National Institute for Public Health
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Ministry of Health, Welfare and Sport

Rotavirus in the Netherlands

Background information for the
Health Council

RIVM Report 2017-0021
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Synopsis

Rotavirus in the Netherlands
Background information for the Health Council

Rotavirus can cause a gastrointestinal infection and is common in young children. There are two vaccines available; both have to be administered via the mouth. The Dutch Health Council will advise the Ministry of Health, Welfare and Sport on how childhood vaccination against rotavirus will be made available. The Minister makes a decision on the basis of this advice.

To support the Health Council, the RIVM has put together background information on rotavirus disease. The information includes the number of people in the Netherlands that become ill from rotavirus every year, the effectiveness and safety of rotavirus vaccines, and how the public thinks about rotavirus vaccination.

A gastrointestinal infection caused by rotavirus is common during the winter months, particularly in children between six months and two years old. The disease is characterized by fever, vomiting and diarrhoea. Usually, rotavirus disease resolves by itself without problems, but can be severe resulting in dehydration. This happens more often in young children, premature children, children with low birth weight and children with congenital problems. These severe cases may need to be admitted to the hospital. Treatment for dehydration consists of oral or intravenous rehydration. In rare cases, a child dies.

Keywords: rotavirus, rotavirus vaccination, burden of disease, cost-effectiveness, safety, acceptation, aspects of implementation

Publiekssamenvatting

Rotavirus in Nederland
Achtergrond informatie voor de Gezondheidsraad

Het rotavirus kan een maagdarminfectie veroorzaken die veel voorkomt bij jonge kinderen en soms ernstig kan verlopen. Er zijn twee vaccins beschikbaar die beide in druppelvorm via de mond worden toegediend. De Gezondheidsraad gaat de minister van VWS adviseren op welke manier vaccinatie van kinderen tegen het rotavirus toegankelijk wordt. De minister neemt op basis van dit advies een besluit.

Om de Gezondheidsraad te ondersteunen heeft het RIVM achtergrondinformatie over het rotavirus bijeengebracht. De informatie betreft onder andere het aantal personen dat er jaarlijks in Nederland ziek door wordt, de effectiviteit en veiligheid van de vaccins, en hoe het publiek denkt over deze vaccinatie.

Een door het rotavirus veroorzaakte maagdarminfectie komt veel in de wintermaanden voor, vooral bij kinderen tussen de 6 maanden en 2 jaar. De ziekte gaat gepaard met koorts, braken en hevige, waterdunne diarree. Doorgaans verloopt de ziekte zonder problemen, maar het komt voor dat de ziekte ernstig verloopt. Dit gebeurt vaker bij jonge kinderen, te vroeg geboren kinderen, kinderen met een laag geboortegewicht, of kinderen met aangeboren afwijkingen. De ziekte kan dan uitdrogingsgevaar veroorzaken. In deze gevallen moet een kind in het ziekenhuis worden opgenomen. De uitdroging wordt dan behandeld door via de mond of een infuus vocht toe te dienen. In zeldzame gevallen overlijdt een kind.

Kernwoorden: rotavirus, rotavirus vaccinatie, ziektelast, kosteneffectiviteit, veiligheid, acceptatie, invoeringsaspecten

Contents

Summary

Rotavirus (RV) is a double-stranded RNA virus that is highly contagious. The virus is mainly transmitted via the direct or indirect contact (faecal-oral) route. RV infection is characterized by a triad of unspecific symptoms, namely diarrhoea, fever and vomiting. Because of these non-specific clinical features and stool characteristics, diagnostic testing is the only way to confirm that the gastroenteritis (GE) is caused by RV.

Vomiting and diarrhoea can quickly lead to dehydration, which is particularly dangerous for very young children and the elderly. Rehydration is given as supportive treatment to prevent or treat dehydration. Premature children and children with low birth weight or congenital pathology are more likely to be hospitalized, to have a longer stay in hospital and to require intensive care. The estimated annual number of hospitalizations in children under five years of age was about 3,500 in the period 2010–2016. One study estimated the number of child deaths in the Netherlands due to RV at around seven per year. Deaths were observed solely among risk-group children. The national estimate of the disease burden due to RV infection for the years 2012–2014 is 1,255 Disability Adjusted Life Years (DALYs) per year.

Overall, in the Netherlands G1P[8] was the most prevalent RV strain in 2008–2012, while thereafter G9P[8] and G4P[8] are upcoming, with G4P[8] being the most prevalent strain in 2015. In the Netherlands, RV incidence follows an annual seasonal pattern; the epidemic starts in January and ends in April/May, with a peak in February/March. However, annual variation in the intensity of RV epidemics is observed. In 2014, the number of RV detections was exceptionally low and followed a delayed seasonal pattern. The 2015 season was average in intensity and timing, but in 2016 the number of RV detections was again remarkably low and the seasonal pattern delayed, comparable to 2014. This could indicate a transition to a biannual RV epidemic pattern in the Netherlands, as observed in some countries with moderate to high RV vaccine coverage rates. Future years will confirm whether this pattern continues.

Two oral RV vaccines have been approved for the European market: Rotarix, a monovalent human RV vaccine, and RotaTeq, a pentavalent human-bovine reassortant vaccine. Both vaccines are live attenuated and should be administered as an oral liquid as two (Rotarix) or three (RotaTeq) infant doses. Across Europe, vaccine effectiveness against severe rotavirus GE for Rotarix and RotaTeq ranges from 78% to 92.8%. The reported vaccine impact on RV hospitalizations in the population under five years varies between 65% and 84% reduction. Overall, both RV vaccines are well tolerated and have low reactogenicity. Given the experience with the previously marketed Rotashield vaccine, particular attention was given in pre-licensure trials to the occurrence of intussusception. Although extensive pre-licensure trials did not show an increased risk of intussusception after either Rotarix or RotaTeq vaccination, post-licensure surveillance has shown a slight increase in the risk of intussusception in the first week after the first vaccine dose,

with an absolute increased risk of intussusception of 1 to 6 cases per 100,000 vaccine recipients.
With regard to possible acceptance of RV vaccination, a discrete choice experiment estimated vaccination uptake of 23% and 86%, depending on the vaccination scenario and implementation strategy.

The major factors that determine whether universal RV vaccination is cost-effective or not are vaccine-related costs, the perspective chosen (societal or third-party payer), discounting, the proportion of cases requiring medical services, the case fatality rate and herd immunity. One cost-effectiveness analysis reported that targeted RV vaccination of high-risk infants with either vaccine (Rotarix or RotaTeq) was cost-effective in the Netherlands, from both the societal and healthcare payer perspective, and potentially cost-saving. However, published cost-effectiveness studies date from a few years ago and thus do not take into account the lower epidemic years (i.e. 2014 and 2016).

Both RV vaccines can be administered simultaneously with other childhood vaccines. For the Netherlands, where vaccination would be incorporated in the NIP, the RV vaccination could be given at 8, 12 and, in the case of RotaTeq, 16 weeks of age simultaneously with the other NIP vaccines given at 8, 12 and 16 weeks.

1 Introduction

In this report, we present relevant background information to support the discussion on the potential introduction of vaccination against rotavirus (RV) disease in the Netherlands. The background information provided in this report will be of use to the Health Council in the Netherlands in preparing RV vaccination advice. We use Health Council criteria to structure the report and thus provide information for a well-informed debate. Chapter 2 provides some background information about RV, the epidemiology and burden of disease in the Netherlands. Chapter 3–6 focus on vaccine effectiveness, safety, acceptance and cost-effectiveness. The final chapter discusses some practical aspects that would need to be considered if universal or targeted RV vaccination would be introduced in the Netherlands.

2 Characteristics of rotavirus disease

Section 2.1 provides some background information on rotavirus (RV). Section 2.2 describes the situation in the Netherlands regarding RV epidemiology, the disease and the disease burden, and Sections 2.4 and 2.5 provide information about RV disease globally.

2.1 Background information on rotavirus

Pathogen
Rotavirus is a double-stranded RNA virus, discovered in young children in 1973 [1]. By electron microscopy, the virus particle has a wheel-like appearance, which is why the virus is named after the Latin word for wheel: rota [2].

The RV particle consists of three protein layers surrounding the viral genome: structural proteins VP1, VP2 and VP3 form the inner layer, the intermediate layer is made up of VP6 and the outer layer is composed of VP4 and VP7 [3]. On the basis of the amino acid sequence of VP6, RV can be divided into seven groups (A–G). Rotavirus groups A, B and C are associated with infection in humans, A being the most common and frequent group. Group A rotaviruses can be further classified into G types, based on the VP7 protein, and P types according to the VP4 protein. More than 70 different G–P combinations have been discovered [3].

Transmission
Rotavirus is highly contagious and is mainly transmitted via the direct or indirect contact (faecal-oral) route. Symptomatic patients may shed as much as 10^{10} RV virus particles per gram of stool [4]. The virus can survive on hands and retains its infectivity for several hours [5]. Because of prolonged virus survival (up to 60 days) on inanimate surfaces, such as toys and door handles, these serve as important sources of transmission [6, 7]. In temperate climates, RV transmission occurs mostly between late autumn and spring [8, 9], but this pattern tends to shift when universal RV vaccination is implemented [10]. In the Netherlands, where RV vaccination has not been implemented, the annual epidemic peak occurs between February and March [11].

Symptoms
The clinical features of RV gastroenteritis are non-specific and similar to those caused by other gastrointestinal pathogens. However, RV gastroenteritis tends to be more severe [12-15]. Following an incubation period of 1–3 days, the illness usually has an abrupt onset. Diarrhoea, vomiting and fever are the most common symptoms [16]. Gastrointestinal symptoms typically resolve within 4–8 days. However, vomiting and diarrhoea can lead quickly to dehydration, which can be dangerous, particularly for young children and elderly people. Timely rehydration is then required. The rate of RV gastroenteritis is highest in children under two years of age [17, 18].

Because the clinical features and stool characteristics caused by RV are non-specific, diagnostic testing is the only way to confirm that the gastroenteritis (GE) is caused by RV [19]. Detection of RV is possible by electron microscopy, ELISA and RT-PCR. ELISA is easy to use and provides fast results and is therefore most often used in laboratories [2]. In the Netherlands PCR is increasingly used by laboratories and can be used for genotyping. PCR is the most sensitive and specific test for RV [2].

Treatment
There is no specific treatment for RV, but supportive treatment to prevent or treat dehydration may be required. Oral rehydration salts, administered orally or by nasogastric tube, are effective in most cases. Occasionally, intravenous fluid replacement therapy is required.

2.2 Rotavirus epidemiology and disease burden in the Netherlands

Estimates of RV disease and disease burden in the Netherlands are based on laboratory-confirmed RV detections as reported by the Working Group Clinical Virology, national Hospital Discharge Data and primary care data from a large sentinel network of general practitioners (GPs) reported by NIVEL. In addition, several independent epidemiological studies have investigated RV incidence in the general (infant) population as well as hospitalizations due to RV.

Rotavirus detections reported by the Working Group Clinical Virology
Weekly RV positive test results are reported by a sentinel network of laboratories serving primary and secondary care. Rotavirus detections from January 2001 until December 2016 are shown in Figure 2.1.

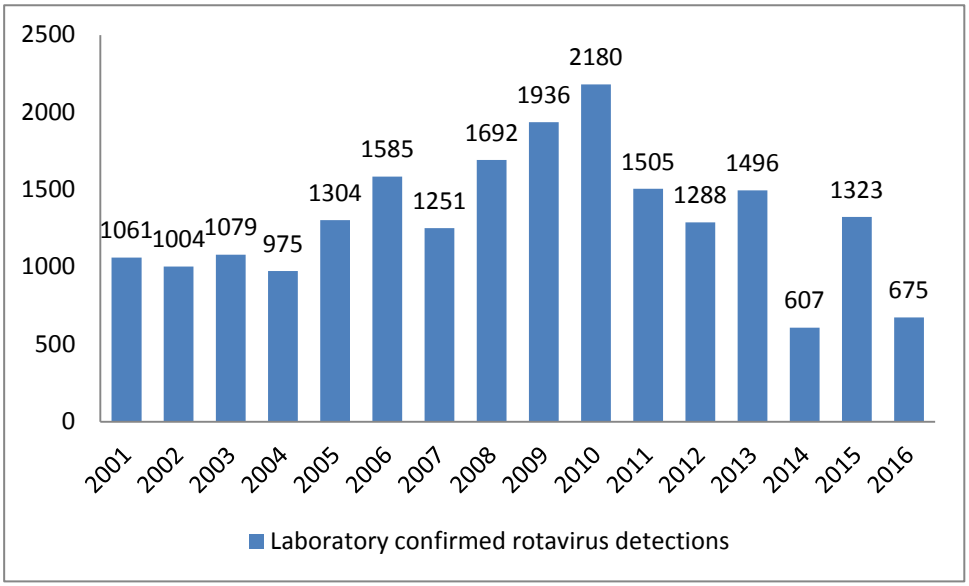


Figure 2.1 Number of reported laboratory-confirmed rotavirus detections by calendar year, 2001–2016

In general, RV incidence follows an annual seasonal pattern; the epidemic starts in January and ends in April-May, with a peak in February/March (Figure 2.2). Inter-seasonal variation in the intensity of rotavirus epidemics is observed with the highest numbers being

reported in 2010. In 2014, the number of rotavirus detections was exceptionally low and followed a delayed seasonal pattern [20]. The following 2015 season was average in intensity and timing, but in 2016 the number of RV detections was again remarkably low and the seasonal pattern delayed, comparable to 2014 (Figure 2.2).

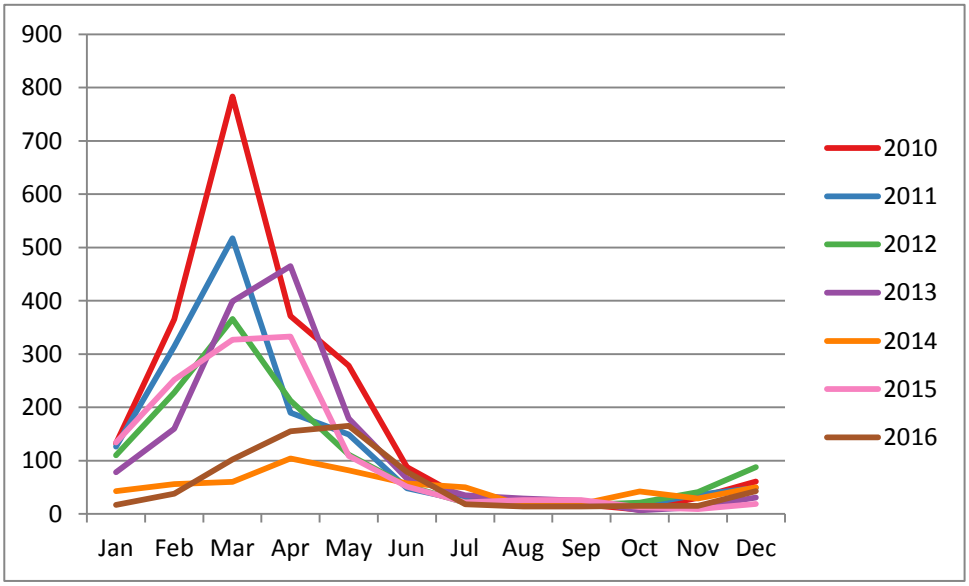


Figure 2.2 Seasonality of rotavirus laboratory-confirmed detections by calendar year, 2010–2016

A repeated low endemic 2016 season could indicate a transition to a biannual RV epidemic pattern in the Netherlands, as observed in some countries with moderate to high RV vaccine coverage rates. Future years will confirm whether this pattern continues. The origin of this recent change in epidemic pattern in the Netherlands is currently unknown and a focus of research at the RIVM.

So far, it has been demonstrated that the marked drop in RV detections in 2014 was associated with a reduced incidence of RV in the population, both symptomatic and asymptomatic, compared with the previous year. This suggests that 2014 was characterized by reduced circulation of RV in the population, rather than a shift in disease severity towards milder or asymptomatic infections [21]. In addition, a time-series analysis exploring the determinants of RV epidemiological patterns showed that proportions of susceptible individuals in the infant population and average daily temperatures were associated with RV incidence and could explain most of the observed seasonal and year-to year variability in RV detections between 2001 and 2013 [22]. However, for 2014, the model overestimated the magnitude of the seasonal peak, suggesting that other factors may have been instrumental in reducing the incidence that year.

GP consultations for all-cause gastroenteritis among children < 5 years of age

Data from a large sentinel network of GP practices, collected by NIVEL, were analysed for the years 2006–2014 to determine the all-cause acute

GE incidence rate among children aged 0–5 years (Table 2.1). Monthly incidence rates were compared with the monthly number of RV detections. The mean weekly GE consultation rate in under-five-year-olds in the GP sentinel surveillance for the RV epidemiological years 2006–2013 was 152 per 100,000 person-weeks (range: 111–201) [20]. The mean consultation rate for the 2013/14 epidemiological season was 97 per 100,000 (a 36% decrease) [20]. In accordance with RV laboratory detections, the decrease in GE consultations in 2014 was most pronounced during February (55%) and March (61%). Furthermore, there was no sign of the usual peak in February/March in GE consultations. GP consultations for all-cause GE in children under five by calendar year up to 2016 are shown in Table 2.1.

Table 2.1 Overview of laboratory diagnoses, GP consultations and hospitalizations for rotavirus in the Netherlands, 2001–2016

Year	Number of laboratory-confirmed RV detections	Mean weekly all-cause GE GP consultations per 100,000 child years under five[A]	Total of hospitalizations for acute gastroenteritis in the Netherlands[B]	Estimation of hospitalizations for acute GE in patients < 5 years [B]	Estimated number of hospitalizations attributable to RV in children < 5 years [C]
2001	1,061	-	17,964	6,054	3,431 (56.7%)
2002	1,004	-	19,016	6,172	3,388 (54.9%)
2003	1,079	-	21,490	7,191	3,585 (49.9%)
2004	975	-	22,386	6,423	3,251 (50.6%)
2005	1,304	-	24,536	7,681	4,473 (58.2%)
2006	1,585	160.9	28,662	9,305	5,244 (56.4%)
2007	1,251	144.9	28,247	8,039	3,855 (48.0%)
2008	1,692	170.7	32,224	9,564	4,635 (48.5%)
2009	1,936	166.5	32,102	8,408	5,095 (60.6%)
2010	2,180	153.0	36,376	8,682	5,932 (68.3%)
2011	1,505	123.3	35,651	7,980	4,048 (50.7%)
2012	1,288	117.7	36,128	7,435	3,455 (46.5%)
2013	1,496	155.3	34,323	6,920	3,952 (57.1%)
2014	607	91.4	32,624	5,330	1,613 (30.3%)
2015	1,323	*194.9*	-	-	3,508 (-)
2016	675	*158.0*	-	-	1,778 (-)

[A]Average per year. 2016 is reported up to week 27. For 2015 and 2016 there is an underestimation due to registration differences [23].

[B] Hospitalization data is available for the RIVM until 2014.

[C] Derived from van Pelt et al.[24]. RV hospitalizations for 2015 and 2016 are estimated on the basis of RV laboratory detections that year and regression estimates for the period 2010–2015. The method of RV estimation is described below.

Abbreviations: GE= gastroenteritis, GP= General practitioner, RV= rotavirus

National Hospital Discharge Data for all-cause gastroenteritis

Annual indirect estimates of RV hospitalization incidence in the Netherlands are made using a method developed by Harris et al. [25] based on the International Classification of Diseases discharge codes (ICD-9 codes 86–93 and 5589, ICD-10 A0, A09 and K52, K529, used from 2012 on) obtained from the national Hospital Discharge Database (Landelijke Medische Registratie) and weekly RV laboratory-confirmed detections (Table 2.1). For the years 1998–2008, estimates of RV

hospitalization incidence varied between 302 and 570/100,000 child-years under five, generating between 3,000 and 5,400 RV hospitalizations each year (average 3,500) [11, 24]. Since 2012, the numbers of RV hospitalizations have been slightly lower. In 2014 and 2016, low RV seasons were observed, with fewer estimated hospitalizations.

Figure 2.3 shows the estimated number of hospitalizations attributable to RV in children under 24 months of age. After six months of age, the number of children hospitalized for RV GE increases. This reflects the loss of maternal antibodies, protecting infants until six months of age. The number of RV hospitalizations decreases after the age of 12 months.

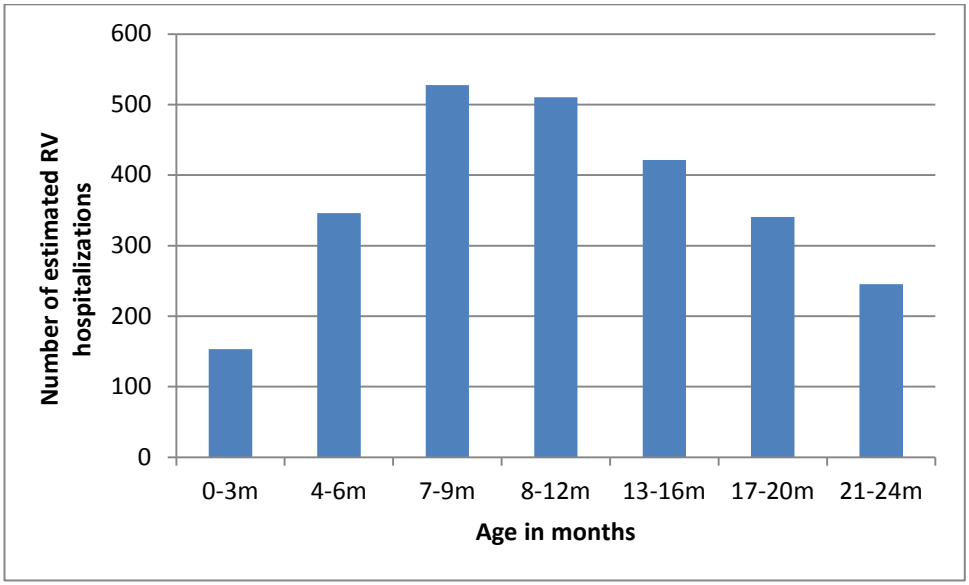


Figure 2.3 Estimated mean RV hospitalizations in children < 24 months of age, between 2001-2016. Abbreviations: m=months of age.

Figure 2.4 shows the estimated RV hospitalizations in all ages for the last five years. As is well known, most RV hospitalizations occur in children under 5 years. However, in recent years a small but steady increase in hospitalizations has been observed in the older population (above 50 years of age).

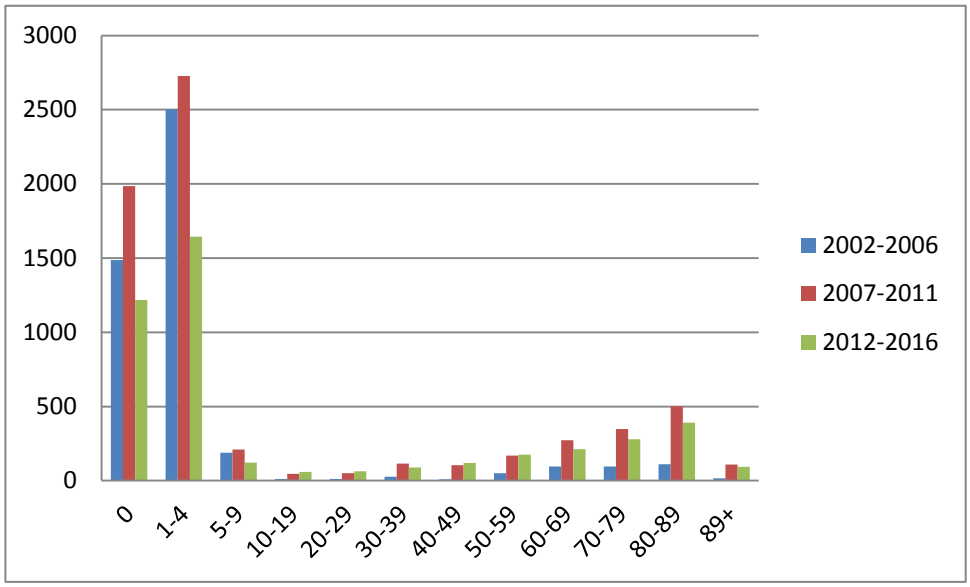


Figure 2.4 Estimated RV hospitalizations all ages (averages of the years 2002–2006, 2007–2011 and 2012–2016)

Studies on rotavirus incidence and hospitalizations
There have been three Dutch studies so far, estimating the incidence and numbers of rotavirus hospitalization in the paediatric population, using different methodological approaches (see Table 2.2).

In 1998, the Surveillance Unit of the Dutch Paediatric Society implemented an RV surveillance programme to obtain comprehensive national data on RV hospitalizations. The surveillance unit monitored the incidence of several paediatric diseases by sending monthly questionnaires to all paediatricians practising in Dutch hospitals. For the year 1998, paediatricians were asked to report all cases of RV hospitalization. In combination with hospital discharge data and RV diagnostics by the laboratory surveillance system, the number of hospital admissions for RV infection in the Netherlands was estimated. The study reported a total of 1,103 RV hospitalizations, corresponding to an incidence rate of 90/100,000 child-years for children under five [26].

A second study on paediatric GE hospitalizations was conducted in six hospitals between May 2008 and November 2009 [27]. Study periods per hospital varied between 8 and 19 months. 144 patients between 0 and 15 years with GE symptoms on admission were included, of whom 73% were younger than two years. From these 144 patients, 97 stool samples were obtained; these tested positive for RV in 54 cases (56%). Sixty-six percent of the 0–1-year-old cases had rotavirus, compared with 31% of the 2–4-year-old cases and none of the older children. The estimated incidence of all-cause GE admissions was 940/100,000 and for RV-related hospitalizations (56%) the incidence was 530/100,000 child-years. Thus, there were 5,000–5,500 RV hospitalizations per year among children under five.

A third study used active prospective surveillance for acute GE in four hospitals during the 2011 RV season, supplemented by retrospective

five-year data (2006–2010) on laboratory-confirmed RV hospitalizations from the same hospitals to estimate the incidence and number of RV hospitalizations of children under 15 [28]. Stool testing for RV was done by commercially available enzyme-immunoassays in all participating hospitals during both study-periods. The study also included nosocomial rotavirus infections. Four study hospitals participated: The Wilhelmina Children's Hospital (University Medical Centre Utrecht), a 220-bed paediatric tertiary care facility, and three general hospitals with paediatric and infant wards providing mainly secondary care (Diakonessen Hospital, Utrecht; Spaarne Hospital, Hoofddorp; Kennemer Hospital, Haarlem). The four hospitals together represented approximately 6% of all paediatric hospitalizations in the Netherlands. An average annual incidence of 4,870 RV hospitalizations was estimated for the years 2006 and 2010. This estimation is based on laboratory confirmed cases identified between 2006 and 2010, multiplied by a correction factor for RV underdetection derived from the 2011 prospective surveillance.
Next, numbers were extrapolated to the Netherlands as a whole, taking into account differences in patient population in general and specialized hospitals. It can thus be used as an overall estimate [28].
Hospitalizations lasted on average 3.7 days in general hospitals and 5.6 days in tertiary care centres, representing between € 2,180 and € 2,550 in healthcare costs. In 57% of nosocomial RV infections, the duration of hospitalization was prolonged resulting in 3.0 excess hospital days on average and an extra € 2,000- 2,130 in healthcare costs per nosocomial infection.

An RIVM report on GE in 2007 in the Netherlands estimated that about half of the acute GE (AGE) hospitalizations in children under five years could be attributed to RV [24], resulting in approximately 3,500 hospitalizations per year. Estimations were performed using the technique by Harris et al. mentioned above [25]. In addition, a slight increase is observed in RV hospitalizations in the older population: the proportion of rotavirus hospital admissions that occurred in patients 60 years and older increased from 1% at the beginning of this century to about 10% in 2013 [23, 24].

All the above-mentioned studies were performed before 2010. Given the remarkable change in RV season and RV incidence since 2014, new studies are needed to give up-to-date estimations of RV-related hospitalizations.

Table 2.2 Annual number of paediatric rotavirus-related hospitalizations estimated in different studies

	Study period	**Method**	**Age-group (years)**	**Estimated annual number of rotavirus hospitalizations**
Bruijning-Verhagen et al.[28]	2006–2010	Numbers of RV hospitalizations were determined from 5-year data on confirmed RV hospitalizations and adjusted for RV underreporting, assessed through active surveillance for AGE during the 2011 RV season	0–5	- 4,870 hospitalizations/year - Incidence rate of 510/100,000 child-years
Friesema et al.[27]	May 2008–November 2009	In six hospitals, faecal samples of symptomatic cases were tested and a questionnaire was filled in	0–5	- 5,000-5,500 hospitalizations/year - Incidence rate of 530/100,000 child-years
de Wit et al.[26]	1998	All Dutch paediatricians were asked to report all cases of RV hospitalization and filled in a questionnaire per case. Case definition: microbiologically confirmed infection	0–5	- 1,103 hospitalizations/year - Incidence rate of 90/100,000 child-years
van Pelt et al.[24]	1998–2008	Hospital discharge data and weekly RV detections using regression analysis method developed by Harris et al. [25]	0–5	- Average of 3,500 hospitalizations/year - Incidence rate of 302 to 570/100,000 child-years

Rotavirus hospitalizations in relation to other causative pathogens
As described above, the RIVM report of 2007 stated that half of the acute GE hospitalizations in children under five years were attributable to rotavirus. There is one other Dutch study determining the aetiology of GE hospitalizations. This study [27] showed that in children 0–15 years old, viruses were detected in 82% (N=79), bacteria in 32% and parasites in 10% of the samples. Of the 79 samples where viruses were detected, RV was the major cause of GE hospitalization (56%), followed by adenovirus (23%) and norovirus (16%).

In children aged 0–1 years, viruses were detected in 96% (71/74) of the cases; the detection rate decreased to 40% (4/10) in the 2–3-year-olds and 17% (2/12) in the children aged 4 years or older. Of the 0–1-year-old cases, 66% had RV, compared with 31% of the 2–4-year-old cases and none of the older children. Rotavirus was mostly found during winter, while norovirus and adenoviruses were both seen throughout the year. The authors indicated that 8 out of 54 children with RV had not reached the age for full RV vaccination. Bacteria were seen less frequently in the youngest children (26%, 0–1 years) than in older children (55%). No parasites were detected in the cases younger than 1 year.

Burden of disease
In the State of Infectious Diseases in the Netherlands 2016 [29], national burden of disease estimates expressed in Disability Adjusted Life Years (DALYs) were presented for 35 infectious diseases in the period 2012–2014. The DALYs metric measures and integrates both morbidity (i.e. years lived with disability (YLD)) and premature mortality (i.e. years of life lost (YLL)). The estimated average annual burden for new cases for the period 2012–2014 were estimated. Rotavirus infection has a relatively low burden at the individual level (0.6 DALYs/100 infections), whereas the disease burden at the population level (1,255 DALYs/year) is rather high. The majority (65%) of the burden is due to life years lost: a total of 820 YLL/year from the 36 fatalities, the majority of them being elderly people (> 25 cases/year), and only 2–3 being children younger than 5 years[1].

2.3 Risk Groups and mortality

An observational study in the Netherlands (RoHo study [28]) demonstrated that children with underlying medical conditions are substantially overrepresented among RV-related hospitalizations [30]. The study consisted of a retrospective observational study to determine the number and characteristics of laboratory-confirmed hospitalized RV patients and the seasonal pattern over a five-year period (described in Section 2.2).

In the RoHo study, the medical records of all confirmed RV patients identified in clinical laboratory reports between December 2005 and November 2010 were reviewed by trained paediatricians and paediatric residents to extract data on patient characteristics, RV disease course

[1] Note that in these estimations age-specific average Dutch life expectancies as reported by Statistics Netherlands were used.

and origin (community-acquired or nosocomial), and admission and discharge dates. Length of stay (LOS) was counted in days, including the day of discharge and the admission day if hospitalization started before 8 pm. Excess LOS in cases of nosocomial RV infection was assessed by counting additional hospitalization days attributable to RV infection beyond a scheduled or expected discharge date on record. If no discharge was scheduled or expected shortly, we conservatively set additional hospitalization days to zero.

A total of 936 RV hospitalizations were assessed. (For details of hospitalizations, hospital durations and outcomes, as found in the RoHo study, see Appendix 1 where Table A9.1 reports the characteristics of identified RV hospitalizations (2006–2010) and Table A9.2 gives the treatment, hospital stay and outcome information stratified by community-acquired and nosocomial rotavirus hospitalizations.) Treatment consists of rehydration, which was given in 83% of all cases. Intensive care unit (ICU) admissions occurred in 1.4% of all infections: in 1.2% and 2.3% of community-acquired and nosocomial infections, respectively. In the RoHo study, seven severe complications associated with RV GE were noted: four cases of necrotizing enterocolitis were observed among premature infants, one patient developed a paralytic ileus, one case of hypovolemia-associated acute renal failure occurred and one case of hypernatremic encephalopathy with convulsions was reported. One premature newborn developed severe encephalopathy after RV infection with RV presence confirmed in cerebrospinal fluid and other causes of encephalopathy excluded. Quantitative data on long-term sequelae after complicated RV infection are lacking. However, given the nature and severity of these complications, it can be assumed that some of these resulted in long-term disability or treatment.

Premature children and children with low birth weight (LBW) or congenital pathology had an increased relative risk of RV hospitalization of respectively 1.7 (95% CI: 1.2–2.8), 1.6 (95% CI: 1.1–2.3) and 4.4 (95% CI: 3.4–5.4) [30]. Table A9.4 (Appendix 1) shows that the mean length of stay is highest among these groups; i.e. 5.2 days in premature children, 5.1 days in LBW children and 6.6. days in children with congenital pathology, in comparison with 3.6 days in healthy infants. The percentage of ICU admission is also higher among groups of infants with perinatal high-risk conditions: 4.8% in premature children, 2.9% in LBW children and 2.6% in children with congenital pathology. In healthy children, the percentage of ICU admissions amounted to 0.6%. In addition, healthcare utilization was increased among high-risk patients compared with otherwise healthy children hospitalized for RV, with increased risk of ICU admission (RR ranging from 4.2 to 7.9), increased duration of hospitalization (1.5 to 3.0 excess days), and higher healthcare costs (by € 648 to € 1,533 per patient). Seven cases of RV-related mortality among children with congenital pathology were observed in the study, translating to an average of 6–7 fatal cases annually in the Netherlands among this patient group. No fatal cases were observed among otherwise healthy children. Among patients with nosocomial RV infection, high-risk children represented 64% of all cases, indicating an increased risk of acquisition among these children as confirmed in a nested case-control study (odds ratios ranging from 3.2 to 3.6 for children with congenital pathology, prematurity or LBW). The

findings of the Dutch study are supported by observations in other countries confirming that premature and LBW infants, as well as those with underlying chronic conditions, are at increased risk of RV hospitalization, nosocomial infection and RV mortality [31-39].

2.4 Circulating genotypes

Rotavirus is a double-stranded RNA virus and belongs to the *Reoviridae* family, genus *Rotavirus*. Two proteins that form the outer viral capsid, VP4 (P protein) and VP7 (G protein), represent prime targets for the immune system to mount a neutralizing antibody response. These proteins are key antigens used to characterize strains. Many G and P genotypes have been identified in strains that cause human infection. There are more than 70 different G–P combinations, G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8] being the most detected strains globally [3].

In Europe, a surveillance network called EuroRotaNet was established in January 2007 to monitor the different genotypes circulating in European countries. EuroRotaNet combines the results of the participating countries to present an overview of circulating genotypes of RV in consecutive RV seasons in Europe and provides annual reports. The genotype distribution varies by European country and there is a higher variability in circulating strains in the peak season compared to out of season strain variability [40].

The RIVM's Centre for Infectious Disease Research, Diagnostics and Screening (IDS) has participated in this network, together with 14 other European countries, since June 2008. Within this project, Dutch microbiological laboratories can send RV-positive faeces samples to the IDS for typing using sequencing.

The annual numbers of Dutch samples genotyped for EuroRotaNet are shown in Table 2.3. The results of typing are shown in Figure 2.5.

Table 2.3 Overview of number laboratory-confirmed RV detections genotyped at the RIVM

Year	Laboratory-confirmed RV diagnoses	Samples at RIVM		Samples typed at RIVM	
		N	% of diagnoses	N	% of samples at RIVM
2008	1692	?	?	168	?
2009	1936	869	44,9	830	95,5
2010	2180	578	26,5	547	94,6
2011	1505	414	27,5	400	96,6
2012	1288	276	21,4	265	96,0
2013	1496	299	20,0	280	93,6
2014	607	150	24,7	139	92.7
2015	1323	289	21,8	272	94,1

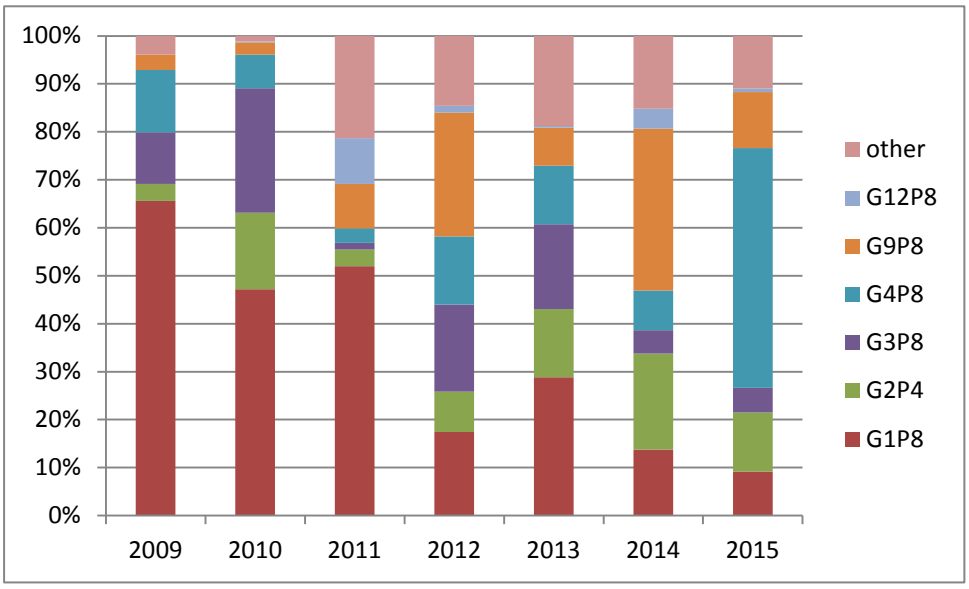


Figure 2.5 Rotavirus types as genotyped by the RIVM, 2009–2015

Overall, G1P[8] was the most prevalent genotype in the Netherlands until 2012; since 2012 G1P[8] has decreased, and G9P[8] and G4P[8] are upcoming. Since 2011 also a slight, but steady relative increase of G2P[4] has been observed. Preliminary observations for 2016 indicate a similar pattern as in 2014, both in numbers and in dominance of G9P[8] (data not shown).

2.5 Rotavirus disease in other countries

Rotavirus being a globally endemic infection, nearly every child is infected at least once before the age of five years [41]. Although it is a self-limiting disease, the high incidence and young age of first infection make RV an important cause of morbidity and mortality. Before vaccines became available, RV was responsible for > 100 million GE episodes globally, 25 million outpatient visits, 2.4 million hospitalizations and 420,000–494,000 deaths per year, deaths occurring mainly in developing countries, where RV is the cause of 37% of all deaths due to diarrhoea among children under five years of age [42-44]. RV can easily be transmitted from an infected hospitalized patient to other, susceptible, hospitalized patients, which makes it also an important nosocomial pathogen.

Worldwide, five strains are most commonly detected; G1P[8]; G2P[4]; G3P[8]; G4P[8]; G9P[8] [45-47]. In Europe, G1P[8] is the predominant serotype, accounting for almost 80% of all infections [47]. In developing countries, the diversity of unusual strains is greater and more strains circulate concurrently at any time [46].

Post-vaccination data indicate large reductions of all-cause diarrhoea and RV hospitalizations among children under five years, although large regional differences exist. Estimated reductions in RV hospitalizations in the first two years following vaccine introduction in high-income countries varied between 49% and 89% [48]. More recently, a review of RV introductions in European countries estimated vaccine effectiveness

against RV hospitalization as ranging between 65% and 84% [49]. Furthermore, the introduction of universal infant RV vaccination has been associated with a 17–55% reduction in all-cause gastroenteritis hospitalizations in children under five worldwide [48]. Post-introduction, changes in the seasonal pattern of annual RV epidemics has been observed: in the US, with RV vaccine coverage rates of 60–79%, biennial peaks of RV infection have been observed since the introduction of vaccination [50, 51], with much lower intensity of epidemics than during the pre-vaccine era. This pattern was previously suggested for high-income countries by modelling projections [52] but has thus far not been confirmed in all other countries with high vaccination coverage rates, such as Australia, Belgium and Austria [53]. In these countries, annual epidemics are described, but with a lower intensity than in the pre-vaccination era.

Post-vaccination era data show reductions not only in RV disease but also in RV infections among age groups that were not vaccinated, suggesting a herd protection effect [48, 54]. For example, in the US, winter GE hospitalizations in non-vaccinated older children and adults declined by 30–45% in the first three years after the introduction of infant RV vaccination [17, 18]. Similarly, a reduction of more than 50% in RV hospitalizations was observed in these age groups in Australia following introduction [55]. As only infants are vaccinated, these indirect beneficial effects imply that infants act as the primary transmitters of infection. In addition, marked reductions up to 95% in nosocomial RV infection rates have been observed, indicating reduced transmission within the hospital setting [16, 19]. More information about RV incidence after vaccination is presented in Section 3.2.

3 Effectiveness of the vaccines

Rotavirus vaccines
Studies on the natural history of RV have demonstrated the protective immunity induced from early infections. First infections are generally symptomatic, but few children have severe disease on re-infection. The protective effect increases with subsequent infections. After the second infection, symptomatic disease is uncommon [41, 56]. These findings provided the scientific rationale for the development of live oral RV vaccines that mimic natural infection, thereby inducing protective immunity. The first RV vaccine (RotaShield; Wyeth-Lederle) was licensed in 1998 in the US and was recommended for routine immunization of all children. This vaccine was, however, withdrawn from the market in 1999 after reports of intussusception – an uncommon form of bowel obstruction in young children – among vaccine recipients [57].

Currently available vaccines
In 2006 and 2008, two new oral rotavirus vaccines were approved for the European market: Rotarix (GlaxoSmithKline, Rixensart, Belgium), a monovalent human rotavirus vaccine (RV1), and RotaTeq (Merck, Whitehouse Station, NJ, USA), a pentavalent human-bovine reassortant vaccine (RV5). Both vaccines are live attenuated and should be administered as an oral liquid in two (Rotarix) or three (RotaTeq) infant doses [58, 59].

On the basis of trials of Rotarix and RotaTeq that included > 70,000 participants each, the current vaccines are licensed for use in infants, with the first dose administered after six weeks of age and the last dose administered no later than 24 (Rotarix) or 32 (RotaTeq) weeks, with a minimal interval of 4 weeks between doses. The European society for paediatric infectious diseases recommends that prematurely born infants should be vaccinated according to their calendar age, as recommended for full-term infants, and that the first dose of vaccine should be administered before 12 weeks of age [60]. Furthermore, they recommend that all HIV-infected or HIV-exposed infants should be vaccinated with oral RV vaccine.

Post-marketing reports have described severe GE with vaccine viral shedding in infants who received RV vaccine and were later diagnosed with severe combined immunodeficiency (SCID) [61-64]. The US Food and Drug Administration therefore approved in 2010 labelling changes for RotaTeq and Rotarix contraindicating administration to individuals with SCID as well as to those with a history of intussusception [65]. Both vaccines are well tolerated among premature infants, with rates of adverse events similar to what has been observed among term infants [66, 67]. Recently, it was demonstrated that RV vaccination was also well tolerated in most infants with intestinal failure [68].

Three other RV vaccines are licensed for national markets only (ROTAVAC, India; Rotavin-M1, Vietnam; Lanzhou Lamb Rotavirus vaccine, China). Furthermore, Brazil, China, India, Indonesia, Australia

and the United States are currently developing new vaccines [69]. One of those is a vaccine developed from an asymptomatic neonatal RV strain [70]. This vaccine should have several advantages over Rotarix and RotaTeq: it can be administered at birth, which will close the gap in protection over the first weeks of life, and it might enhance coverage, as no safety issues such as intussusception apply. The main advantage of this vaccine, however, is that it will reduce the differences in vaccine effectiveness between low-income and high-income countries; more information about this is given in Section 3.2.

International use of rotavirus vaccination
The World Health Organization (WHO) recommended in 2009 the use of RV vaccines in all national immunization programmes, particularly in South and Southeast Asia and sub-Saharan Africa [69, 71]. As of 1 May 2016, 81 countries had introduced RV vaccination into their national immunization programmes. Canada, India, Italy, the Philippines, Thailand and Sweden made phased or regional introductions. European countries with a national, publicly funded RV programme include Armenia, Austria, Belgium, Estonia, Finland, Georgia, Germany, Israel, Latvia, Luxembourg, Moldova, Norway, United Kingdom and Uzbekistan [72]. Table 3.1 gives an overview of the vaccines in use and their year of introduction.

Table 3.1 Overview of rotavirus vaccination in European countries.

Country	World bank classification	Year of introduction	current vaccine
Armenia	LMIC	2012	Rotarix
Austria	HIC	2006	RotaTeq
Belgium	HIC	2007	Rotarix & RotaTeq
Estonia	HIC	2014	RotaTeq
Finland	HIC	2009	RotaTeq
Georgia	LMIC	2013	Rotarix
Germany	HIC	2013	Rotarix & RotaTeq
Israel	HIC	2010	RotaTeq
Latvia	HIC	2015	RotaTeq
Luxembourg	HIC	2006	Rotarix
Moldova	LMIC	2012	Rotarix
Norway	HIC	2014	Rotarix
United Kingdom	HIC	2013	Rotarix
Uzbekistan	LMIC	2014	Rotarix

Source: http://sites.path.org/rotavirusvaccine
Abbreviations: LMIC= lower middle income country, HIC= high income country

3.1 Efficacy

Several clinical studies have been conducted in Europe, Africa, Asia and Latin America to evaluate the protective efficacy of Rotarix and RotaTeq against RV GE. Both vaccines were highly immunogenic and vaccine efficacy against severe GE and RV-associated hospitalizations ranged between 30.5% and 98%. The highest vaccine efficacy was observed in Europe and the US, where vaccination reduced RV-related hospitalizations by 94–96% compared with a placebo during two years of follow-up [73-75]. Lower vaccine efficacy of between 40% and 85% has been observed in Latin American, Asian and African studies [76-78]. The differences in vaccine performance have been attributed to greater local RV strain diversity in developing countries, altered host-immune responses, and interference by maternal immunity.

In 2012, a Cochrane systematic review of RV vaccines was published [79]. The review included 29 trials with 101,671 participants testing Rotarix versus a placebo, and 12 trials with 84,592 participants testing RotaTeq versus a placebo. In countries with low-mortality rates, Rotarix prevented 86% and 85% of severe RV diarrhoea cases among children aged less than one year and less than two years, respectively. For RotaTeq, this was estimated at 87% for children aged less than one year and 82% for children aged up to two years.

Clinical trials have shown that after the second dose of Rotarix, an efficacy of 90.8% against GE due to RV caused by G1P[8] was demonstrated, 86.9% protection against G3P[8], G4P[8], or G9P[8], and 45.4% protection against severe RV GE caused by G2P[4] [80]. For RotaTeq, these numbers were slightly higher, with protection rates above 87.6% against G1–G4 and G9 serotypes. In addition, a 100% reduction rate against G12 was reported [81].

Limited data are available on vaccine performance in high-risk populations such as premature infants and those with congenital pathology. Vaccine efficacy for the subgroup of premature infants was determined in the Phase III safety and efficacy trial on RotaTeq and the results were comparable to those for term infants, although confidence intervals were wide (efficacy against RV hospitalization: 100%; 95% CI: 53–100%, efficacy against RV gastroenteritis of any severity: 63.6%; 95% CI: -8.9–89.8%) [82]. The number of early premature infants (< 32 weeks gestational age) was too low in this study to determine vaccine efficacy (166 infants, 74 vaccine recipients and 92 placebo recipients). The efficacy of Rotarix in preterm infants has not been determined. There are no data on vaccine efficacy for other high-risk groups such as those with congenital malformations or chromosomal disorders. RV vaccines have been in use for more than seven years and several case-control studies have been performed after implementation of RV vaccination that evidence the high effectiveness of RV vaccines [75, 83-87]. None of these studies, however, addressed vaccine performance among high-risk populations.

The immunologic mechanisms by which the two vaccines protect against RV GE are not completely understood [88]. For this reason clinical endpoints are used in trials to determine vaccine efficacy. A systematic

review assessed the possible correlation between anti-rotavirus serum IgA antibody titres after vaccination to determine RV vaccine efficacy [89]. It concluded that IgA titres may be a useful predictor of vaccine performance, as a consistent correlation was found between these titres and the efficacy of Rotarix and RotaTeq. Overall, IgA titres <90 appeared to be associated with lower efficacy and to wane during the second year after vaccination. The identification of a critical titre of IgA antibody needed for adequate vaccine efficacy at the individual level was not possible within this review, as it was based upon group data. Although a trend in antibody levels and efficacy exists, other effectors are likely to contribute to host defence.

3.2 Effectiveness

Many studies on different continents have been performed to assess RV vaccination effectiveness in the post-vaccination era. Results vary but overall show high protection against RV disease in the community. Across Europe, vaccine effectiveness for Rotarix and RotaTeq ranges from 78% to 92.8% when measured by laboratory-confirmed RV cases after a full course of vaccination [49]. The impact on RV hospitalizations is slightly lower: reviews showed 65–84% reductions in RV hospitalization [49, 90], which is consistent with estimations in the US, where a 50–90% reduction was reported [91]. Reductions were also seen in older children and adults, suggesting a herd effect [49]. A modelling study predicted that the greatest reduction in cases of RV occurs immediately following vaccination introduction until about 10 to 12 years after introduction, after which the total incidence of RV infection is expected to return to near pre-vaccination levels [92].

The protection provided by the licensed vaccines is not the same in all countries. The effectiveness of Rotarix and RotaTeq is much lower (49% and 39%, respectively) [77, 93] in low-income countries with a high burden of RV disease than that reported in high-income countries (about 82% and 85%, respectively) [80, 94]. This disparity might result from interference of breastmilk antibodies or environmental enteropathy with vaccine efficacy [95-97]. In addition, in low-income countries, children are younger when they become infected with RV for the first time. This creates a gap in the first period in their life when it comes to protection against RV. It is for this reason that a vaccine is being developed that can be given at birth. In a phase IIa trial, the safety of this birth-dose strategy with a vaccine developed from an asymptomatic neonatal RV strain was assessed [70]. The results showed that this RV3-BB vaccine was well tolerated when given as a three-dose neonatal or infant schedule.

Herd immunity

Herd immunity is the phenomenon that unvaccinated individuals are protected by being in a population with vaccinated individuals [98, 99]. It does not mean that they are less susceptible, but that they are in a community with less virus circulation, and are therefore less likely to come into contact with the virus.

If a sufficiently large part of the population is protected by vaccination (or immune from natural infection), infections can be eliminated from a

population even if the vaccination degree is below 100%, due to herd immunity [98]. For RV this is practically impossible for two reasons: the first reason is that it is highly infectious, i.e. the basic reproduction ratio (number of secondary cases per primary case in a susceptible population) is extremely high: in the range of 25–50 in the US and England & Wales [52, 100], which means that the required vaccination degree with a perfectly lifelong immunizing vaccine should be 98% ($1 - 1/R_0$) [98]. The second reason is that the vaccines are so far only 87% effective, and probably never will be 100% effective, because natural infections do not provide lifelong immunity either [41]. That means that there will always be sufficient susceptible individuals in the community to enable RV circulation.

Although elimination is impossible, herd immunity can still reduce incidence in unvaccinated individuals, and it can change the course of yearly outbreaks. A modelling study for the US population predicted almost no herd immunity against severe diarrhoea, but also predicted that the mean age at which it occurs can go from 1.5 to 3 years, possibly reducing its severity (vaccination coverage 70%) [52]. Another modelling study, for the UK population, predicted a reduction in RV notification of 3% due to herd immunity on top of the 55% due to direct effect (coverage 91%) [101]. Both studies predicted an increase in the mean age of RV notifications and hospitalizations, a delayed peak of the yearly epidemic, and a possible biennial pattern of yearly outbreaks instead of the yearly pattern before vaccination.

Another source of information on herd immunity due to RV vaccination is the experience of countries where vaccination is in effect. However, it is very difficult to get good estimates of protection due to herd immunity. Evidence for herd immunity can be obtained only by comparing with the pre-vaccination era, but several years of data are needed for three reasons: first, because of a possible 'honeymoon effect' [99, 101], which is the expected more pronounced effectiveness in the first year when a large part of the population is still immune as a result of natural infection; second, because of the possible change in periodicity as predicted by the modelling studies; and third, because of the possible change in the age pattern of first infection and to be able to correctly assess the longer-term effects related to waning immunity [102]. Any observed reduction in RV incidence in non-vaccinated individuals should therefore be interpreted with care [102].

In a systematic review, five publications with a total of 12 years of observations across several countries were considered to be of good enough quality to assess herd immunity against RV-specific gastroenteritis (RVGE). Herd effects were highly variable, with a 0–40% reduction of RVGE incidence per year, and no relationship with coverage [103]. In the US specifically, dynamics have clearly changed to a biennial pattern, with peak epidemics in 2009, 2011, etc. Herd protection in infants is limited [104], but in children (5–14 years) and young adults (14–25 years) RVGE hospitalizations are clearly reduced in non-peak years (about 70–80% reduction), though only slightly in peak years. A reduction is also seen in adults in non-peak years (30–50%), but not in peak years [105]. According to a cost-effectiveness study, in the first year after the introduction of vaccination (2008) $ 204 million

was saved, of which 20% in 5–24 year-olds, due to herd immunity [106].

In Europe, a clear relation was seen between vaccine coverage and RV hospitalizations [107], but the extent to which herd immunity played a role here is uncertain. A five-month non-vaccination period in 2010 in Spain resulted in a drop in coverage that year from 49% to 22%, and an almost immediate doubling in RV hospitalizations among < 12 month-olds in 2011, but no clear sign of a change in herd immunity [108]. Austria started vaccinating in 2007 and reached a coverage of about 85%; this resulted in a reduction of community-acquired RV hospitalizations of more than 50% across all age groups including infants [109]. Belgium has had a high coverage of 86% from the start in 2007, with a reduction in incidence in infants of 80–86% (uncertain role of herd immunity), but also a 50% reduction in > 10-year-olds. Hospitalizations were even more reduced (89% in infants, 63% in > 10-year-olds) giving clear evidence of herd immunity [53].

Thus, whereas modelling studies predicted only a limited effect of herd immunity, data since the implementation of vaccination (after 2006) in several countries suggest that there can be considerable reductions in incidence in unvaccinated age groups, at least if coverage levels are high, as in the USA, Austria and Belgium. Herd protection is most pronounced in children 2 to 5 years old and in those too young to be vaccinated, but it varies substantially [55, 110-115]. Whether this is a long-term effect is less certain, as waning immunity in vaccinated individuals may increase incidences in higher age groups in the future.

RV vaccination reduces the circulation of RV strains in the population which may result in a lower incidence in unvaccinated age groups. However, it results also in decreased boosting of immune levels induced by natural exposure. It is unknown and very hard to predict whether this will influence the level of maternal antibodies in newborns or whether the protective age window until the first dose of vaccination is shorter for young infants, putting them at risk of RV infection at very young ages. So far, no such signs have been described, but research in very young infants is limited.

Vaccine-induced strain replacement
Protecting hosts against one or more pathogen strains with a vaccine may drive new dominant pathogen strains to emerge [116]. Therefore, before implementing a new vaccine, strain replacement is an important aspect to consider.

For RV vaccination, it seems that there is no phenomenon of strain replacement so far. Although several studies describe a shift towards strains less controlled by the current vaccines (in areas vaccinating with Rotarix or RotaTeq an increase in G2P[4] or G3P[8], respectively, was seen), all studies hold that a natural shift in strains - unrelated to vaccination - cannot be ruled out [92, 117-119]. In addition, EuroRotaNet concluded in its last report that there is no evidence of the emergence of RV vaccine escape strains due to RV vaccination programmes in Europe [120]: no novel emerging strains have been detected in any of the countries participating in EuroRotaNet. In

addition, a recently published review showed that vaccine-induced selective pressure did not occur [121]. However, surveillance efforts should be maintained and it is crucial to identify the emergence of new strains due to vaccination, or as result of vaccination in surrounding countries [121].

4 Safety and (adverse) consequences of the vaccines

This chapter describes the adverse events following immunization with RV vaccines.

4.1 Reactogenicity

Both Rotarix and RotaTeq are well tolerated and have a low reactogenicity profile when given alone. Nor do they cause clinically significant increases in reactogenicity when co-administrated with other routine childhood vaccines [122, 123]. For both vaccines, increased incidences of fever, vomiting, diarrhoea and irritability were measured in clinical trials within 14 days of immunization with any dose [81, 124-128]. However, these symptoms were generally mild and transient.

Not only in children, but also in the elderly RV may be an important causative agent of acute GE. Lawrence et al. [129] demonstrated that RotaTeq was generally safe and well tolerated in healthy adults, whereas 9% of placebo recipients and 27% of RotaTeq recipients experienced a vaccination-related adverse event of mild or moderate intensity. Therefore, further evaluation of RotaTeq as a candidate vaccine in this age group may be warranted.

Decline in childhood seizures
Two studies have described a decline in hospitalizations for childhood seizures after the introduction of RV vaccination [130]. Clinical neurologic illness has been linked to RV infection in numerous studies and case reports, which has prompted the hypothesis of a potential vaccination effect on childhood seizure incidence. In Spain, reductions in hospitalizations for childhood seizures of between 16% and 42% have been observed since the introduction of RV vaccination, with higher reductions seen in the years with higher RV vaccine coverage rates [131]. In the US, data from the Vaccine Safety Database were used to compare the incidence of hospitalization or visiting the emergency department for seizures in cohorts of vaccinated and unvaccinated children. A statistically significant protective association was observed between a full course of RV vaccination vs. no vaccination for both first-ever seizures (risk ratio = 0.82; 95% CI: 0.73–0.91) and all seizures (risk ratio = 0.79; 95% CI: 0.71–0.88) [111].

4.2 Intussusception

Post-licensure surveillance showed that the previously marketed RV vaccine, RotaShield, carried an attributable risk of intussusception estimated at 1:10,000 recipients [57, 71, 88, 132-134]. This adverse event, the invagination of one segment of the intestine into an adjacent segment, causes intestinal obstruction leading to bleeding, intestinal perforation and possible death [132]. The pathogenesis of RotaShield-associated intussusception has not been determined. The greatest risk of intussusception occurred between 3 and 14 days after the first dose, with a smaller risk after the second dose [57, 135]. There is evidence suggesting that when the first dose of RotaShield was given at > 3 months of age, the risk of intussusception was increased [136], as most

of the cases of intussusception occurred in children who were older than three months at the time of immunization. For this reason, particular attention has been focused on this side effect and in assessments of the safety of the two new vaccines.

For Rotarix and RotaTeq, large Phase III clinical trials were undertaken and no association between either vaccine and intussusception was found [80, 81, 88, 134, 137]. However, post-licensure data from Mexico, Australia, Germany and the US have shown a slight increase in the risk of intussusception, particularly after post dose 1. A 4- to 9-fold increase in the risk of intussusception in the first week after the first vaccine dose has been observed in different studies, generating an absolute risk of intussusception of 1 to 6 cases per 100,000 vaccine recipients [138-145]. It was found that the risk of intussusception especially increased with age. Administration of the first and last dose of Rotarix and RotaTeq inside the recommended age window has not shown any impact on the incidence of serious adverse events including intussusception. No data are available on the possible risk of such events outside the recommended age window [71]. For this reason, the American Academy of Paediatricians and WHO recommend that the first dose of RV vaccine be administered as soon as possible after 6 weeks but before 14 weeks of age, along with diphtheria-tetanus-pertussis (DTP) vaccination [71], although the WHO also mentions that this policy could exclude a substantial number of children from vaccination in settings where the DTP doses are given late. For these settings, the WHO advises that RV vaccine be administered with DTP regardless of the time of vaccination. The European society for Paediatric infectious diseases recommends that prematurely born infants should be vaccinated according to their calendar age, as recommended for full-term infants. Furthermore, they recommend that all HIV-infected or HIV-exposed infants should be vaccinated with oral RV vaccine. Although specific information on many immunodeficiency’s is lacking, infants with known SCID should not receive live RV vaccine [122].

In France, RV vaccination is not included in the routine infant immunization schedule [11], in large part because of two infant deaths and many serious side effects. The two deaths following vaccination were due to very severe forms of intussusception. A third death following RV vaccination was also notified; this was due to necrotizing enterocolitis in an infant treated by a human varicella-zoster immunoglobulin. Furthermore, there were 508 notifications of side effects (103.8/100,000), of which 201 were serious (40.9/100,000). There were also 47 intussusceptions and, among them, 14 (29.8%) required surgical treatment. Most of them occurred after the first dose, and the median age for post-vaccinal intussusception was three months. The conclusion of the pharmacovigilance committee was that the rate of side effects was worrying when compared with other paediatric vaccines. It noted that the intussusceptions were severe – probably, in part, because they occurred in young infants (i.e. about three months of age).There are no plans, at least in the short term, to reconsider the statement of the High Council of Public Health to recommend to include RV vaccination in France's immunization schedule (personal communication Daniel Levy-Bruhl, 18 January 2017).

In the Netherlands, two studies calculated baseline incidences of intussusception with the purpose of assessing whether there would be any possible increase if RV vaccination were introduced in the Netherlands. The first study was done using Hospital Discharge Data for the entire Dutch population. The second study was conducted in the population that was registered in a GP medical records database. The incidence of intussusception appeared to be lower than rates reported in the neighbouring countries of Germany and Denmark [146-148] (Figures 4.1 and 4.2). Whether this reflects a truly lower incidence or incomplete coding practices is currently unknown. Furthermore, data on the severity of intussusception among Dutch infants, including the rate of surgical procedures and resection, the occurrence of long-term sequelae or deaths, are currently lacking.

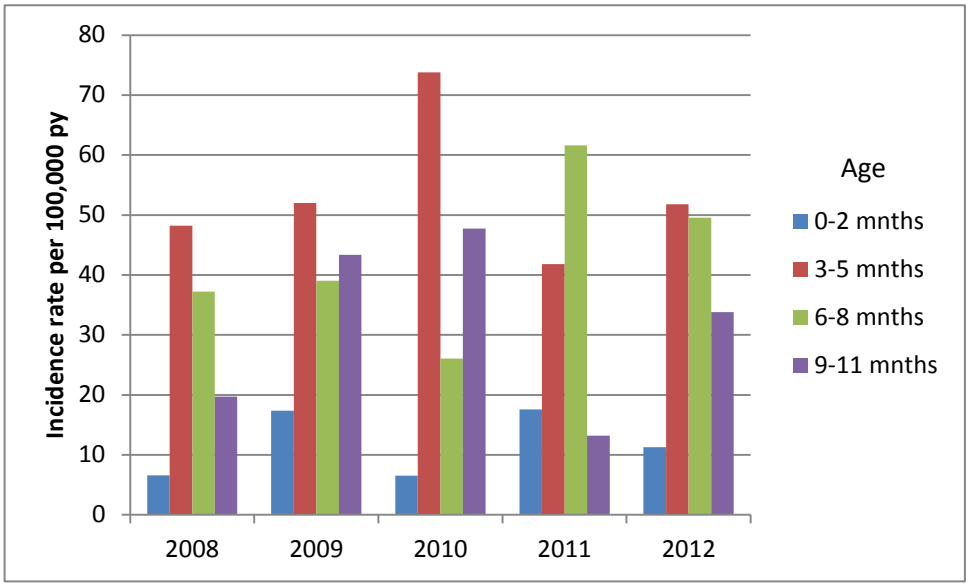


Figure 4.1 Intussusception incidence rate in children < 1 year of age per 100,000 person-years, age category and by calendar year 2008–2012, based on non-validated cases from the Dutch Hospital Data.

Abbreviations: py= person-years, mnths= months of age.

Analyses were adjusted for the estimated decline in national coverage of Dutch Hospital Data of about 88% in 2008 to about 82% in 2012.

Source: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (LBZ) from 2010 onwards.

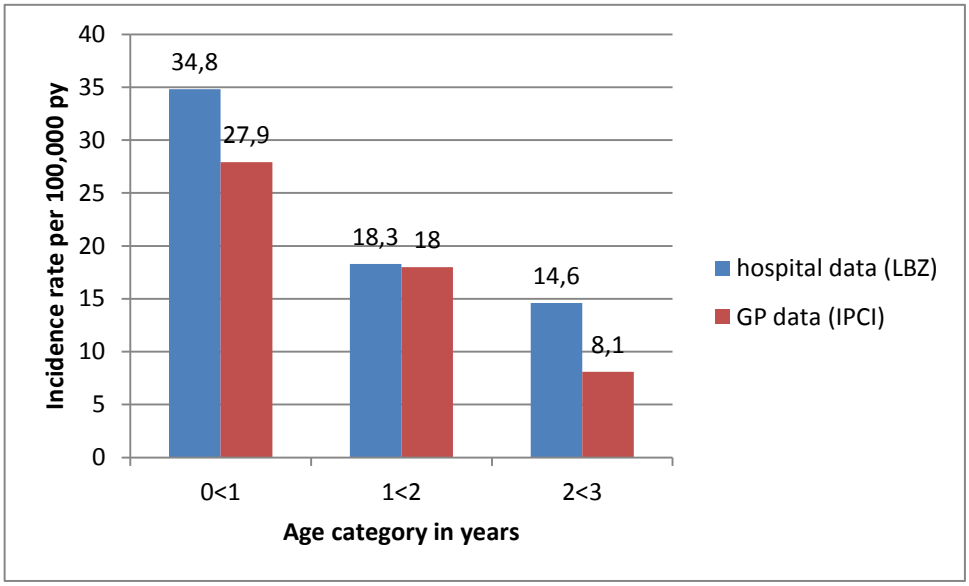


Figure 4.2 Intussusception incidence rate (95% CI) per 100,000 person-years by age and database (study period 1 Jan 2008 – 31 December 2012)

4.3 Shedding and transmission

Rotarix and RotaTeq are equally effective in preventing RV disease and have similar safety profiles, but some differences exist in viral shedding. After administration of either RV vaccine, viral shedding is common, in particular after the first dose. Shedding is detected in up to 90% of healthy infants after the first dose, with a peak between three and seven days after vaccination [149-151]. One comparative study evaluating vaccine strain shedding rates in Rotarix- and RotaTeq- vaccinated infants, found no difference between the two vaccines when using identical detection methods (immune-assay and RT-PCR), but the viral load in stools was significantly higher in infants vaccinated with Rotarix [149]. Transmission to placebo recipients was not observed in any of the pre-licensure trials of RotaTeq [151]. In a study with twins one of whom was vaccinated with Rotarix, the vaccine strain was detected in 15/80 contacts [152]. This is evidence of transmission, but too little to enable 'vaccine outbreaks', as the basic reproductive ratio based on this number (and contact rates among all infants as between the twins) would be < 0.5 [153]. For this reason, shedding and transmission are not considered significant safety concerns in the general population.

For the hospitalized patient population, there is very little evidence of the transmission of vaccine strains due to viral shedding. One recent study evaluated the effect on ward-mates of vaccinating infants with RotaTeq in the NICU setting. This retrospective observational study assessed the occurrence of gastrointestinal symptoms in 801 neighbouring ward mates in the 15 days following vaccination of 96 index infants. No post-vaccination symptoms could be attributed to RotaTeq [154]. Although the methodology used in this study has clear limitations, this is a first indication that vaccination in the NICU setting can be safely performed. Further circumstantial evidence comes from Australia where both Rotarix and RotaTeq have been administered to hospitalized infants, including NICU patients, with standard infection

control precautions since nationwide implementation in 2007 [155]. There have been no reports of vaccine strain transmission-related disease (personal communication Christine Macartney, 4 December 2013).For RV specifically, so far, no serious cases have been described, like for example vaccine-derived polio. Although it is very difficult to monitor, it is of importance to screen for possible vaccine strain transmission-related disease.

Vaccine virus shedding and transmission to unvaccinated contacts are generally regarded as adverse events after vaccination with live virus vaccines. The transmission of live vaccine virus to non-vaccinated contacts could theoretically stimulate immune responses in non-vaccinated individuals, resulting in increased protective immunity [151]. However, this phenomenon is uncontrolled and therefore might be seen as an adverse event. Although vaccine strain transmission is realistic when RV vaccination is implemented in the hospital setting, in Canada, the implementation of RV vaccination in one NICU setting resulted in a decrease in nosocomial infection without any apparent safety issues [156]. Similar observations come from Australia, where nosocomial RV infection is nearly extinct since the introduction of universal RV vaccination [157]. The occurrence of vaccine strain transmission in the hospital setting is realistic when hospitalized infants are being vaccinated, but has not been observed or proven so far.

The potential for transmission may be higher when Rotarix is used. However, despite nearly eight years of post-licensure observation, there is no evidence that horizontal transmission of Rotarix is harmful, although theoretically this may be the case in severely immunocompromised patients. The use of RotaTeq is probably associated with lower vaccine strain transmission rates, but harbours a risk of reassortment events resulting in the formation of a virulent recombinant RV strain with the potential for transmission. Both Rotarix and RotaTeq have the potential to reassort with other non-vaccine RV strains but with RotaTeq, reassortment events can also occur between the different strains; contained in the vaccine and, on rare occasions, result in the formation of a virulent recombinant RV strain, as illustrated by case reports [158-161]. The need for good monitoring of possible reassortment is therefore emphasized [157].

4.4 Vaccine contamination

In 2010, researchers made the unexpected finding that RotaTeq vaccines contained DNA from porcine circovirus type 1 and 2 (PCV 1 and PCV 2), and DNA from porcine circovirus type 1 (PCV 1) was found in Rotarix [64, 162]. PCV 1 and PCV 2 viruses are common in swine but, according to the FDA, not associated with illness in either pigs or humans [163, 164]. In Spain, the detection of circovirus in both vaccines resulted in a ban of Rotarix and RotaTeq from the market from June to November 2010 [165]. This led to a pronounced and immediate increase in hospitalizations of children under one year of age, and a subsequent decrease after the resumption of vaccination. In the 12–23 months age group an increase in the incidence of RV infection was also seen, which persisted despite the resumption of vaccination, as catch-up vaccination is not possible in this age group due to strict age restrictions

for RV vaccination. Since November 2010, only RotaTeq has been available in the Spanish market, and although it is recommended by the Spanish Association of Paediatrics, it is still not included in the national immunization programme [166].

The European Medicines Agency (EMA) found in a review that porcine trypsin, a reagent used in the vaccine production process, was the most likely reason for the presence of PCV. The EMA also concluded that the unexpected presence of viral DNA in these vaccines does not pose a risk to public health [167]. The company that markets Rotarix is currently developing a vaccine free of PCV 1 [168].

5 Acceptance of vaccination

5.1 Acceptance of individual vaccination and vaccination included in the NIP

Several questionnaire studies have been performed by the RIVM/Centre of Infectious Disease Control about the acceptance of new vaccinations among parents with one or more children under four years old. These questionnaires also asked about the parents' intention to vaccinate their child(ren) against RV (Figure 5.1; see Appendix 2, Table A10.1 for background information on the different studies). The reported positive intention ranged between 38% and 54% in the case of the proposition that the vaccination should be included in the NIP. The participants' intention was lower in the proposition that they would have to pay for the vaccination. In addition to intention, the 2012 questionnaire included other questions about RV vaccination (see Figure 5.2)

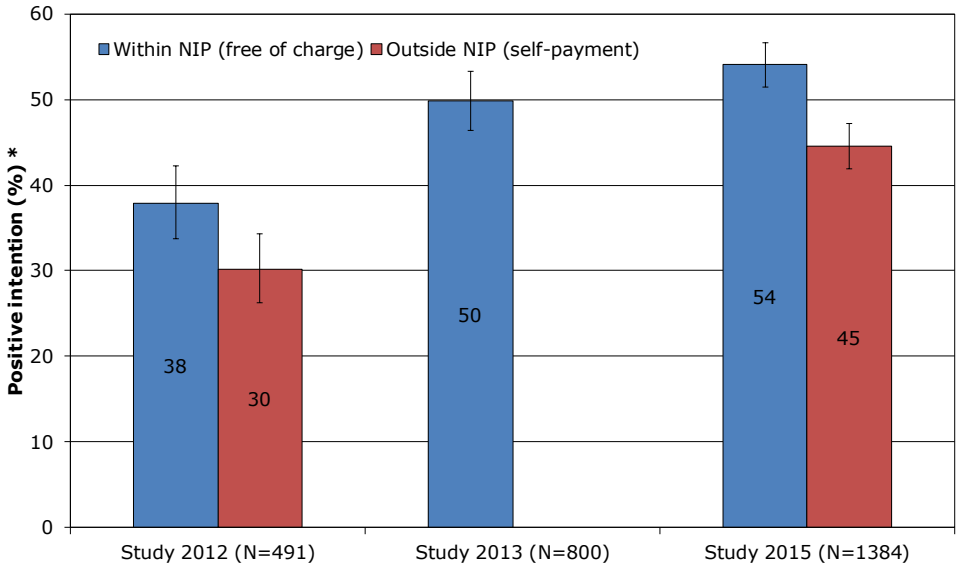


Figure 5.1 Percentage of parents with a positive intention to vaccinate their child(ren) against rotavirus infection, by study

Although the levels of disease-specific intentions between the studies are somewhat different, in all three studies the same ranking from high to low positive intention is evident (Figure 5.3):

1. Meningococcal B disease
2. Hepatitis A (included only in 2015 study)
3. RSV infection (included only in 2013 and 2015 studies)
4. Rotavirus infection
5. Varicella
6. Influenza.

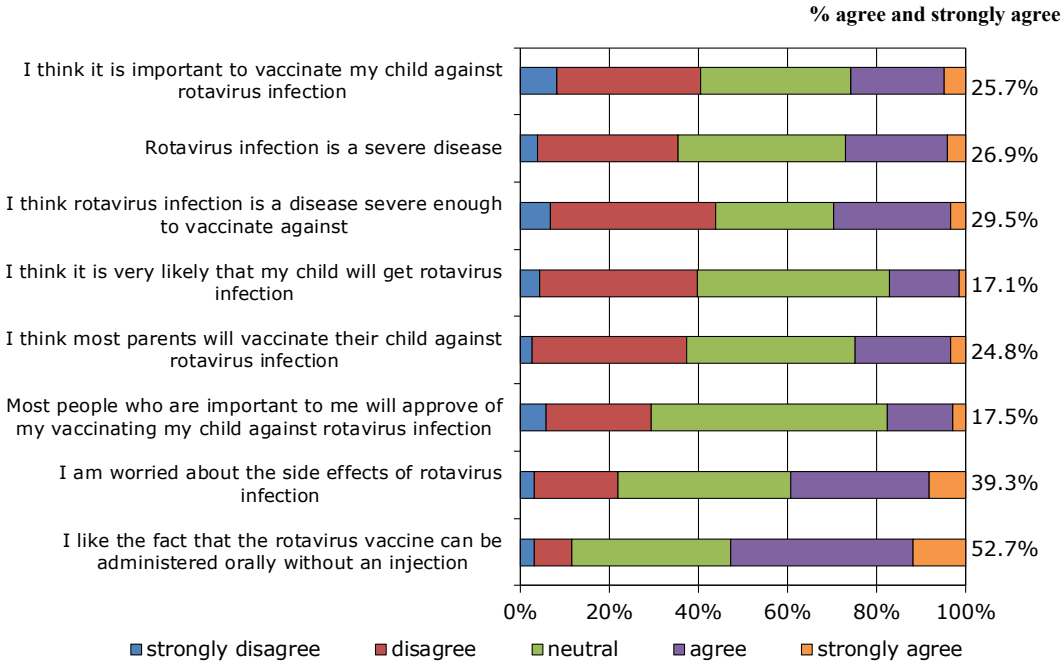
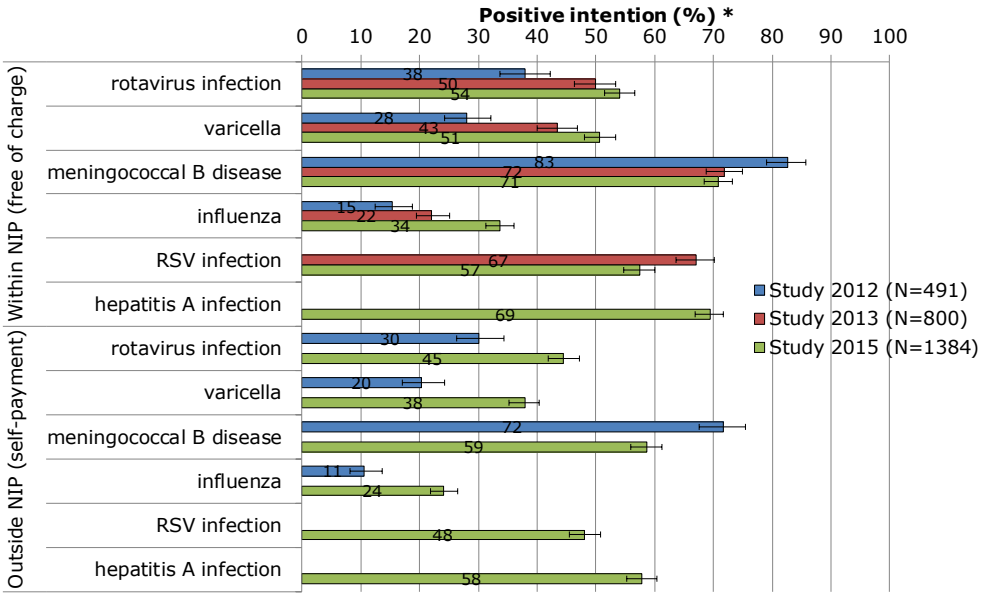


Figure 5.2 Agreement with statements on vaccination against rotavirus infection (2012 study, N=491)



* In 2012 intention was measured on a 5-point scale (positive intention = score 4-5); in 2013/2015 intention measured on a 7-point scale (positive intention = score 5-7).

Figure 5.3 Percentage of parents with a positive intention to vaccinate their child(ren) against several diseases, by study

Another survey was conducted among people working at a child welfare centre (medical doctors and nurses); 25 managers asked 1,427 employees to participate and 423 (30%) responded [169]. This study generated the same ranking of diseases in response to the question whether or not vaccination within the NIP is necessary (measured on a 7-point Likert scale): meningococcal B disease (mean score 4.63), RSV

infection (mean score 4.50), rotavirus infection (mean score 4.13), varicella (mean score 3.09), influenza (mean score 2.78).
Besides the studies mentioned above, a discrete choice experiment (DCE, see text box) questionnaire was sent to parents of 1,250 six-week-old children (response: N=466 (37.3%)). The DCE consisted of the following five attributes (levels): vaccine effectiveness (55%, 75%, 95%), frequency of severe side effects (1 in 10,000, 1 in 100,000, 1 in 1,000,000), protection duration (1 year, 3 years, 6 years), healthcare facility of vaccine administration (child welfare centre, general practitioner), out-of-pocket costs (0, 30, 140 euros). All attributes, except for the healthcare facility that administrates vaccination, were significantly associated with the decision of parents to vaccinate their newborn. Regarding the relative importance of these attributes, out-of-pocket costs were most decisive for parents in their decision about vaccination, followed by vaccine effectiveness, protection duration, and frequency of severe side effects. Parents were willing to accept lower vaccine effectiveness if this would mean a lower frequency of severe side effects (1 in 1,000,000 instead of 1 in 10,000) or longer protection duration (3 years instead of 1 year). Potential vaccination coverage ranged between 22.7% and 86.2%, depending on the vaccine scenario (i.e. vaccine effectiveness, protection duration, chance of severe side effects) and implementation strategy (i.e. out-of-pocket costs and healthcare facility that administrates vaccination) (see Table 5.1).

Discrete choice experiment (DCE)
DCEs are used to determine the relative importance of different interventions or medical treatment characteristics. DCEs may also be used to estimate participants' willingness to pay as well as to estimate potential participation rates (e.g., vaccination coverage). Any intervention or treatment can be described by its characteristics or 'attributes' (such as vaccine effectiveness). The individual's preference for an intervention or treatment is determined based on the levels (e.g. vaccine effectiveness of 50% versus 80% versus 95%) of those attributes. Respondents are provided with a series of 'choice tasks' that consist of at least two scenarios. They have to choose the scenario they prefer within each choice task.

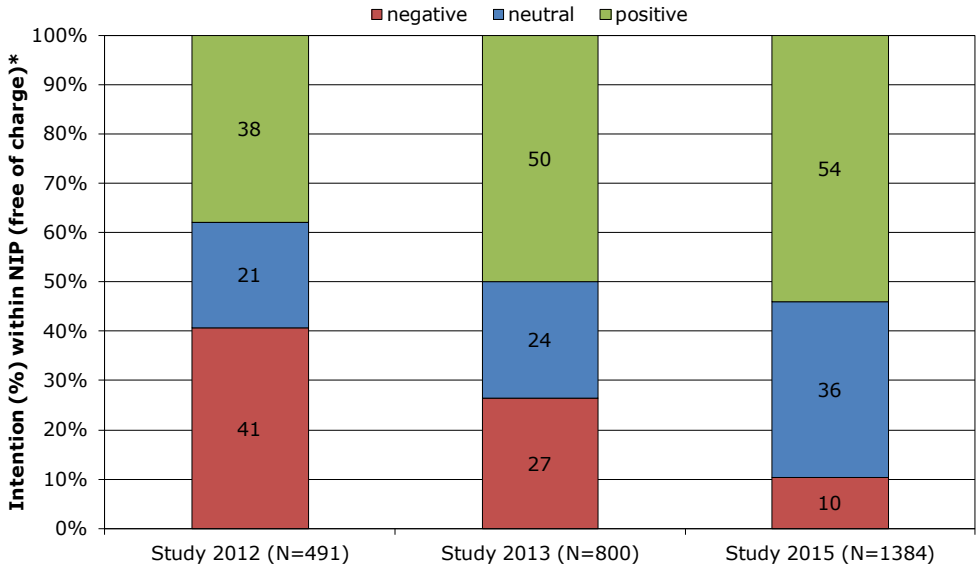
The questionnaire also covered social concepts. Having read the general information about RV infection, 62% of parents reported that they considered a possible RV infection of their child to be 'very serious', while 64% thought their newborn could become seriously ill from such an infection. Of all parents, 24% thought their newborn had a high chance of becoming infected with RV. Finally, 77% considered vaccination a good way to protect a newborn against RV infection and 79% reported that they would vaccinate their newborn against RV infection if a vaccine would became available.

Table 5.1 Potential coverage for vaccination against rotavirus infection for different vaccination scenarios stratified by implementation strategy.

	Implementation strategy###			
Vaccination scenario	**Part of the NIP - € 0 - administered at CWC#**	**Part of NIP+ - € 30 - administered at CWC#**	**Health care insurance - € 30 - administered by GP##**	**Private market - € 140 - administered by GP##**
Vaccine effectiveness 55%				
1 year protection Severe side effects: 1 in 100,000	48.3	45.2	43.3	22.7
3 years protection Severe side effects: 1 in 100,000	64.2	60.3	60.4	37.3
Vaccine effectiveness 75%				
1 year protection Severe side effects: 1 in 100,000	63.8	59.5	59.3	36.2
3 years protection Severe side effects: 1 in 100,000	75.7	74.8	74.2	52.0
Vaccine effectiveness 95%				
1 year protection Severe side effects: 1 in 100,000	75.1	74.8	74.3	52.2
3 years protection Severe side effects: 1 in 100,000	86.2	85.2	84.7	67.8

Child Welfare Centre. ## General practitioner. ### The 'NIP' implementation strategy automatically implies no out-of-pocket costs and administration at a CWC. The'NIP+' strategy is an implementation strategy where the vaccination is part of the NIP but requires an additional out-of-pocket payment of € 30. The 'healthcare insurance' implementation strategy means that the vaccination is not part of the NIP, but healthcare insurance will pay (part) of the vaccination costs when parents decide to vaccinate their newborn against RV infection (i.e. leaving an additional out-of-pocket payment of € 30). In this strategy, parents will have to go to their GP to have their newborn vaccinated. The 'private market' implementation strategy implies the necessity to visit the GP for administration and an out-of-pocket payment of € 140 [170].

It must be kept in mind that most parents are probably not familiar with the term rotavirus infection, because laboratory testing is not common practice for diarrhoea, except in severe cases. In the 2015 study, only 36% of parents knew of the disease. Besides the differences in study design (see Appendix 2, Table A10.1), this may explain the differences in intention between the studies, and may explain why a considerable percentage of parents are undecided regarding vaccination against RV infection (Figure 5.4).



* In 2012 intention measured was on a 5-point scale (negative = score 1-2, neutral = score 3, positive = score 4-5); in 2013/2015 intention measured on a 7-point scale (negative = score 1-3, neutral = score 4, positive = score 5-7).

Figure 5.4 Intention to vaccinate against rotavirus infection within the National Immunization Programme (NIP), by study

6 Cost-effectiveness of vaccination

6.1 Cost-effectiveness of individual and universal vaccination in the Netherlands

Several analyses have been made to determine the cost-effectiveness of RV vaccination in the Netherlands, with varying results [30, 171-177]. All these studies estimated the cost-effectiveness of universal vaccination in the Netherlands. Only Bruijning et al. [30] investigated the cost-effectiveness of both targeted RV vaccination of high-risk infants and universal vaccination in the Netherlands. Vaccine-related costs, the perspective chosen (societal or third-party payer), discounting of in particular QALYs/DALYs, the proportion of cases requiring medical services, case fatality rate and herd immunity were the major factors that determined whether RV vaccination was cost-effective or not [30, 174, 176, 178]. However, the published studies on cost-effectiveness were performed a few years ago and are therefore not standardized to current cost levels. In addition, the lower epidemic years of 2014 and 2016 are new observations, and taking into account these low endemic years this may lead to less favourable cost-effectiveness estimates.

An initial estimate of cost-effectiveness was made by Zomer et al. in 2008 [172]. Based on available list prices, this study assumed vaccine-related costs per vaccinated child to be € 153 (Rotarix) and € 157 (RotaTeq). The authors estimated that the vaccination of children under five years old would annually prevent 34,000 RV infections, 2,150 hospitalizations and 2.5 fatal cases, resulting annually in 190 DALYs prevented and € 5.8 million saved (~€ 4.8 million in healthcare costs and € 1 million in productivity losses). Taking a societal perspective, and applying 4% and 1.5% discount rates for costs and effects, respectively, the estimated incremental cost-effectiveness ratio (ICER) was € 119,000/DALY.

Using a Markov model for a hypothetical birth cohort of 187,910 children, Goossens et al. [171] reported in 2008 a cost-effectiveness ratio of € 21,900 per QALY for Rotarix. In contrast to Zomer et al. they assumed lower vaccine-related costs/vaccinated child (€ 90 vs. € 153), a higher vaccine effectiveness (100% for hospitalized and fatal cases vs. 84.7%) and a higher proportion requiring a GP consultation (33% vs. 19%). According to their findings 58,388 RV infections, 21,954 GP consultations, 2,940 hospitalizations and 2 fatal RV cases would be prevented in children younger than five years, resulting in 274 QALYs gained and € 10.3 million savings (€ 8.1 million in healthcare costs, € 1.4 million in productivity losses and € 0.8 million in patient costs) with consequently a more favourable ICER of € 21,900/QALY (societal perspective, and applying 4% and 1.5% discount rates for costs and effects, respectively).

Mangen et al. (2010) [174] used a stochastic multi-cohort decision model to simulate the introduction of RV vaccination in the Dutch population using a time horizon of 20 years. Vaccine-related costs were similar to Goossens et al. (€ 100 vs € 90), but in contrast to Goossens et

al. they used more conservative estimates for vaccine effectiveness and GP consultations (19.4% vs. 33%). Annual RV incidences were based on a 10-year average (1996–2006). Mangen et al. estimated that Rotarix vaccination would annually prevent 43,000 RV infections in children younger than 5 years, 2,900 RV hospitalizations and 3 fatal cases, resulting in 240 DALYs avoided and € 7.9 million saved (€ 6.4 million in healthcare costs and € 1.1 million in productivity losses). Note that the estimates for RotaTeq were of the same magnitude. Taking a societal perspective, and applying 4% and 1.5% discount rates for costs and effects, respectively, the ICER was € 49,000/DALY. In a sensitivity analysis, the authors showed that herd immunity effects would result in more favourable ICERs, while cost-effectiveness was less favourable in low endemic years. Here it should be noted that the assumed incidence in 'a low endemic year' was still higher than the estimated incidence for the low endemic year 2014.

Jit et al. [173] calculated in 2009 the cost-effectiveness for Belgium, England & Wales, Finland, France and the Netherlands, using the same incidences and cost data as in Mangen et al. [174]. However, these authors used a discount rate of 3% for both costs and QALYs and applied a healthcare-payer perspective (NB Dutch guidelines recommend to take the societal perspective and to use a discount rate of 4% for costs and 1.5% for effects). These estimates were updated in 2010 [174] when newly available vaccine effectiveness data became available. They concluded that RV vaccination would be cost-effective only in Finland and not in Belgium, England &Wales, France or the Netherlands [173, 175].

In 2011, Rosenbaum et al. investigated this topic using a Markov chain model, with extra attention given to the factors responsible for the differences in the previous studies [176]. Using RV incidences and RV-associated costs from Mangen et al.[174], they investigated in particular the impact of changes in assumed vaccine costs per vaccinated child and in assumed QALY per prevented RV infection. They estimated that vaccination would prevent 34,214 RV infections, 2,779 RV hospitalizations and 0.48 fatal cases, resulting in 109 QALYs gained and € 7.3 million saved (€ 6.2 million in healthcare costs and € 1.1 million in productivity losses). Assuming baseline vaccine-related costs of € 75/vaccinated child they obtained an ICER of € 46,717/QALY (societal perspective, and discount rates of 4% and 1.5% for costs and effects, respectively). The theoretical maximum vaccine-related cost per vaccinated child were estimated to be € 57.76 and € 77.71 assuming a willingness-to-pay thresholds of € 20,000 and € 50,000 per QALY, respectively. In a sensitivity analysis, the authors demonstrated that indirect effects would result in more favourable results.

Tu et al. [177] updated the cost-effectiveness analysis of Rozenbaum et al. [176] by updating in particular the number of annual RV-related hospitalizations in children younger than five years from 3,300 (estimate used in all earlier cost-effectiveness analyses [171-174, 179]) to 4,875, according to two Dutch epidemiological studies [27, 28] (as shown in Table 2.2), resulting in an ICER of € 15,600/QALY gained. With simulated herd protection of up to 5 and 25 years, the ICER was € 3,800/QALY and € 3,200/QALY, respectively.

Bruijning et al. [30] investigated in 2013 the relative cost-effectiveness of targeted RV vaccination of high-risk infants and universal vaccination in the Netherlands using an age- and risk- group-structured stochastic multi-cohort model representing the Dutch population from 0 to 15 years of age. Simulations were run for 20 years. Children with prematurity, low birth weight and congenital pathology formed the so-called high-risk group that would be eligible for vaccination under a targeted infant RV vaccination programme. All other children were considered 'low risk' and ineligible for targeted vaccination. RV hospitalization incidence, mortality[2] and the healthcare costs of RV hospitalization for high-risk and low-risk children were based on a Dutch epidemiological study on RV hospitalizations [28]. All other incidence and cost estimates were the same as in Mangen et al. [174]. Vaccine-related costs were assumed to be € 75 per vaccinated child for universal vaccination (similar to Rozenbaum et al. [176]), and € 100 per vaccinated child for targeted vaccination. Targeted RV vaccination, irrespective of whether using Rotarix or RotaTeq, was cost-saving from a societal perspective and for various applied discount rates (4% for costs and 1.5% for effects as well as 3% and 5% for both costs and effects) (Table 6.1). For universal vaccination, and taking a societal perspective and using Dutch discount rates, the mean ICER was € 21,200/QALY for Rotarix and € 33,700/QALY for RotaTeq.

Table 6.1 Disease burden and healthcare costs for rotavirus using base case assumptions for three alternative strategies; no vaccination; targeted vaccination and universal vaccination against rotavirus.

	RV disease burden			**RV costs (€ million)**	
	Disease episodes (x1,000)	*Hospitalizations*	*Fatal cases*	*Direct healthcare costs*	*Total societal costs*
No vaccination	74.1	4870	6.5	11.9	18.2
Targeted RV vaccination (percentage reduction)	67.3 (8%)	4370 (10%)	0.7 (89%)	10.5 (12%)	16.4 (10%)
Universal RV vaccination (percentage reduction)	40.6 (45%)	1370 (72%)	0.4 (94%)	3.4 (71%)	5.9 (67%)

As highlighted by several authors [30, 174, 176, 178], applying discount rates other than those recommended by Dutch health economic guidelines always resulted in less favourable ICERs than using the Dutch discount rates of 4% for costs and 1.5% for effects. For example, Bruijning et al. [30] estimated for universal vaccination with Rotarix that the mean ICERs would have been € 30,300/QALY and € 36,700/QALY when applying for both costs and effects 3% and 5%, respectively,

[2] Note that when modelling, life expectancy among high-risk children was assumed to be far lower than for low-risk children. Only Bruijning et al. made this distinction; all other studies used average life expectancies for case fatalities.

whereas with Dutch discount rates the estimated mean ICER was €21,200/QALY. It should be remembered that all these studies were performed with RV incidence numbers from before 2010.

7 Aspects of implementation

As described in Chapter 3, the current RV vaccines are licensed for use in infants, with the first dose administered after 6 weeks of age and the last dose administered no later than 24 (Rotarix) or 32 (RotaTeq) weeks with an interval of at least four weeks between doses. Rotarix vaccination consists of two doses, while RotaTeq requires three doses. For the Netherlands, several strategies are possible: such as universal vaccination within the NIP; targeted vaccination, whether reimbursed by health insurance or not; and no vaccination implementation at all.

Several countries offer universal RV vaccination within their NIP: the timing of RV vaccination in these countries is shown in Table 7.1. Both RV vaccines (Rotarix and RotaTeq) can be administered simultaneously with other childhood vaccines: they do not interfere with, for example DTaP, Hib, IPV, hepatitis B and pneumococcal conjugate vaccines [19, 122]. The WHO recommends administering Rotarix orally in a 2-dose schedule at the time of DTP1 and DTP2 with an interval of at least four weeks between doses. RotaTeq should be administered orally in a three-dose schedule at the time of the DTP1, DTP2 and DTP3 contacts, with an interval of at least 4 weeks between doses [71]. For the Netherlands, if vaccination were incorporated in the NIP, the RV vaccination could be given at 8, 12 and, in the case of RotaTeq, 16 weeks simultaneously with the other NIP-vaccines given at 8, 12 and 16 weeks of age.

In the case of targeted RV vaccination, children who are at high risk of RV infection would be vaccinated. These are mainly premature children and children with LBW or a congenital pathology. However, given the tight age restrictions and commonly interfering medical issues, delivering RV vaccination to high-risk infants within the appropriate age window is challenging, especially when relying on routine immunization visits at well-baby clinics. During the first months of life, when RV vaccination should be administered, these infants rely mostly on secondary and tertiary paediatric care for their medical follow-up. In addition, infants with prolonged hospitalization could miss the strict age window for administering the first dose of vaccine, unless vaccination is offered within the hospital setting. In a recent study on RV vaccination among premature infants, a quarter of recruited infants (10/41) aged out of the strict vaccine window prior to discharge [180]. Secondary and tertiary paediatric care could therefore provide an environment to reach RV vaccine coverage rates in high-risk infants and to ascertain timely vaccination. There is, however, little experience in the Netherlands of organizing immunization programmes through secondary paediatric care, apart from respiratory syncytial virus immunoprophylaxis which is managed by pharmaceutical home-care teams.

When administering live attenuated vaccines in the hospital setting, special attention should be paid to safety and viral shedding with respect to the ward mates of vaccinated infants (see Chapter 4). Existing guidelines on administering RV vaccines in the hospital setting are limited and practices vary by country. Only the UK, where Rotarix is used exclusively, offers some guidance by recommending the use of

gloves and aprons in contact with infants who have received RV vaccine in the hospital setting. Therefore, the exact nature of the implementation of RV vaccination by secondary- and tertiary- care units should be further discussed.

Given the ease of administration of RV vaccine, in specific studies parents administered the vaccine to their child themselves. However, this may not be desirable, because it will be unknown whether the vaccine has actually been administered, has been administered according to the protocol or has been stored under the right conditions (2–8 °C). Parents should always be informed about possible side effects and intussusception risk, no matter who administers the vaccination in what setting.

Table 7.1 Overview of European rotavirus vaccination schedules

	Weeks	Months				
	6	2	3	4	5	6
Austria		Rota		Rota		Rota[1]
Belgium		Rota	Rota	Rota[1]		
Czech Republic	Rota[2]	Rota[2]	Rota[2]			
Estonia		RV5	RV5	RV5		
Finland		RV5	RV5		RV5	
Germany	Rota	Rota	Rota[1]			
Greece		Rota[2]		Rota[2]		Rota[2]
Latvia		RV5		RV5		RV5
Luxembourg		RV1	RV1			
Norway	RV1[3]		RV1[3]			
Poland	Rota[2]					
UK		RV1	RV1			

[1] optional dose depending on the type of vaccine being used
[2] Recommended only. Not included in the national immunization schedule.
[3] for those born from September 2014, 2 doses at 6 weeks and 3 months of age.
Abbreviations: RV1= Rotarix, RV5=RotaTeq

Currently, hardly any RV vaccinations are prescribed or administered in the Netherlands. An RIVM factsheet on RV vaccination will be developed for professionals, as for other vaccines that are not included in the NIP but are considered to be beneficial for individuals ('Vaccinatie op maat').

Surveillance
As with all vaccine-preventable diseases for which vaccines have been introduced, monitoring and active surveillance are essential. These should cover for example safety, vaccine effectiveness, vaccination coverage and pathogen surveillance. Monitoring considerations will vary according to the vaccination strategy.

For all diseases included in the NIP, except human papilloma virus, there is a notification requirement. Mandatory notification of RV disease is not

yet included in the Public Health Law. However, making RV disease notifiable is almost impossible, since RV diagnoses are mainly based on clinical symptoms, and laboratory testing is rarely applicable.

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Appendix 1

Table A9.1. Characteristics of identified rotavirus hospitalizations between 2006 and 2010 in the four Dutch hospitals, participating in the RoHo study.

	Community-acquired N=770	**Nosocomial** N=176	**Total** N=936
Hospital			
A (WKZ)	157 (21%)	102 (58%)	259 (28%)
B (Diak)	157 (21%)	30 (17%)	187 (20%)
C (SZ)	283 (37%)	35 (20%)	318 (34%)
D (KG)	163 (21%)	9 (5%)	172 (18%)
Male	413 (54%)	93 (53%)	506 (54%)
Median Age (range)	13 months (3 days-18 years)	6 months (4 days-11 years)	12 months (0-18 years)
Age < 15 weeks	65 (8%)	67 (38%)	132 (14%)
Presence of complex chronic condition	105 (14%)	114 (65%)	219 (23%)
Disease category			
Respiratory	10 (10%)	15 (13%)	25 (11%)
Cardiovascular	10 (10%)	20 (18%)	30 (14%)
Gastrointestinal	21 (20%)	21 (18%)	42 (19%)
Neurodevelopmental	23 (22%)	19 (17%)	42 (19%)
Haemato-immunologic	14 (13%)	11 (10%)	25 (11%)
Malignancy	5 (5%)	6 (5%)	11 (5%)
Renal	6 (6%)	5 (4%)	11 (5%)
Metabolic	4 (4%)	5 (4%)	9 (4%)
Other congenital or genetic defect	12 (11%)	12 (11%)	24 (11%)

Table A9.2. Rotavirus hospitalizations in the RoHo study; treatment, hospital stay and outcome

	Community-acquired N=770	**Nosocomial** N=176	**Total** N=936
Rehydration			
Any	669 (87%)	109 (63%)	778 (84%)
Oral	596 (78%)	86 (49%)	682 (73%)
IV	177 (23%)	50 (29%)	227 (24%)
Unknown	5 (0.6%)	2 (1.1%)	7 (0.7%)
RV reason for admission or prolonged stay	755(98%)	100(57%)	855(91%)
Mean (excess) LOS (95%CI)	4.2 (3.4; 5.1)	3.0 (2.4; 3.6)	
General hospital (95%CI)	3.7 (3.5; 3.8)	2.6 (1.9; 3.4)	
University hospital (95%CI)	5.6(5.3; 5.9)	3.3 (2.3; 4.2)	
ICU admission	9 (1.2%)	4 (2.3%)	13 (1.4%)
Mean LOS in ICU (range)	4.0 (2-8)	8.5 (5-12)	5.4 (2-12)
Severe complications	2 (0.3%)	5 (2.8%)	7 (0.7%)
Death	1 (0.1%)	1 (0.6%)	2 (0.2%)

Table A9.3. Comparison of rotavirus disease burden by underlying health status in the RoHo study.

	All cases N=936	**Complex chronic conditions[1] N=219**	**Crude OR/ mean difference (95%-CI)**	**Adjusted OR/ mean difference (95%-CI)†**
Rehydration				
Any (%)	778 (84%)	164 (74%)	0.48 (0.33; 0.69)	0.72 (0.44; 1.20)
Intravenous (%)	227 (29%)	75 (46%)	2.59 (1.81; 3.71)	1.88 (1.24; 2.88)
> 5 days (%)	62 (8%)	48 (29%)	17.50 (9.56;34.06)	9.42 (4.44; 19.99)
Length of stay				
Mean days (95%CI)	4.04 (3.82; 4.26)	6.65 (6.10; 7.21)	3.01 (1.94;4.07)	2.56 (1.89; 3.22)
> 7 days (%)	48 (6%)	29 (30%)	14.03 (7.50;26.82)	10.63 (5.13;22.04)
Mean excess days nosocomial (95%CI)	3.01 (2.39; 3.62)	3.31 (2.44; 4.18)	1.00 (-0.12; 2.13)	0.51 (-0.77; 1.80)
ICU				
ICU admission (%)	13 (1%)	6 (3%)	2.86 (0.89; 8.90)	2.47 (0.81; 7.58)
Mean ICU days (95%CI)	5.38 (3.47;7.30)	5.50 (2.33; 8.67)	0.21 (-3.79;4.22)	*
Severe RV related complications (%)	7 (0.7%)	6 (2.7%)	18.00 (2.95; 467.48)	*
Death (%)	2 (0.2%)	2 (0.9%)	*	*

† Multilevel analysis with random effects for hospital site and adjusted for age and origin of infection (community-acquired or nosocomial) where applicable

* numbers too small for model parameterization

[1] Patients were classified as suffering from a complex chronic condition (CCC) or 'previously healthy'. Presence of CCC was determined on the basis of a definition previously used in health research, representing defined ICD-9-CM code groupings of paediatric respiratory, renal, gastrointestinal, metabolic, hematologic, congenital or genetic defect, malignancy, cardiovascular, and neuromuscular diagnoses that (1) are expected to last longer than 12 months and (2) involve either several organ systems or one organ system severely enough to require specialist paediatric care and hospitalization [181, 182].

Table A9.4. Relative Risk of Rotavirus hospitalization between healthy individuals and individuals with perinatal high-risk conditions under three months of age, where vaccination is applicable.

		Perinatal High Risk Conditions					
	Healthy (N=657)	*GA < 36 weeks (N=83)*		*LBW (N=104)*		*Congenital pathology (N=116)*	
Outcome and healthcare utilization	**N (%)**	**N (%)**	**RR (95% CI)**	**N (%)**	**RR (95% CI)**	**N (%)**	**RR (95% CI)**
ICU admission	4 (0.6)	4 (4.8)	7.9 (2.0; 31.1)	3 (2.9)	4.7 (1.1; 20.9)	3 (2.6)	4.2 (1.0; 18.7)
RV related death (number, %)	0	0		0		2 (1.7)	NA
			Mean difference (95% CI)		**Mean difference (95% CI)**		**Mean difference (95% CI)**
LOS (mean, SD)	3.6 (2.1)	5.2 (4.7)	+1.6 (0.1; 3.0)	5.1 (4.5)	+1.5 (0.3; 2.7)	6.6 (4.2)	+3.0 (1.9; 4.1)
Healthcare costs (mean, SD)	2203 (2113)	3001 (3407)	+798 (28; 1568)	2851 (3206)	+648 (-2; 1297)	3737 (3500)	+1533 (867; 2199)

Abbreviations: GA= Gestational Age, LBW= Low Birth Weight, SD= Standard Deviation, 95% CI= 95% Confidence Interval, NA = not applicable

Appendix 2

Table A10.1 Characteristics of studies performed in 2012, 2013 and 2015

Characteristics	2012 study	2013 study	2015 study
Study design	Online survey, random sample	Online survey, random sample	Online survey, random sample
Study population	Parents with child(ren) aged 0–4 years	Parents with child(ren) aged 0–3.5 years	Parents with child(ren) aged between 3 months and 3.5 years
Population source	Praeventis (national immunization register)	Flycatcher panel (nationally representative)	Praeventis (national immunization register)
Total N	1,500	2,150	8,000
Participation N (%)	491 (33%)	800 (37%)	1,384 (17%)
Date of survey	November 2012	January 2013	September 2015
Description of rotavirus infection in questionnaire	Extensive description: 'rotavirus infection usually starts with nausea and vomiting, followed by diarrhoea. After a few days the vomiting stops, where-after the diarrhoea diminishes slowly. Known complications include dehydration'.	Short description: 'severe diarrhoea in children'.	No description.
Scale used to measure agreement with statements	1–5 point Likert scale	1–7 point Likert scale	1–7 point Likert scale
Diseases included	Meningococcal B disease Rotavirus infection Varicella Influenza	Meningococcal B disease Rotavirus infection Varicella Influenza RSV infection	Meningococcal B disease Rotavirus infection Varicella Influenza RSV infection Hepatitis A infection

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