section ‘Vaccination of infants with immunodeficiency and immunodeficient close contacts’ above). Early identification of SCID (e.g. new-born screening) could prevent inadvertent live rotavirus vaccine administration [216, 217].

Intussusception

Disease

Intussusception (IS) is a condition characterised by telescoping of the intestine onto itself. Intussusception commonly occurs at the ileo-cecal junction (see Figure 9). The incidence is about twice as high in male infants as female infants. IS can be treated by air/barium enema or, if necessary, manual reduction during surgery. However, treatment traditions vary within the EU/EEA and in some EU/EEA Member States or regions surgery may be the first treatment option. According to a recent review, 77% of treatments provided in Europe are by air/barium enema [218].

Figure 9. Schematic overview of the most common form of intussusception (when ileum enters cecum)



NB. Other types of intussusception are known to occur, such as when a part (the intussusceptum) of the ileum or jejunum prolapses into itself. Intussusception can be treated by air/barium enema (see below) or, if necessary, by manual reduction during surgery.

There is a ~50% chance of a non-surgical reduction if the reduction is initiated within 24–48 hours from onset of symptoms. In a review of a IS case series, presence of reported symptoms for at least two days before hospital admission was an independent predictor of the need for surgical reduction (adjusted odds ratio 2.7 95% CI 1.5–4.8) [219]. If not repaired or repaired late, entrapment will lead to intestinal wall oedema, possibly followed by necrosis and intestinal perforation. The latter leads to fever, peritonitis, septicaemia, shock and, if not reversed, death. Moreover, in the above-mentioned case series fever at admission was noted to significantly increase risk of surgical reduction (adjusted odds ratio 2.7, 95% CI 1.2–6.0). Mortality due to intussusception is very rare, estimated in the US at 2.1 per 1 million live births [220] and the EU/EEA studies mentioned below confirm that mortality is rare.

The pathogenesis of intussusception is not fully understood. IS may occur in any child, although a few gastrointestinal malformations are known to induce intussusceptions, such as polyps, which are often referred to as a 'lead point'. Structural lead points were identified in 3% in a systematic review of IS cases reported in the WHO European region from 1995 onwards [221]. In this review recurrence was reported in approximately 1 in 10 IS patients and only one death was reported. A few studies have identified the presence of wild-type rotavirus in the stool or intestine of infants with intussusception; however this association seems uncommon, while adenovirus was strongly associated (OR 44 reported from Australia) [222, 223].

Incidence of IS in the EU/EEA

Six European countries have assessed background incidence for intussusception in preparation for rotavirus vaccine introduction [221, 224-231], see Table 6. The background incidence varies somewhat between countries, being between 24 and 66 per 100 000 but not to the extent observed in other parts of the world (see p.38). In addition, variation may be observed between studies conducted in the same country dependent on whether validation according to the established Brighton Collaboration criteria was conducted or not as in the case of the United Kingdom when the study from 2013 only accepted validated cases and observed a lower incidence than presented earlier (Table 6) [94, 225].

Table 6 Background intussusception incidence in five European countries without rotavirus vaccination

Country	National/regional	Incidence per 100 000	(95%CI)
Austria [228]	National	42	NA*
Denmark [231]	National	66	NA*
Germany [226]	National	60.4	48.3–72.1
Germany [229]	National	61.7	54.5–70.1
Germany [227]	National	51.5	41.7–61.1
Germany [221]	National	52.2	NA*
Ireland [225]	National	24.2	15.0–37.0
Switzerland [230]	National	38 (first year of life) 31 (second year of life) 26 (third year of life)	NA
United Kingdom/England [224]	National	66	NA
United Kingdom [225]	National	24.8	21.7–28.2

*Not available

Source: [224, 226, 229, 230]

Further assessment of the incidence of IS per month during the first year of life has been conducted in Germany and the United Kingdom (England). Interestingly, the peak in Germany was noted to occur at the age of 180 to 269 days while in the United Kingdom (England) the peak was noted to be earlier, in infants aged 120–149 days (see Table 7). The reason for such differences is unknown.

Table 7. Incidence of intussusception by month, first year of life assessed in two EU/EEA countries

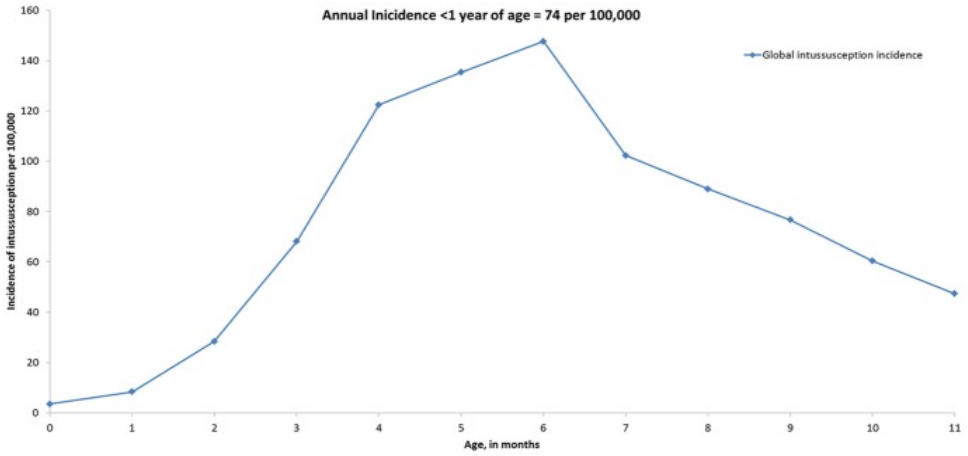
Germany		United Kingdom (England)	
Age/incidence per 100 000 (95% CI) (R)		Age/incidence per 100 000 (95% CI) (R)	
0-89 days	19.2 (12.5-30.4)	0-29 days	3.6 (0.4–13.0)
		30-59 days	26.9 (15.1–44.4)
		60-89 days	46.7 (30.5–68.5)
90-179 days	61.4 (48.0-79.4)	90-119 days	30.6 (17.8–48.9)
		120-149 days	50.3 (33.4–72.7)
		150-179 days	43.1 (27.6–64.2)
180-269 days	98.5 (80.9-120.6)	180-209 days	28.8 (16.4–46.7)
		210-239 days	37.8 (23.4–57.7)
		240-269 days	45.0 (29.1–66.4)
270-365 days	67.9 (53.6-86.5)	270-299 days	14.4 (6.2–28.3)
		300-329 days	10.8 (4.0–23.5)

Source: [221, 226]

Few studies have assessed the treatment needed to resolve IS before rotavirus vaccine introduction. In a Swiss study including 288 IS cases, confirmed with the Brighton Collaboration standardised case definition, spontaneous devagination occurred in 38 patients, enemas reduced IS successfully in 183 cases, while surgical treatment was required in 67 cases. In this series of cases all patients recovered without sequelae [230, 232]. Management practices have also been mapped in the United Kingdom and Ireland [232].

In a recently published international literature review the global intussusception incidence was estimated at 74 per 100 000, peaking at 3–9 months [218] (see Figure 10). However the variation was significant, with the lowest incidence of 9 per 100 000 reported from Bangladesh compared to 328 per 100 000 reported from South Korea.

Figure 10. Global incidence of intussusception per month during first year of life



Source: [218]

Intussusception following vaccination with first generation of oral live attenuated rotavirus vaccine

An earlier, now withdrawn, US-licensed rotavirus vaccine RRV-TV (Rotashield) used in 1998–1999 in the US routine immunisation programme was associated with an estimated excess risk of one additional case of intussusception (IS) per 4 670 to 9 474 infants vaccinated (11–21 additional cases per 100 000 vaccinees) [56, 57]. Regulatory agencies such as EMA and FDA therefore requested clinical trials for new second generation oral live attenuated rotavirus vaccines (RV1 and RV5) large enough to be able to exclude the risk of one additional case of IS per 10 000 children (the definition for a very rare adverse event) and >70 000 children were included in the randomised clinical trials conducted. Of particular interest are the results from investigations that followed the use of RRV-TV and the contributing role of age to development of intussusception. No child receiving dose 1 of RRV-TV before the age of 89 days developed intussusception, in spite of 1 935 doses being administered to infants younger than 30 days and 69 123 doses administered to infants aged 30–59 days [233]. However, it should be noted that naturally occurring IS, although rare does occur in the very young (see Table 7). The biological mechanism behind development of IS following RRV-TV vaccination is not yet fully understood.

No increased risk of intussusception with second generation of oral live attenuated rotavirus vaccines (RV1 and RV5) in pre-authorisation randomised controlled trials

The risk of intussusception was evaluated in RV1 recipients in a randomised double blind placebo-controlled clinical trial conducted in Latin America and Finland with 63 225 children enrolled. This trial provided evidence of no increased risk of intussusception in the RV1 group (n=31 673) receiving dose 1 at 6–13 weeks of age when compared to the placebo group (n=31 552) within 31 days after each vaccine dose [158]. The median age at study entry was 8.2 $\pm$ 2.39 weeks. The relative risk (RR) for intussusception post dose 1 was calculated to 0.50 (95% CI 0.07–3.80) and post dose 2 was 0.99 (95% CI 0.31–3.21).

Similarly, the risk of intussusception was evaluated in RV5 recipients in a randomised double blind placebo-controlled study in 6–12 week old infants [71]. The median age at study entry was 10 weeks. During the combined 42-day period following each dose, there were six cases of intussusception in 34 837 RV5 recipients compared with five cases in 34 788 placebo recipients. The relative risk (RR) for intussusception was calculated as 0.8 (95% CI 0.22–3.52).

No clustering of cases was identified in the early period after each dose with either vaccine or placebo [158, 159]. In conclusion, in the pre-authorisation trials which served as the basis for vaccine authorisation in the EU, no increased risk of intussusception was observed in recipients of either rotavirus vaccine, RV1 or RV5, compared to the placebo groups.

This was also the conclusion in a Cochrane systematic review published in 2012 [160]. However, a risk of IS lower than one additional case per 10 000 vaccinated individuals could not be excluded in the conducted trials and further post-licensure monitoring of intussusception was required by the European Medicines Agency in the risk management plans for both vaccines.

Assessment of reports of intussusception following routine use of second generation oral live attenuated rotavirus vaccines (RV1 and RV5) through adverse event spontaneous reporting systems

Cases of intussusception in temporal relationship with the receipt of rotavirus vaccines were documented in the routine monitoring systems of adverse events following immunisation in Australia, Brazil, Germany, Mexico and the Unites States after the introduction of rotavirus vaccines into the national immunisation programmes. Subsequently formal pharmacoepidemiological studies were initiated in all these countries. For results see section 'Assessment of intussusception reports following use of second generation oral live attenuated rotavirus vaccines (RV1 and RV5) using observed versus expected analysis' below.

The US experience from routine reporting has been summarised in the scientific literature: during the period February 2006–April 2012 the Vaccine Adverse Event Reporting System (VAERS) received 584 confirmed intussusception reports following RV5 administration (182 after dose 1) and 52 following RV1 administration (25 after dose 1). Clustering of cases was observed three to six days after administration of either vaccine [234]. The age of the children involved was not reported. Furthermore, there was no significant increase in reporting of cases following dose 2 or 3. The authors conclude that this clustering can translate to a slightly increased risk of intussusception, which is outweighed by the benefits of rotavirus vaccination.

Although there are several limitations assessing reports retrieved through spontaneous reporting of adverse events, an extract of submitted spontaneous intussusception reports from the EMA Eudravigilance database following rotavirus vaccination in EU/EEA countries was analysed for this ECDC expert opinion[12]. It is important to note, however, that essential information was often missing in these submitted IS reports (e.g. age at vaccination, time to onset of symptoms, treatment provided and clinical outcome of IS).

In total, 296 spontaneous reports of IS were retrieved from the Eudravigilance database, 198 following RV1 administration and 98 following RV5. Time to onset of symptoms was known for 251/296 infants (85%). A total of 193 of these cases occurred within 21 days of vaccination, the internationally accepted risk window, and a majority (159/193) occurred in clusters during the first seven days following vaccination with dose 1 (see Figure 7) of both rotavirus vaccines.

The mean age for administration of dose 1 was known for 202/296 infants (68%). It was 92 d ± 33 for RV1 and 95 d ± 43 for RV 5. The observed mean age for infants that had received dose 1 and developed IS following either of the two RV vaccines was significantly higher than the mean age in the conducted clinical trials that served as the basis for authorisation.

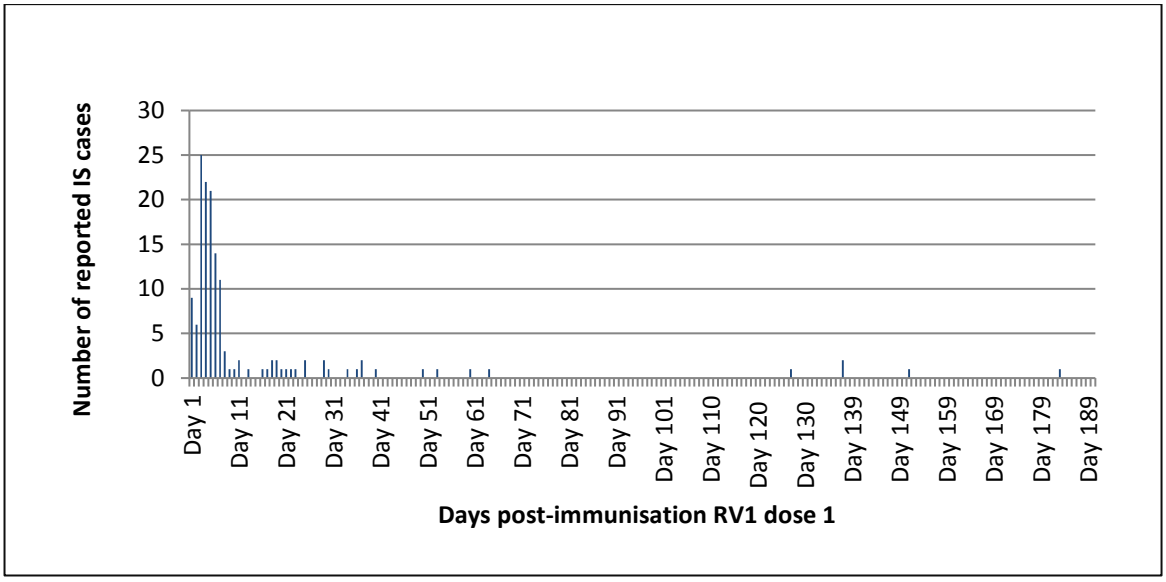
The outcome of the IS cases at the time of reporting was known for 182/296 infants (62%). Cases were often reported as resolved. However, 23/125 cases (18%) with known outcome following RV1 and 6/57 cases (10%) following RV5 were unresolved at the time of reporting. Reported complications included ascites, intestinal abscesses, intestinal necrosis, intestinal resection, hypotonia, bradycardia or shock. No cases with fatal outcome were reported in the time period assessed (to 1 July 2014). Although no fatalities due to intussusception were reported to the Eudravigilance database during the period assessed above, two cases of intussusception with fatal outcome in rotavirus-vaccinated infants were subsequently reported from France in 2015[13].

Additional limitations of this review are that case confirmation by chart review was impossible and that there was a lack of reliable denominator for rate calculation and lack of adjustment for under- or over-reporting.

[12] The analysis and interpretation of EudraVigilance data presented may not be understood or quoted as being made on behalf of the European Medicines Agency or one of its committees or as reflecting the position of the European Medicines Agency, one of its committees or one of its working parties.

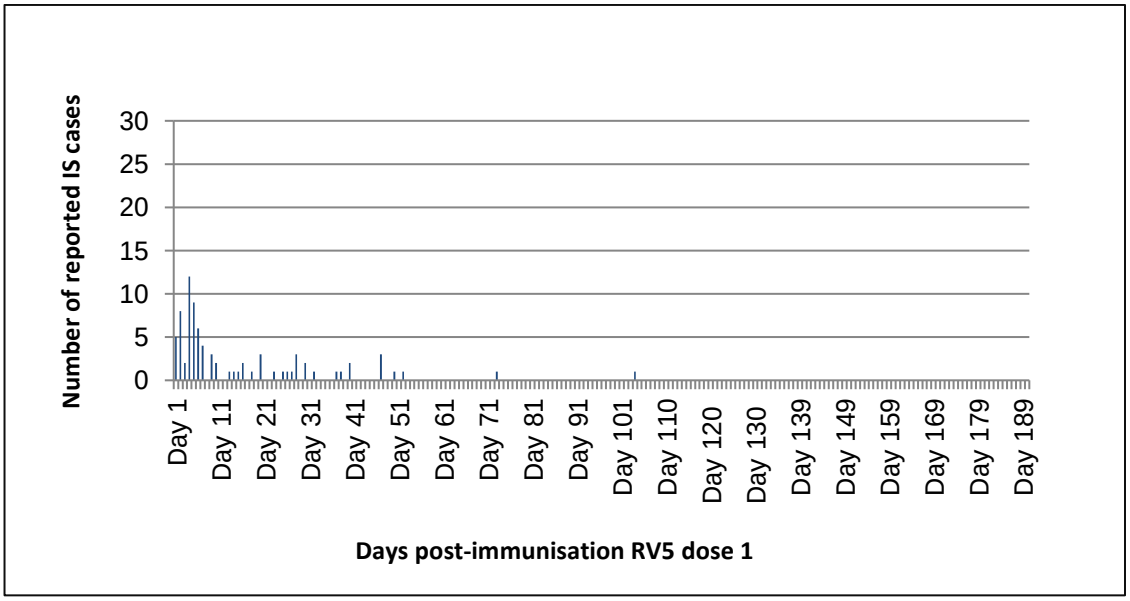
[13] http://ansm.sante.fr/S-informer/Actualite/Vaccins-contre-les-rotavirus-RotaTeq-et-Rotarix-et-rappel-sur-la-prise-en-charge-de-l-invagination-intestinale-aigue-du-nourrisson-Point-d-Information

Figure 11a. Cases reported to the EMA Eudravigilance database (not validated with chart review) to 1 July 2014 with known interval between dose 1 vaccination of RV1 and development of IS (n=164)



A cluster of cases is observed during first seven days following dose 1.

Figure 11b. Cases reported to the EMA Eudravigilance database (not validated with chart review) to 1 July 2014 with known interval between dose 1 vaccination of RV5 and development of IS (n=86)



A cluster of cases is observed during the first seven days following dose 1.

Assessment of intussusception reports following use of second generation oral live attenuated rotavirus vaccines (RV1 and RV5) using observed versus expected analysis

To conduct an observed versus expected assessment of a medical outcome requires knowledge of the background incidence for this entity. This is commonly done using historical data, often from medical outcome databases in countries where such population-based data is available. An alternative is to retrieve cases of intussusception through an epidemiological study, engaging paediatric departments or paediatric radiology departments. Common limitations for observed versus expected studies are the use of historical controls that do not check for temporal trends and the use of unconfirmed cases not validated by chart review.

Three studies conducted in non-EU/EEA countries were identified assessing a possible association between intussusception and rotavirus vaccination (RV1 and RV5) using the observed versus expected methodology (see Tables 8–9) [235-237]. All studies used historical controls and validated their cases according to the Brighton Collaboration criteria (see Annex 2) [94]. The conducted studies showed an attributable risk ranging from 1 per 199 000 to no elevated risk for RV5, while for RV1 the estimate was 1 per 19 000 vaccinated infants (see Tables 8–9).

The only assessment of the intussusception safety signal in the EU/EEA using the observed versus expected methodology was conducted in Germany. In an analysis of 15 intussusception cases reported following vaccination with RV1 and 12 cases reported following vaccination with RV5 in infants aged 3–5 months, a significantly increased risk for intussusception was found in the risk window of 1–7 days after the first dose of either rotavirus vaccine (standardised morbidity ratio for RV1 4.6 95% CI 1.5–10.7 and for RV5 5.8 95% CI 1.2–17.1) [237]. Since this risk was not observed in children vaccinated when aged under 89 days, the investigators, and subsequently the German Standing Committee on Vaccination (STIKO), recommended initiation of rotavirus vaccination as early as possible during the recommended age window of 6–12 weeks for dose 1 [163, 164, 237].

Assessment of intussusception reports following use of second generation oral live attenuated rotavirus vaccines (RV1 and RV5) in formal pharmacoepidemiological studies

Observational studies to assess a possible association between rotavirus vaccination and development of intussusception have been conducted in non-EU/EEA countries (Australia, Brazil, Mexico and the Unites States) using self-control case-series, case-control and cohort study designs (see Tables 8–9) [235-244]. Although different study methodology has been employed they all report similar results and indicate an increased relative risk/attributable risk of intussusception, mainly during the first seven days following dose 1, ranging from 1 per 20 000 to 1 per 69 000 for RV1 vaccinated infants and 1 per 14 000 to 1 per 67 000 for RV5 vaccinated infants in the different studies, except in the first studies by Belongia et al, Shui et al and Haber et al, conducted using VAERS or VSD data where no increased risk of intussusception following RV5 was observed, possibly due to small sample size [234, 235, 245]. A meta-analysis of studies conducted has been published [246] and showed that the overall estimate of the relative risk of intussusception during the seven days post-dose 1 was 5.4 (95% CI: 3.9–7.4, three studies) for RV1 and 5.5 (95% CI: 3.3–9.3, three studies) for RV5. The overall estimate for relative risk of intussusception during the seven days post-dose 2 was 1.8 (95% CI: 1.3–2.5, four studies) for RV1 and 1.7 (95% CI: 1.1–2.6, three studies) for RV5. These epidemiological studies carry a greater scientific weight than the observed versus expected assessments mentioned above and suggest a class-specific effect.

Severity of intussusception observed following use of second generation oral live attenuated rotavirus vaccines (RV1 and RV5)

Two retrospective studies have assessed the severity of intussusception that developed following vaccination with either rotavirus vaccine (e.g. whether surgery was needed for reduction of the intussusception). In an observed versus expected study from Germany reporting severity in 27 cases of IS following either RV1 or RV5 vaccination, 13 (48.1%) underwent surgical reduction [237] while in a self-case control study from Australia assessing severity in 110 cases of IS rates of surgery were 39% [242]. Both of these studies were rather small and therefore further studies are needed, carefully considering treatment traditions in the area where the study is conducted.

Table 8. Risk estimates for intussusception and RV1 (based on Brighton Collaboration Level 1 case definition including surgical criteria, radiological criteria demonstration of intestinal invagination by either air or liquid contrast barium enema, or demonstration of an intra-abdominal mass with specific features by ultrasound, or autopsy criteria)

Vaccine, author, year	Source population and methods	Risk window / dose no	Relative risk / attributable risk / incidence ratio	95% CI
Patel et al, 2011 [238]	Mexico Self-controlled case series and case control	Days 1-7 following dose 1 Days 1-7 following dose 2	1.9 cases per 100 000 vaccinated infants or 1 per 51 000 vaccinated infants. 1.4 cases per 100 000 vaccinated infants or 1 per 69 000 vaccinated infants	Not available
Escolano et al 2011 [247]	Worldwide reports to the manufacturer Case-series analysis	Incidence ratio of IS days 3-7 following dose 1 versus 2	Incidence ratio 4.97	1.72-14.3
Velazquez et al 2012 [240]	Mexico Self-controlled case series	Days 0-6 following dose 1	3.7 cases per 100 000 vaccinated infants or 1 case per 27 000 vaccinated infants	1.2–7.3 cases per 100 000 vaccinated infants or 1 case per 14 000 to 83 000 vaccinated infants
Carlin et al 2013 [241]	Australia TGA (regulatory agency) Self-controlled case-series and case-control	Days 1-7 following dose 1 Days 8-21 following dose 1 Days 1-7 following dose 2	5.0 cases per 100 000 vaccinated infants or 1 per 20 000 vaccinated infants	1.9-10.7 cases per 100 000 vaccinated infants or 1 per 9 000 to 53 000 vaccinated infants
Weintraub et al 2014* [236]	US VSD Observed versus expected using historical rates Total doses: 208 000 Dose 1: 116 000 Dose 2: 92 000	Day 1-7 following dose 1 Day 1-7 following dose 2	5.34 cases per 100 000 vaccinated infants or 1 per 19 000 vaccinated infants	Not available Not available
Oberle et al 2014* [237]	Germany Observed versus expected using historical rates	Days 1-7 following dose 1	Standardised morbidity ratio 4.6	1.5-10.7
Quinn et al 2014* [242]	Australia Self-controlled case series	Days 1-7 following dose 1 Days 1-21 following dose 1	Relative incidence 11.1 Relative incidence 5.5	2.6 - 48.0 1.7 - 17.8
Yung et al 2015* [248]	Singapore Self-controlled case series	Day 1-7 following dose 1	Relative incidence 8.4	2.4 – 29.0

*Published after the literature review was conducted

Table 9. Risk estimates for intussusception and RV5 (based on Brighton Collaboration Level 1 case definition including surgical criteria, radiologic criteria demonstration of intestinal invagination by either air or liquid contrast barium enema, or demonstration of an intra-abdominal mass with specific features by ultrasound, or autopsy criteria)

Vaccine, author, year	Source population and study methods	AR calculation based on risk detection with respective dose	Relative risk/attributable risk	95%CI
Belongia et al [245]	US VSD 2006-2008 Observed versus expected using historical rates in VSD Total number of doses: 207 621 Total number of dose 1: 87 201	Day 1-30 following any dose	No elevated risk identified	-
Shui et al 2012 [235]	US VSD 2006 – February 2010 Observed versus expected using historical rates in VSD Total number of doses 786 725 Total number of dose 1: 309 844	Day 1-7 following dose 1 Day 1-30	1 per 1.8 million vaccinated infants	Not reported
Haber et al 2013 [234]	US VAERS Self-controlled risk interval	Day 3-6 following dose 1	0.74 per 100 000 vaccinated infants or 1 per 135 000 vaccinated infants	0.24 – 1.71 cases per 100 000 vaccinated infants or 1 per 58 000 to 417 000 vaccinated infants
Carlin et al 2013 [241]	Australia TGA (regulatory agency) Self-controlled case-series and case-control	Days 1-7 following dose 1 Days 8-21 following dose 1 Days 1-7 following dose 2	6.9 cases per 100,000 vaccinated infants or 1 per 14 000 vaccinated infants	3.1-13.6 cases per 100,000 vaccinated infants 1 per 7 000 to 32 000 vaccinated infants
Weintraub et al 2014 [236]	US VSD Observed versus expected using historical rates Total number of doses: 1.3 million Dose 1: 494 000	AR estimate day 1-7 following dose 1	0.5 per 100 000 vaccinated infants or 1 per 199 000 vaccinated infants	0-1.77 cases per 100,000 vaccinated infants or 1 per 30 000 to infinite vaccinated infants
Yih et al 2014 [244]	US PRISM Self-controlled risk interval, cohort study Total number of doses: 1.28 million Total number of dose 1: 508 000	Day 1-7 following dose 1 Day 1- 21 following dose 1	1.5 cases per 100 000 vaccinated infants 1.1 cases per 100 000 vaccinated infants or 1 per 67 000 vaccinated infants 1 per 91 000 vaccinated infants	0.2 – 3.20 cases per 100 000 or 1 per 30 000 to 520 000 vaccinated infants
Oberle et al 2014 [237]	Observed versus expected using historical rates	Days 1-7 following dose 1	Standardised morbidity ratio 5.8	1.2-17.1
Escolano et al 2015 [239]	World-wide reports to manufacturer Self-controlled case series	Days 3-7 following dose 1	Incidence risk ratio relative to the control period 3.45	1.84-6.55

Updates of the EU Summary of Product Characteristics on intussusception in 2014

Benefit/risk assessments for the two rotavirus vaccines RV1 and RV5 have been formally conducted by the following regulatory agencies: EMA (EU/EEA), FDA (United States), TGA (Australia) and found to be positive, given the severity of rotavirus disease and availability of treatment for cases of intussusception. The EU Summary of Product Characteristics has been updated as follows, in line with results obtained in the above-mentioned pharmacoepidemiological studies, stressing that prompt attention should be given to infants with clinical symptoms indicative of intussusception.

EU SPC Section 4.4 (Warnings and precautions for use)

'As a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever) since data from observational safety studies indicate an increased risk of intussusception, mostly within 7 days after rotavirus vaccination (see section 4.8). Parents/guardians should be advised to promptly report such symptoms to their healthcare provider'.

EU SPC Section 4.8 (Adverse events)

'Data from observational safety studies performed in several countries indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively. There is limited evidence of a smaller increased risk following the second dose. It remains unclear whether rotavirus vaccines affect the overall incidence of intussusception based on longer periods of follow up (see section 4.4)'.

Risk mitigation strategies aiming to further reduce the risk of intussusception

Following the results of observed versus expected analyses and pharmacoepidemiological studies where a risk of intussusception after rotavirus vaccination has been observed, public health agencies or national immunisation technical advisory groups (NITAGs) in three EU/EEA countries have embarked on risk mitigation strategies. In 2013, the German STIKO committee recommended that rotavirus vaccines should be provided as early as possible from six weeks of age. In Norway and the parts of Sweden (Stockholm and Jönköping regions) that initiated rotavirus vaccination programmes in 2014, the vaccines are offered at six weeks of age. Whether these mitigation strategies will have an impact on the incidence of intussusception following rotavirus vaccination is currently unknown. Studies have been initiated in Norway and Sweden.

Kawasaki disease

During review of RV5 clinical trial data a higher, though not statistically significantly rate of Kawasaki Disease (KD) was observed among RV5 vaccinees than placebo recipients. Therefore risk management plans for both rotavirus vaccines included post-authorisation requirements to monitor KD. In a review of all KD reports received by US Vaccine Adverse Event Reporting System (VAERS) from 1990 to mid-October 2007, no clustering of cases and no increased risk of KD in the post-authorisation phase for the RV5 vaccine was observed [249]. Instead, the reporting rate for RV5 (1.47/100 000 person-years) was lower than the US background rate.

Other adverse events

Other undesirable effects noted in the initial RCTs are listed in Table 1.

Conclusions

Severe gastroenteritis with vaccine viral shedding in patients with severe combined immunodeficiency.

- A review of US VAERS identified nine reports of severe gastroenteritis with vaccine viral shedding in patients who were subsequently diagnosed with severe combined immunodeficiency (SCID). This observation resulted in a label change in the SPCs in 2013 for both rotavirus vaccines, stating that SCID is a contraindication for rotavirus vaccination.

Intussusception

- In pre-authorisation RCTs with these second generation rotavirus vaccines, which served as the basis for vaccine authorisation in 2006 in the EU, no increased risk of intussusception was observed in recipients compared to the placebo groups. This was also concluded in a 2012 Cochrane systematic review assessing vaccine safety in randomised placebo-controlled clinical trials published in 2012. However, a risk of IS lower than one additional case in 10 000 vaccinated individuals could not be excluded and risk management plans from regulatory agencies requested post-authorisation monitoring.

- After the introduction of rotavirus vaccines into routine immunisation programmes, IS cases following vaccination with RV1 and RV5 were initially reported in early adopter countries (Australia, Brazil, Germany, Mexico and the Unites States). Similarly, IS cases have been reported to the EU/EEA Eudravigilance database following vaccination with both rotavirus vaccines.
- Formal observational studies conducted in non-EU/EEA countries such as Australia, Brazil, Mexico, Singapore and the US indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within seven days of vaccination. An observational study conducted in Germany confirms the reported increased risk. Following these studies the EU/EEA SPC have been updated: 'Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 intussusception episodes per 100,000 infants per year, respectively'.
- Strategies for IS risk minimisation are currently being explored, with vaccinators and healthcare workers caring for affected children being trained for early recognition of symptoms suggestive of intussusception and vaccines being provided early in the recommended age window from six weeks of age. However, no results are available yet on the impact of these strategies.
- Regulatory agencies in low-mortality rotavirus countries such as those in the EU/EEA have concluded that the benefits of rotavirus vaccination outweigh the risks.

Kawasaki disease

- No increased risk of Kawasaki disease has been observed in the post-authorisation period.

Identified knowledge gaps and needs for capacity building

- Published background incidence of IS by month during the first year of life is lacking in most EU Member States. Developing this data in more Member States will be useful for observed versus expected analysis of IS.
- Risk minimisation strategies, to reduce IS incidence following rotavirus vaccination, are being undertaken in three countries. The impact of these strategies is currently unknown and ought to be carefully studied to inform others.
- Training material for vaccinators/healthcare personnel is needed to ensure adequate and prompt treatment, should an IS case be encountered.
- In the EU/EEA the reporting of IS cases by vaccinators following RV vaccination could be improved. Future monitoring of adverse events would benefit from completeness of reporting by vaccinators and chart review for validation.
- Protocols for observational studies to assess IS risk, should be developed for conduct in early adopter EU/EEA countries if needed. Multi-country EU/EEA studies could enhance sample size and speed of results.
- The question of whether new (third generation) rotavirus vaccines/vaccine candidates (e.g. live oral neonatal rotavirus strains, inactivated parental whole virus or subunit) will offer better benefit-risk profiles than the current second generation oral live attenuated vaccines needs to be investigated in continued randomised clinical trials.

Cost-effectiveness studies performed in EU/EEA countries

In an economic context, where public funding is scarce, the need to adopt more efficient strategies for all public interventions is paramount. Population health can be influenced directly by many different factors (behaviour, environment, etc.) or indirectly (education, unemployment, etc.), therefore the impacts of public health intervention are not straightforward. As a consequence, there is a need for a sound framework to assess the potential impacts of different policy interventions. Economic assessments help facilitate the decision making process in EU/EEA Member States.

There are several economic analytical models for prioritising different policy interventions; cost-benefit and cost-effectiveness analyses being the most commonly used.

Cost-benefit analysis is a formal technique to summarise the health benefits and resources utilised by public health interventions so that decision-makers can select appropriate options. It appraises in monetary value the overall expected costs and total expected benefits of an intervention in order to choose the best or most beneficial solutions. However, costs and benefits may occur in different time frames, hence the monetary value of both is expressed in present value using a discounting factor. Cost-benefit analysis is often utilised when there is only one policy intervention option, however when there are many different policy alternatives then cost-effectiveness-analysis is the technique of choice.

Contrary to cost-benefit analysis, for cost-effectiveness analysis, the expected benefits from the intervention do not need to be expressed in monetary value and the number of cases or any other indicators can also be adopted. Rules are then determined in order to facilitate decision-making based on the cost-effectiveness-analysis. In Europe, cost-effectiveness analysis is widely adopted as the technique to identify the most effective utilisation of limited resources.

Furthermore, in cost-effectiveness studies epidemiological outcomes, such as the number of cases prevented, number of life years gained, or so-called 'utility' indicators, such as quality-adjusted life years (QALY) gained or disability adjusted life years (DALY) prevented are often used. The latter two capture the impact of the intervention, both for mortality and morbidity outcomes. QALYs are the product of the time spent in a certain health state and of a quality of life utility weight corresponding to this health state. DALYs reflect the total amount of healthy life year(s) lost, whether from premature mortality or from some degree of disability.

There is no EU-wide adopted threshold for cost-effectiveness analysis, and only a few countries have set a formal threshold defining a cost-effective intervention. For example, in England and Wales, the threshold used by the National Institute for Health and Clinical Excellence (NICE) is GBP 30 000 (EUR 29 000) for health services and personal services and in the Netherlands the threshold used is often set at EUR 20 000 per life year or QALY gained.

To the best of the authors' knowledge, no similar thresholds have been adopted in northern, central, eastern or southern Europe and they would probably vary significantly anyway, as such a threshold depends on the wealth of the country and organisation of the healthcare system.

Assessing cost-effectiveness is often one of several important factors considered when a new vaccine is evaluated for possible introduction into a routine programme. However, the measurement of the reduction in quality of life for a disease affecting young children, such as in the case of rotavirus vaccines, poses unsolved methodological challenges. This is particularly relevant because any assessment has to be made by proxy through a caregiver. With the high morbidity but low mortality attached to rotavirus-induced gastroenteritis in EU/EEA countries, estimation of cost-effectiveness ratios based solely on life years gained would lead to an underestimation of the benefits of vaccination.

This chapter summarises published evaluations of cost-effectiveness for the introduction of rotavirus vaccines into national immunisation programmes in the EU/EEA.

Cost-effectiveness studies in EU/EEA

As of 2014, fifteen cost-effectiveness studies, from Belgium, Finland, France, England and Wales, Italy, Ireland, the Netherlands, Spain and the United Kingdom, had been identified with the appraisal of cost-effectiveness for universal infant rotavirus immunisation based on use of either RV1 or RV5 vaccines [145, 155, 250-260]. To date no EU/EEA Member States in central or eastern Europe have published cost-effectiveness data for rotavirus vaccines. Study methodology and results are summarised in Tables 10 and 11.

Studies included a variety of main assumptions and parameter values and are therefore not comparable. The assumptions and parameter values that varied were the perspective of analysis (healthcare provider costs only or societal costs in addition), whether quality of life (QALY) was included, different discount rates, whether nosocomial infections were included, varying vaccine efficacy assumptions, and expected vaccine prices. Studies were either conducted by vaccine manufacturers supporting academia or by public health experts/academia independent of industry.

Based on the list price in the respective country for a complete course of rotavirus vaccination with two or three doses available at the time of analysis (range EUR 75–187), few studies have deemed the intervention to introduce rotavirus vaccine as cost-effective or cost-saving over the current practice of rehydrating the severely affected children as in-patients. The exception is Finland, probably due to low healthcare provider costs per QALY gained (EUR 20 359 to 37 763), compared to Spain, for example, which has the highest cost of EUR 280 338/QALY gained (see Table 11). Most researchers therefore opted to also calculate threshold prices for making the intervention cost-effective or even cost-saving. These threshold prices also varied significantly, as expected, with cost-effective threshold prices from the healthcare payer's perspective varying within the range of EUR 44-120. Meanwhile, cost-saving vaccine threshold prices focussing on the healthcare provider's perspective varied from EUR 20 to EUR 70. Overall, a lower threshold price was obtained in studies conducted by independent investigators, such as in the study by Jit et al in England and Wales [261, 262].

The comparison between studies is further complicated by the availability of two vaccines with different prices for a complete course, with possibly slightly different efficacy/effectiveness. Moreover, the choice of different end-point measurements in the clinical trials complicates the analysis (see Annex 1 for a comparison of the two severity scales used in the clinical trials). This is accounted for in the tables by showing ranges of results, depending on the vaccine costs and effectiveness values considered in the studies for each vaccine. For the sake of simplification, although all studies included sensitivity analysis, only results for the base-case scenarios are presented.

The main differences between studies lie in:

- *Scope of analyses*. Four types of costs can be distinguished; direct medical costs (costs of treatment), direct non-medical costs (home assistance, transportation, etc.), indirect costs (care-providers leave of absence due to disease in child or disease in care-provider, etc.) and intangible costs (loss in quality of life, etc.). The societal perspective usually includes the non-medical direct costs borne by the families and the indirect costs, resulting from time off work inducing loss in productivity and/or loss in wages for the carers whereas the healthcare associated cost perspective takes into account the medical and non-medical costs only.

- *Rates of discounting* (i.e. conversion of future values of costs or health effects to their present values). The impacts of a public health intervention are usually not observed at the same time as the funding of the intervention, hence usually both intervention benefits and costs are discounted to their present values. All studies but one discounted the costs at a rate between 3 and 4% but the rates used for the benefits vary more widely (1.5–5%). The range of discounting rate adopted is in line with results from different economic studies [263]. It is worth noting that the higher the discounting rate the lower the present value. In many studies (mainly for the Netherlands and Belgium), asymmetric discounting rates have been adopted with a higher discounting rate for costs of intervention than for the impact of the intervention, thus increasing the present value of related impacts from an intervention. Such a choice favours vaccination rather than no vaccination.
- *Quality of the epidemiological parameters and cost estimates*. Most rotavirus-induced infections are self-limiting and their true incidence (see Table 5) and associated costs are often poorly measured. Acute gastroenteritis is frequent in children under five years but the contribution of rotaviruses is not well quantified. Even for severe cases leading to hospitalisations, the percentage attributable to rotaviruses is largely unknown, leading to varying estimates, as the clinical management is independent of the pathogen causing the diarrhoea. Choices regarding whether or not to include in the analysis cases for which no care is sought are likely to partially explain the heterogeneity in the results of the different studies. This has been identified as the main factor contributing to the discrepancy in the results obtained in two UK cost-utility studies. The burden of nosocomial infections is very difficult to assess and many studies having neglected them on the basis of the lack of data.

Only one study by Bruijning-Verhagen et al conducted in the Netherlands suggests targeted rotavirus vaccination of high-risk infants as a low cost and highly cost-effective alternative to universal vaccination [264].

Conclusions

- There is no clear consensus among the identified studies on cost-effectiveness for universal rotavirus vaccination in the EU/EEA. The inclusion of societal costs significantly affects the estimated cost-saving threshold, and the majority of studies, particularly those that do not take into account societal costs, conclude that the vaccines would have to be priced more competitively to make this intervention cost-effective.
- There is significant difference among Member States, not only in the conclusions of the studies but also in the impact of the studies on whether countries have introduced the rotavirus vaccine into their programmes. Until now eight out of eleven countries that have undertaken economic assessments have introduced rotavirus vaccines into their programmes (Austria, Belgium, Finland, Germany, Ireland, Norway, Sweden and the United Kingdom).

Identified knowledge gaps and needs for capacity building

- Lack of a tradition for conducting cost-effectiveness analyses before introducing new vaccines was identified in a majority of EU/EEA Member States.
- Sharing available health economic models of rotavirus vaccination cost-effectiveness should be encouraged so that they can be used in various settings in interested EU/EEA countries and the new option of an EU-level joint procurement for Member States could also be explored.

1742 **Table 10. Main assumptions and parameter values of cost-effectiveness studies conducted in the**
1743 **EU/EEA of infant rotavirus vaccination – base case analysis**

Country	First author/year of publication	Perspective of analysis[1]	Quality of life included	Discount rates	Nosocomial rotavirus disease infections included	Vaccine efficacy against severe forms of rotavirus disease	Vaccine coverage (%)	Vaccine price (full series)
Belgium	Bilcke, 2008 [145]	HCP/societal	Yes	Cost: 3% Effect: 1.5%	Yes	96% to 100% + waning rate	98	EUR 111
Finland	Salo, 2007	HCP/societal	Yes	Cost: 3% Effect: 3%	Yes (in sensitivity analysis)	?	100	EUR 79/88.5
France	Melliez, 2008 [250]	Societal (direct costs)	Yes	Cost: 3% Effect: 3%	No	85 %	75	EUR 150
UK (1)	Lorgelly, 2008 [155]	HCP/societal	No	Cost: 3.5% Effect: 3.5 %	No	92 %	91	GBP 60 (≈ EUR 88)
UK (2)	Martin , 2009 [251]	HCP/societal	Yes	Cost: 3.5% Effect: 3.5 %	Yes	100% year 1 92,2 % year 2	88	GBP 83.76 (≈EUR 122)
England & Wales	Jit, 2007 [265]	HCP/societal (in sensit. analysis)	Yes	Cost:3.5% Effect: 3,5% (3% after 30 years)	Yes	94 %	95	GBP 70/75 (≈ EUR 102/110)
Germany	Aidelsburger, 2014 [266]	HCP/societal	Yes	Cost:3% Effect: 3%	Yes	87% for Rotarix yr 2 92% for RotaTeq yr 2	80	EUR 135
Netherlands (1)	Goossens, 2008 [253]	Societal	Yes	Cost: 4% Effect: 1.5 %	Yes	100 %	100	EUR 80/100
Netherlands (2)	Zomer, 2008 [254]	HCP /societal	Yes	Cost:4% Effect: 1.5%	Yes	84,7% to 94,5%	97	EUR 135/138
Netherlands (3)	Mangen, 2010 [255]	TP/societal	Yes	Cost: 4% Effect: 1.5%	Yes	88% (RotaTeq) 92% (RotaRix)	97	EUR 84 (RV5) EUR 90 (RV1)
Netherlands (4)	Rozenbaum, 2011 [256]	Societal	Yes	Cost: 3.5% Effect: 3.5%	Yes	94.5%	95	EUR 75
Italy	Giammanco, 2009 [257]	HCP/societal	No	Cost: 3 % Effect: 3 %	No	85 % to 90 % + waning rate	90	EUR 164.1 EUR 65.6 (estimate used if bought by NHS)
Ireland	Tilson, 2011 [258]	HCP/societal	Yes	Cost: 4% Effect: 4%	Yes	100%	90	EUR 100
Spain (Catalonia)	García-Basteiro, 2011 [120]	HCP	No	Cost: nd Effect: nd	Yes	81.8-100%	96	EUR 187
Spain (Castilla y León)	Pérez-Rubio, 2011 [267]	HCP/societal	Yes	Cost: 5% Effect: 5%	No	94%	100	EUR 139 (RV5) EUR 187.1 (RV1)
Spain	Imaz et al [268]	HCP/Societal	Yes	Cost: 3% Effect: 3%	Yes	74%	96	EUR 133.5 (RV5)

1744 1: HCP: healthcare payer, TP: third payer

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1746 **Table 11. Main results of cost-effectiveness studies conducted in the EU/EEA of infant rotavirus**
1747 **vaccination – base case analysis**

Country	First author	Main results	Vaccine price threshold analysis (cost of full series)
Belgium	Bilcke [145]	HCP: EUR 51 030 to EUR 65 767/QALY gained Societal: EUR 7 572 to EUR 30 227 /QALY gained	HCP: Cost saving if vaccine price ↘ by 64%-72%
Finland	Salo	HCP: EUR 20 359 to EUR 37 763 /QALY gained (base case) EUR 13 141 to EUR 26 678/QALY gained (incl. home treated ar nosocomial cases) Societal: cost saving to EUR 7 543/QALY gained	
France	Melliez [250]	Societal: EUR 138 690/QALY gained (EUR 298 000/life year saved)	Cost-saving (HCP): < EUR 27 Cost-effective (HCP): < EUR 65
Germany	Aidelsburger [266]	HCP (Statutory health insurance): RV1 EUR 116 973 per QALY gained, RV5 EUR 142 732 per QALY gained	Cost-saving (HCP): < EUR 56.56 (RV1), < EUR 52.95 (RV5) Cost-effective:
UK (1)	Lorgelly [155]	HCP: GBP 177 212/life year saved (≈ EUR 258 700/life year saved)	Cost-saving (HCP): < GBP 13 53 (≈ < EUR 19.8) Cost-saving (society): < GBP 67 83 (≈ < EUR 99)
UK (2)	Martin [251]	HCP: GBP 23 298/QALY gained (≈ EUR 34 015/QALY gained) Societal: GBP 11 459/QALY gained (≈ EUR 16 730/QALY gained)	NA
England & Wales	Jit [265]	HCP: GBP 61 000 to 79 900/QALY gained (≈ EUR 89 000 to EUR 116 600/QALY gained) Societal: GBP 54 500 to GB{ 74 000/QALY gained (≈ EUR 79 600 to 108 000/QALY gained)	Cost-effective (HCP): < GBP 30 to 38 (≈ < EUR 44 to 55) Cost- effective (society): < GBP 36 to 44 (≈ <EUR 53 to 64)
Netherlands (1)	Goossens [253]	Societal: EUR 21 900 to EUR 35 076/QALY gained	
Netherlands (2)	Zomer [254]	HCP: EUR 124 000/DALY prevented Society: EUR 119 000/DALY prevented	Cost-effective (HCP): < EUR 46 Cost-saving (society): < EUR 24
Netherlands (3)	Mangen [255]	TP: EUR 58 000/ DALY prevented (RV5); EUR 53 000/DALY prevented (RV1) Society: EUR 54 000/DALY prevented (RV5); EUR 49 000/DALY prevented (RV1)	Cost-saving (TP): <EUR 34 (RV5); <EUR 36 (RV1)
Netherlands (4)	Rozenbaum [256]	Societal: EUR 46 717/QALY gained; EUR 44 841/DALY prevented	NA
Italy	Giammanco [257]	NA	Cost-saving (HCP) < EUR 46.25 Cost-saving (society) < EU 117.5
Ireland	Tilson [258]	HCP: EUR 112 048/QALY gained (EUR 68,896/QALY gained if one caregiver considered) Societal: EUR 72 736/QALY gained (EUR 43 916/QALY gained if one caregiver considered)	Cost-saving (HCP and society) <EUR 75
Spain (Catalonia)	García-Basteiro [120]	NA	Cost-saving (HCP) <1.93
Spain (Castilla y León)	Pérez-Rubio [267]	HCP: EUR 74 959/QALY gained (RV5); EUR 52,603/QALY gained (RV1) Societal: EUR 45 624/QALY gained (RV5); EUR 23 435/QALY gained (RV1)	Cost-effective (HCP): <EUR 105 (RV5); <EUR 120 (RV1) Cost-saving (society): <EUR 105 (RV5); <EUR 120 (RV1)
Spain	Imaz et al [268]	HCP: EUR 280 338/QALY gained Societal: EUR 210 167/QALY gained	Cost-effective: <EUR 63 (RV5)

1748 QALY: quality adjusted life years
1749 Exchange rates on 01/06/06: GBP 1 = EUR 1.46, USD 1 = EUR 0.78)

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Attitudes to rotavirus vaccination among parents and healthcare workers

Knowledge and attitude towards rotavirus vaccination among parents and healthcare workers has rarely been investigated in the EU/EEA, in fact no published studies were identified addressing parental attitudes to rotavirus vaccination. One study conducted in 2012 describing knowledge and attitudes of public health residents (n=1 304) originating from five European countries (France, Italy, Portugal, Spain and the United Kingdom) to immunisation programmes discussed self-reported knowledge on vaccines, awareness of epidemics and prevention campaigns and attitudes towards vaccination (perceived importance) [269]. This group of healthcare workers in training will often be responsible for implementing and monitoring immunisation programmes however ~25% of residents reported their own level of knowledge on vaccines to be insufficient, with the lowest levels of knowledge in relation to the new vaccines: rotavirus, varicella, and HPV vaccination for men. The authors of this study conclude that public health residents do not always feel sufficiently educated to deal with vaccine-related issues and there is room for improvement.

The high vaccination coverage (60–90%) reported by EU/EEA countries that have initiated rotavirus vaccination is an indirect indication of good acceptance, both among parents and healthcare workers (see Table 4).

Conclusions

- No information was identified addressing parental attitudes to rotavirus vaccination in the EU/EEA.
- Limited information was identified addressing healthcare worker attitudes to rotavirus vaccination, suggesting a need for further education.

Identified knowledge gaps and needs for capacity building

- Research addressing parental and healthcare worker attitudes towards rotavirus vaccination and other vaccinations needs to be strengthened.

4. Options for monitoring and evaluating impact of rotavirus vaccination

Building on the results obtained in the literature review, the experts identified options for monitoring and evaluating the impact of rotavirus vaccination.

Efficacy, effectiveness and safety information for both RV1 and RV5 vaccines are available from randomised clinical trials and from the initial phase of implementing the vaccines into routine paediatric vaccination programmes in a number of countries in the Americas, Australia and Europe. However, information needs to be collected systematically on long-term vaccine effectiveness, vaccine safety and possible rotavirus strain replacement with clinical significance for continuous evidence-based benefit-risk assessments.

The main objective of vaccination against rotavirus is to protect against moderate-to-severe disease and thereby prevent hospitalisation and death. In addition, it is likely that consultancy for moderate/severe rotavirus disease in emergency departments will be significantly reduced.

Preparing for rotavirus vaccine introduction

Before implementing rotavirus vaccination consideration should be given to how such a programme can be prioritised within a wider public health context. It is therefore recommended that information is obtained on severe burden of disease leading to hospitalisation and that circulating rotavirus genotypes are characterised. Traditionally this has been done in epidemiological studies but another option is to establish routine or sentinel surveillance systems for assessing burden of disease and circulating rotavirus strains. This may include:

- development of a case definition for severe rotavirus disease;
- establishment of universal or sentinel reporting of severe rotavirus disease leading to hospitalisation and/or death;
- establishment of sampling frames and genotyping methods which provide representative and comparable data within each country and possibly across countries;

Furthermore, it is becoming more common for cost-effectiveness analyses to be required in the decision-making process for introduction of new vaccines.

Monitoring impact of rotavirus vaccine programmes

Vaccine exposure/coverage

It should be ensured that individual exposure data are available, including:

- name
- gender
- date of birth of infant
- date of vaccination
- which rotavirus vaccine was provided, including batch number
- which dose in the series was administered.

It should also be ensured that vaccine is administered on a timely basis, in line with national vaccine programme recommendations, and that the vaccine coverage obtained is monitored.

Monitoring of rotavirus vaccine safety

- Country-specific background incidence rate data for intussusception should be collected to facilitate observed-versus-expected assessment of reported intussusception cases, if needed.
- Should intussusception cases occur, it should be ensured that vaccinators or healthcare workers responsible for treatment of affected children report all the relevant information needed for regulatory, public health agencies or market authorisation holders to assess the individual case (see checklist of information needed in Annex 3). In addition to the individual exposure data mentioned above, the following information is needed: date of onset of symptoms suggestive of intussusception; detailed description of clinical symptoms and possible complications; detailed description of diagnosis confirmation with radiology and/or ultrasound; treatments needed to resolve the intussusception (date of interventions and, if several interventions were needed, dates for each one), and the final outcome including any residual sequelae in each affected infant. It is most helpful for assessors if a copy of the discharge note from the hospital stay is attached to the case report.

Monitoring of short-term rotavirus vaccine effectiveness

The second generation rotavirus vaccines will not induce sterilising immunity. Therefore rotaviruses will continue to circulate in European populations and are expected to provide natural boosters to vaccinated individuals throughout life. However, circulating viruses may reassort and new emerging strains may be imported, making it essential to monitor rotavirus strains. Methods to assess the impact of rotavirus vaccines and the immunisation programmes implemented in European settings at clinically-relevant disease endpoints may include the following elements:

- monitoring reduction in hospitalisations for rotavirus disease
- monitoring reduction in number of laboratory samples sent for rotavirus diagnosis
- sentinel surveillance of circulating rotavirus strains, including samples for genotyping from possible breakthrough infections
- specifically-designed impact studies (ECDC protocols available for case-control, cohort and impact studies.)[14]

When evaluating reduction in hospitalisation, historical controls are often useful, especially in countries that are able to achieve high immunisation coverage from the initial phase of the routine programme.

Upon introduction of rotavirus vaccines in infants, it is expected that there will be a gradual reduction in the number of children hospitalised with severe rotavirus disease, as follows:

- first season - reduction expected in children aged 2–3 to 6 months
- second season - reduction expected in children aged 2–3 to <12 months, perhaps also in the age group 12–24 months
- third season - reduction expected in children aged 2–3 to 24 months, perhaps also in the age group > 24 months.

A potential shift of the disease to older age groups (increased proportion of older children) ineligible for vaccination will naturally be seen during the initial phase but, if the vaccines provide long-term protection as well as herd immunity, this is expected to subside within four to five years.

Monitoring of long-term rotavirus vaccine effectiveness

In order to survey vaccine effectiveness in the long-term it is essential to use appropriate population-based sampling procedures among vaccinated and unvaccinated individuals. Routine surveillance of hospitalised cases caused by rotaviruses is encouraged. It is particularly important to test suspected rotavirus disease in fully immunised children to monitor possible rotavirus strain replacement. Generic study protocols for rotavirus vaccine effectiveness and impact studies are available should formal studies be needed (ECDC protocols available for case-control, cohort and impact studies - see footnote 14 below).

[14] Three generic study protocols for rotavirus vaccine effectiveness and impact studies using different methodologies are available on the ECDC website: http://ecdc.europa.eu/en/press/news/_layouts/forms/News_DispForm.aspx?ID=82&List=8db7286c-fe2d-476c-9133-18ff4cb1b568

5. Conclusions and possible implications for public health practice and research

Burden of disease studies assessing severe rotavirus disease leading to hospitalisation conducted in eighteen EU/EEA countries suggest that there are ~75 000–150 000 hospitalisations in children under five years annually, although mortality is low. Two rotavirus vaccines for use in routine immunisation programmes have been authorised for prevention of rotavirus-induced gastroenteritis and shown, in a series of studies, to be effective in preventing severe rotavirus-induced gastroenteritis leading to hospitalisation. Vaccine effectiveness against rotavirus-related hospitalisation ranges between 85–90% in countries with low mortality due to rotavirus disease (all EU/EEA countries are categorised as low-mortality countries). Furthermore, herd immunity contributes to the overall impact of vaccination programmes. A risk of up to six additional intussusception cases per 100 000 vaccinated infants has been identified for both rotavirus vaccines. Benefit-risk has been assessed by many regulatory agencies throughout the world (including EMA, FDA, and TGA) and was found to be positive, given the severity of rotavirus disease and availability of treatment for cases of intussusception. However, options for risk minimisation with the current vaccines should be explored. It is important for parents and healthcare workers to be vigilant to ensure that affected infants are promptly cared for, as recommended in the EU/EEA SPC. Research should be undertaken to further reduce this risk, for example by developing new rotavirus vaccines. Finally, available health economic models of cost-effectiveness for rotavirus vaccination should be shared so that they can be used by those EU/EEA countries interested. Moreover, the new option of EU-level joint procurement for Member States could also be explored.

The expert panel suggests the following set of data and monitoring to be considered at the EU-level and in EU/EEA Member States before and after introduction of rotavirus vaccine into a routine programme:

- consider developing a case-definition for severe rotavirus disease relevant for disease surveillance and epidemiological studies suitable to assess burden of disease and impact of implemented rotavirus immunisation programmes;
- consider organising case-based EU-wide, country-wide or sentinel surveillance of severe rotavirus disease leading to hospitalisation and/or death before and after vaccine introduction;
- consider investigating suspected and reporting laboratory-confirmed breakthrough rotavirus disease infections in fully vaccinated individuals (including genotyping and sequencing of causing rotavirus strain);
- consider organising virological surveillance in a statistically sound and geographically representative sample of circulating RV strains;
- consider collecting data on individual rotavirus vaccine exposure (including batch number) and overall rotavirus vaccine coverage;
- consider compiling country-specific background incidence rates of intussusception (by month of age during the first year of life) in additional EU/EEA Member States since geographical differences have been observed;
- assess long-term impact (including monitoring for strain replacement, vaccine effectiveness and safety) of rotavirus vaccines used in immunisation programmes from a statistically sound and geographically representative sample within the EU/EEA.

6. Strengths of methodology used in this expert opinion

The evidence for this report was collected using different methods: a literature review in PubMed, Embase and Cochrane databases, referrals to additional literature identified by a panel of experts and information on spontaneously reported cases of intussusception to the EMA Eudravigilance database.

Meta-analyses of rotavirus vaccine efficacy and effectiveness data are provided.

The opinion provided is based on scientific evidence identified in the literature review and the opinions of a group of independent EU/EEA public health experts reviewing the evidence.

7. Limitations of methodology used in this expert opinion

The literature search was limited to publications released until February 2014. The additional literature provided by the experts proved useful as it allowed the inclusion of relevant evidence that would have otherwise been omitted.

Although the literature search was made according to standards for a systematic review with meta-analysis, the evaluation was conducted with less resources than recommended for a systematic review (only one reviewer for some of the abstracts retrieved). Furthermore, it was impossible to grade the quality of evidence.

Additional limitations are that cases reported spontaneously to the EMA Eudravigilance database could not be confirmed by chart review due to data protection laws; there was no reliable denominator for rate calculation and no adjustment for under- or over-reporting.

8. Next steps

A draft expert opinion document will be posted for public consultation on the ECDC website in August 2016 for six weeks. An updated version of the scientific advice contained in this document will then be disseminated by ECDC through the European Commission's Directorate General for Health and Food Safety (SANTE), the Health Security Committee, the ECDC Advisory Forum and the ECDC Vaccine Advisory Group (EVAG). The document will also be published on the ECDC website.

9. Expert opinion update

Should new information relevant to public health and the use of rotavirus vaccines in immunisation programmes in the EU/EEA become available, this expert opinion will be updated.

10. Annexes

Annex 1. Rotavirus disease severity scales used in clinical trials

Availability of objective clinical severity scales for assessing the disease is important for vaccine efficacy and effectiveness studies. The two severity scales, the Vesikari 20-point scale and the Clark 24-point scale, used to assess rotavirus gastroenteritis in clinical trials differ and have recently been compared (Table A1) [270]. A comparison of the severity assessment results revealed that more than 50% of the cases defined as severe by the Vesikari scale were defined as moderate (63%) and mild (2%) by the Clark scale. Furthermore, 19% defined as mild by the Clark scale were defined as severe by the Vesikari scale. It was also impossible to analyse the results from the two severity scales statistically because the distribution categories were not even; the Clark scale is divided into three ranges (<9, 9-16 and >16), while the Vesikari scale is divided into two ranges (<11 and >11). The authors attempted to further divide the children in the study by creating three categories using the Vesikari scale. This improved the correlation between the two scales but still did not achieve a high correlation, since only 55% of those with a scoring of >15 in the Vesikari scale were defined as severe by the Clark scale. The authors concluded that future rotavirus vaccine trials should use only one severity scale for uniformity, or use clinical parameters fitting to both the Clark and Vesikari scales, enabling the calculation of both severity scores. This would facilitate the interpretation of the efficacy results and comparisons between current and future rotavirus vaccines.

Table A1. Overview of the Clark 24-point and the Vesikari 20-point severity scoring scales used in the efficacy trials

	Point values		
	1	2	3
Clarke scale (ref)			
Diarrhoea			
Number of stools/day	2-4	5-7	≥8
Duration in days	1-4	5-7	≥8
Vomiting			
Number of emeses/day	1-3	4-6	≥7
Duration in days	2	3-5	≥6
Rectal temperature			
Temperature (C°)	38.1-38.2	38.3-38.7	≥38.8
Duration in days	1-2	3-4	≥5
Behavioural symptoms/ signs			
Description	Irritable/less playful	Lethargic/listless	Seizure
Duration in days	1-2	3-4	≥5
Vesikari scale (ref)			
Duration of diarrhoea (days)	1-4	5	≥6
Maximum number of diarrhoea stools/24h	1-3	4-5	≥6
Duration of vomiting (days)	1	2	≥3
Maximum number of vomiting episodes/24h	1	2-4	>5
Temperature (C°)	37.1-38.4	38.5-38.9	>39.0
Dehydration	-	Mild	Moderate to severe
Treatment	Rehydration	Hospitalisation	-

According to the Vesikari scale, an episode of gastroenteritis with a score of ≥11 is considered severe, while the Clark scale considers an episode with a score 9–16 as moderate to severe and an episode with a score of >16 as severe.

Annex 2. Brighton collaboration diagnostic criteria for intussusception

Diagnostic certainty [94]	
Level 1	• Surgical criteria – demonstration of invagination of the intestine at surgery • Radiological criteria – demonstration of invagination of the intestine by air or barium contrast enema or intra-abdominal mass, demonstrated by ultrasound that is proven to be reduced by enema on post-reduction ultrasound.
Level 2	• Two major or one major and three minor criteria (see below)
Level 3	• Four or more minor criteria (see below)

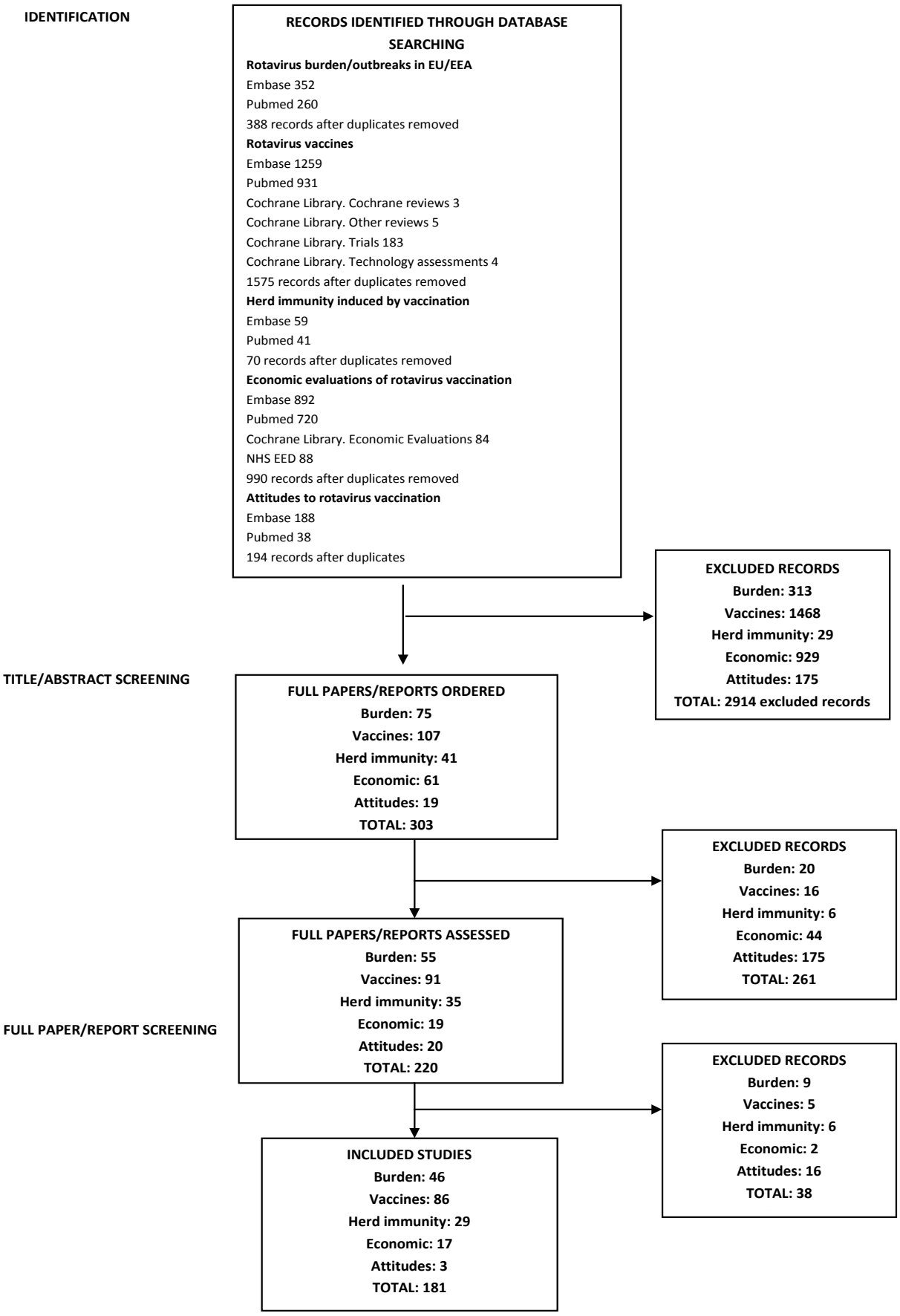
Major criteria	Minor criteria
Evidence of intestinal obstruction • History of bile-stained vomiting • Abdominal distension or no bowel sounds • Radiograph showing fluid levels and dilated bowel loops Features of intestinal invagination • Abdominal mass or rectal mass or intestinal prolapse or radiographs/ultrasound showing a visible intussusceptum or soft tissue mass. Evidence of intestinal vascular compromise or venous congestions • Passage of blood per rectum or blood detected on rectal examination or passage of stool containing 'red currant jelly' material.	Age <1 year Male sex Abdominal pain Vomiting Lethargy Pallor Hypovolemic shock Radiograph showing abnormal but non-specific bowel-gas pattern.

Annex 3. Checklist for vaccinators submitting intussusception ADR reports

The following information will be helpful for assessors of ADR reports:

- Date of birth
- Gender of infant
- Vaccine provided, including batch number
- Vaccine dose number in series provided
- Date of vaccination
- Date of onset of symptoms suggestive of intussusception
- Intussusception confirmed by radiology or surgery
- Date of first treatment, please specify treatment (e.g. barium/air enema or surgery)
- Date of second treatment if needed, please specify treatment (e.g. barium/air enema or surgery)
- Other treatments provided
- Clinical complications observed, please specify complications
- Need for intensive care
- Any sequelae (including if and how much intestinal resection was needed)?
- Length and dates of hospitalisation
- Copy of discharge note
- Copy of confirmatory radiology/ultrasound test and, if available, surgical report.

Annex 4. Overview of search strategies and results



Annex 5. Search strategies for rotavirus expert opinion

Rotavirus burden of disease/outbreaks in Europe

Pubmed

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#2 'adverse drug reaction'/exp OR 'adverse effect':ti,ab OR 'adverse effects':ti,ab OR 'side effects':ti,ab OR 'side effect':ti,ab OR 'adverse reaction':ti,ab OR 'adverse reactions':ti,ab OR 'undesirable effects':ti,ab OR 'undesirable effect':ti,ab OR 'injurious effect':ti,ab OR 'Injurious effects':ti,ab OR 'complication':ti,ab OR complications:ti,ab OR 'immunology'/exp OR immunology:ti,ab OR 'pharmacology'/exp OR pharmacology:ti,ab OR immunogenicity:ti,ab

OR toxicity:ti,ab OR toxicities:ti,ab OR toxic:ti,ab OR contraindicat*:ti,ab OR hazard*:ti,ab OR harm:ti,ab OR danger:ti,ab OR dangers:ti,ab OR dangerous:ti,ab OR poisoning:ti,ab OR 'safety'/exp OR safe:ti,ab OR safety:ti,ab OR safely:ti,ab OR intussusceptions:ti,ab OR 'intussusception'/exp OR Intussusception:ti,ab OR 'treatment outcome'/exp OR 'drug efficacy'/exp OR efficacy:ti,ab OR effective:ti,ab OR effectiveness:ti,ab OR effectivity:ti,ab OR efficiency:ti,ab OR 'risk'/exp OR 'risk benefit analysis'/exp OR risk:ti,ab OR risks:ti,ab OR benefit:ti,ab OR benefits:ti,ab OR 'therapeutic use':ti,ab OR unfavorable:ti,ab

#3 'practice guideline'/exp OR 'Practice Guideline':ti,ab OR 'Practice Guidelines':ti,ab OR 'practice parameter':ti,ab OR 'practice parameters':ti,ab OR guideline:ti,ab OR guidelines:ti,ab OR consensus:ti OR recommendation:ti OR recommendations:ti OR 'consensus development'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti OR 'clinical trial (topic)'/exp OR 'case control study'/exp OR (case NEAR/3 control):ab,ti OR 'cohort analysis'/exp OR (cohort NEAR/3 (study OR studies)):ab,ti OR (cohort:ab,ti AND analys*:ab,ti) OR (follow*up NEAR/3 (study OR studies)):ab,ti OR (observational NEAR/3 (study OR studies)):ab,ti OR longitudinal:ab,ti OR retrospective:ab,ti OR 'cross-sectional study'/exp OR (cross:ab,ti AND sectional:ab,ti) OR 'meta analysis'/exp OR 'meta analysis':ti,ab OR 'meta analyses':ti,ab OR metaanal*:ti,ab OR 'systematic review'/exp OR (systematic NEAR/3 (review* OR overview)):ti,ab OR 'systematic review (topic)'/exp OR 'review'/exp OR review:ti

#4 #1 AND #2 AND #3

#5 'animal'/exp NOT 'human'/exp

#6 #4 NOT #5

Limits: English, date from 1995 , Embase

Cochrane Library (Cochrane systematic reviews, other reviews, clinical trials)

#1 MeSH descriptor: [Rotavirus Infections] explode all trees

#2 MeSH descriptor: [Rotavirus] explode all trees

#3 rotavirus:ti,ab,kw or rotaviruses:ti,ab,kw or "rota virus":ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Vaccinnes] explode all trees

#6 MeSH descriptor: [Immunization] explode all trees

#7 vaccine*:ti,ab,kw or vaccination*:ti,ab,kw or immunization*:ti,ab,kw or immunisation*:ti,ab, kw

#8 #5 or #6 or #7

#9 MeSH descriptor: [Rotavirus Vaccines] explode all trees

#10 rotarix:ti,ab,kw or rotateq:ti,ab,kw or Rotashield:ti,ab,kw or "RIX4414 vaccine":ti,ab,kw or "RIX4414 vaccines":ti,ab,kw

#11 #10 or #9

#12 #4 and #8

#13 #11 or #12

Limits: EnglisH, date from 1995

Herd immunity

Pubmed

#1 (("Rotavirus Infections"[Mesh] OR "Rotavirus"[Mesh] OR rotavirus[tiab] OR rotaviruses[tiab] OR "rota virus"[tiab]) AND ("Vaccination"[Mesh] OR "Vaccines"[Mesh] OR Vaccine*[tiab] OR vaccine*[tiab] OR vaccination*[tiab] OR immunization*[tiab] OR "Viral Vaccines"[Mesh])) OR "Rotavirus Vaccines"[Mesh] OR "RIX4414 vaccine"[Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR rotarix[tiab] OR rotateq[tiab] OR Rotashield[tiab] OR "RIX4414 vaccine"[tiab] OR "RIX4414 vaccines"[tiab]

#2 "herd immunity"[tiab] OR "Immunity, Herd"[Mesh]

#3 #1 AND #2

Limits: English, date from 1995

Embase

#1 (('Rotavirus infection'/exp OR 'Rotavirus'/exp OR rotavirus:ti,ab OR rotaviruses:ti,ab OR 'rota virus':ti,ab) AND ('vaccination'/de OR 'vaccine'/exp OR vaccine*:ti,ab OR vaccination*:ti,ab OR immunization*:ti,ab OR 'virus vaccine'/exp)) OR 'Rotavirus vaccine'/exp OR rotarix:ti,ab OR rotateq:ti,ab OR Rotashield:ti,ab OR 'RIX4414 vaccine':ti,ab OR 'RIX4414 vaccines':ti,ab

#2 'herd immunity'/exp OR 'herd immunity':ab,ti

#3 #1 AND #2

Limits: English, date from 1995, Embase

Cost benefit analysis/burden

Pubmed

#1 (("Rotavirus Infections"[Mesh] OR "Rotavirus"[Mesh] OR rotavirus[tiab] OR rotaviruses[tiab] OR "rota virus"[tiab]) AND ("Vaccination"[Mesh] OR "Vaccines"[Mesh] OR vaccine*[tiab] OR vaccination*[tiab] OR immunization*[tiab] OR "Viral Vaccines"[Mesh])) OR "Rotavirus Vaccines"[Mesh] OR "RIX4414 vaccine"[Supplementary Concept] OR "RotaTeq" [Supplementary Concept] OR "rhesus rotavirus vaccine" [Supplementary Concept] OR "rotavirus vaccine 89-12" [Supplementary Concept] OR rotarix[tiab] OR rotateq[tiab] OR Rotashield[tiab] OR "RIX4414 vaccine"[tiab] OR "RIX4414 vaccines"[tiab]

#2 Costs and Cost Analysis"[Mesh] OR ec[sh] OR "Economics"[Mesh] OR Cost[tiab] OR costs[tiab] OR economic*[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR (expenditure*[tiab] NOT energy[tiab]) OR "Cost effective"[tiab] OR "Cost effectiveness"[tiab] OR "value for money"[tiab] OR budget*[tiab] OR burden[tiab] OR burdens[tiab]

#3 #1 AND #2

Limits: English, date from 1995

Embase

#1 'rotavirus infection'/exp OR 'rotavirus'/exp OR rotavirus:ab,ti OR rotaviruses:ab,ti OR 'rota virus':ab,ti AND ('vaccination'/de OR 'vaccine'/exp OR vaccine*:ab,ti OR vaccination*:ab,ti OR immunization*:ab,ti OR 'virus vaccine'/exp) OR 'rotavirus vaccine'/exp OR rotarix:ab,ti OR rotateq:ab,ti OR rotashield:ab,ti OR 'rix4414 vaccine':ab,ti OR 'rix4414 vaccines':ab,ti

#2 'economic aspect'/exp AND 'economics'/exp AND 'economic evaluation'/exp OR Cost:ab,ti OR costs:ab,ti OR economic*:ab,ti OR costly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices:ab,ti OR pricing:ab,ti OR pharmacoeconomic*:ab,ti OR (expenditure*:ab,ti NOT energy:ab,ti) OR 'Cost effective':ab,ti OR 'Cost effectiveness':ab,ti OR 'value for money':ab,ti OR budget*:ab,ti OR burden:ab,ti OR burdens:ab,ti

#3 #1 AND #2

Limits: English, date from 1995, Embase

Cochrane Library

1 MeSH descriptor: [Rotavirus Infections] explode all trees

#2 MeSH descriptor: [Rotavirus] explode all trees

#3 rotavirus:ti,ab,kw or rotaviruses:ti,ab,kw or "rota virus":ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Vaccination] explode all trees

#6 MeSH descriptor: [Vaccines] explode all trees

#7 MeSH descriptor: [Immunization] explode all trees

#8 vaccine*:ti,ab,kw or vaccination*:ti,ab,kw or immunization*:ti,ab,kw

#9 #6 or #7 or #8

#10 MeSH descriptor: [Rotavirus Vaccines] explode all trees

#11 rotarix:ti,ab,kw or rotateq:ti,ab,kw or Rotashield:ti,ab,kw or "RIX4414 vaccine":ti,ab,kw or "RIX4414 vaccines":ti,ab,kw

#12 #11 or #10

#13 #5 and #9

#14 #12 or #13

Limits: English, date from 1995

CRD HTA

((rotavirus)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) FROM 1995 TO 2014

Attitude to rotavirus vaccination

Pubmed

#1 (("Rotavirus Infections"[Mesh] OR "Rotavirus"[Mesh] OR rotavirus[tiab] OR rotaviruses[tiab] OR "rota virus"[tiab]) AND ("Vaccination"[Mesh] OR "Vaccines"[Mesh] OR vaccine*[tiab] OR vaccination*[tiab] OR immunization*[tiab] OR "Immunization"[Mesh] OR immunisation*[tiab] OR "Viral Vaccines"[Mesh])) OR "Rotavirus Vaccines"[Mesh] OR "RIX4414 vaccine"[Supplementary Concept] OR "RotaTeq"[Supplementary Concept] OR "rhesus rotavirus vaccine"[Supplementary Concept] OR "rotavirus vaccine 89-12"[Supplementary Concept] OR rotarix[tiab] OR rotateq[tiab] OR Rotashield[tiab] OR "RIX4414 vaccine"[tiab] OR "RIX4414 vaccines"[tiab]

#2 "Attitude"[Mesh] OR "Health Behavior"[Mesh] OR "Life Style"[Mesh] OR "Health Promotion"[Mesh] OR attitude[ti] OR attitudes[ti] OR "health personnel attitude"[tiab] OR "health personnel attitudes"[tiab] OR "family attitude"[tiab] OR "family attitudes"[tiab] OR "parental attitude"[tiab] OR "parental attitudes"[tiab] OR "paternal attitude"[tiab] OR "paternal attitudes"[tiab] OR "staff attitude"[tiab] OR "staff attitudes"[tiab] OR behaviour[ti] OR behaviours[ti] OR behaviors[ti] OR behavior[ti] OR perception[ti] OR perceptions[ti] OR acceptance[ti] OR "health attitude"[tiab] OR "health attitudes"[tiab] OR "health behaviors"[tiab] OR "health behavior"[tiab] OR "health behaviour"[tiab] OR "health behaviours"[tiab] OR "life style"[tiab] OR "life styles"[tiab] OR lifestyle[ti] OR lifestyles[ti] OR "patient nonadherence"[tiab] OR "patient noncompliance"[tiab] OR refusal[tiab] OR elopement[tiab] OR compliance[tiab] OR "promotion of health"[tiab] OR "health promotion"[tiab] OR "wellness program"[tiab] OR "wellness programme"[tiab] OR "wellness programmes"[tiab] OR "wellness programming"[tiab] OR "wellness programs"[tiab] OR "health campaign"[tiab] OR "health campaigns"[tiab]

#3 #1 AND #2

Limits: English, date from 1995

Embase

#1 'rotavirus infection'/exp OR 'rotavirus'/exp OR rotavirus:ab,ti OR rotaviruses:ab,ti OR 'rota virus':ab,ti AND ('vaccination'/de OR 'vaccine'/exp OR vaccine*:ab,ti OR vaccination*:ab,ti OR immunization*:ti,ab OR 'immunization'/exp OR immunisation*:ti,ab OR 'virus vaccine'/exp) OR 'rotavirus vaccine'/exp OR rotarix:ab,ti OR rotateq:ab,ti OR rotashield:ab,ti OR 'rix4414 vaccine':ab,ti OR 'rix4414 vaccines':ab,ti

#2 'attitude'/exp OR 'health behavior'/exp OR 'lifestyle'/exp OR 'health promotion'/exp OR attitude:ti OR attitudes:ti OR 'health personnel attitude':ab,ti OR 'health personnel attitudes':ab,ti OR 'family attitude':ab,ti OR 'family attitudes':ab,ti OR 'parental attitude':ab,ti OR 'parental attitudes':ab,ti OR 'paternal attitude':ab,ti OR 'paternal attitudes':ab,ti OR 'maternal attitude':ab,ti OR 'maternal attitudes':ab,ti OR 'staff attitude':ab,ti OR 'staff attitudes':ab,ti OR behaviours:ti OR behaviour:ti OR behavior:ti OR behaviours:ti OR perception:ti OR perceptions:ti OR acceptance:ti OR 'health attitude':ab,ti OR 'health attitudes':ab,ti OR 'health behaviors':ab,ti OR 'health behavior':ab,ti OR 'health behaviour':ab,ti OR 'health behaviours':ab,ti OR 'life style':ab,ti OR 'life styles':ab,ti OR lifestyle:ti OR lifestyles:ti OR 'patient nonadherence':ab,ti OR 'patient noncompliance':ab,ti OR refusal:ab,ti OR elopement:ab,ti OR compliance:ab,ti OR 'promotion of health':ab,ti OR 'health promotion':ab,ti OR 'wellness program':ab,ti OR 'wellness programme':ab,ti OR 'wellness programmes':ab,ti OR 'wellness programming':ab,ti OR 'wellness programs':ab,ti OR 'health campaign':ab,ti OR 'health campaigns':ab,ti

#3 #1 AND #2

Limits: English, date from 1995, Embase

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