The Immunisation Advisory Centre

Antigen Literature Review for the New Zealand National Immunisation Schedule, 2017: Rotavirus

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Executive summary

Infection with rotavirus can cause severe gastroenteritis in infants and young children. Dehydration due to this infection is a major cause of hospitalisation of young children worldwide and leads to death in regions of the world without access to good health care. Rotavirus infections have also been linked to seizures in young children and in the most severe cases, secondary bacterial blood infections caused by intestinal bacteria flora. Almost all children experience rotavirus infection within their first 3 years of life, regardless of sanitation standards.

Two live reassortant rotavirus vaccines are licensed currently in New Zealand. They are administered orally to infants younger than 6 or 8 months of age, depending on the vaccine. Rotarix® (RV1; GlaxoSmithKline) contains one reassortant rotavirus strain and RotaTeq® (RV5; Merck Sharpe and Dohme) contains five reassortant rotavirus strains. Rotavirus vaccination was introduced to infants on the New Zealand National Immunisation Schedule in July 2014, following which there was a dramatic decline in rotavirus and gastroenteritis related hospitalisations of children younger than 5 years of age.

This review summarises selected literature published from January 2013 to August 2017 around the use of rotavirus vaccines in high income countries.

Safety

Rotavirus vaccines are generally well tolerated. Mild fever, abdominal pain and mild diarrhoea and vomiting have been reported following vaccination. Mixed schedules using both RV1 and RV5 are safe, although there may be a slightly increased risk of solicited symptoms, such as fever and vomiting, when RV1 is followed by RV5, compared with RV1 only doses.

The overall incidence of severe gastroenteritis following vaccination is small. Where gastroenteritis occurs following vaccination, alternative diagnoses have usually been linked to the symptoms. Detection of vaccine rotavirus in the stools of recently vaccinated infants does not prove a causal link since virus is often shed asymptomatically.

Vaccine-type virus has been detected in stool samples of some vaccinated infants for over a month after vaccination. However, the incidence of horizontal transmission of vaccine-type rotavirus to a close contact is infrequent (less than one in five) and asymptomatic. Only one case of severe gastroenteritis has been reported in a close contact. Following whole genome sequencing, the rotavirus detected in this case had genetic similarities to the RV1 strain with changes to the genes coding for virulence, but it was not determined whether the vaccine strain had mutated.

An increased incidence of intussusception (bowel obstruction) has been temporally associated with receipt of rotavirus vaccination, but no overall increase in risk has been observed in countries vaccinating against rotavirus. A conclusive causal link between rotavirus vaccination and intussusception has not been established. However, the relative risk of intussusception occurring within a week is highest following the first vaccine dose. The peak incidence of intussusception in vaccinated children occurred at a younger age than those who had not been vaccinated (at 2-6 months versus 6-8 months). In some studies, the incidence of intussusception was lower in vaccinated children than those who were unvaccinated.

Overall, rotavirus vaccination appears to be safe and well tolerated when given to premature infants in neonatal units.

Immunogenicity

The immunity against rotavirus is not fully understood and there is uncertainty around a reliable correlate of protection. Rotavirus vaccines induce serum IgA, which has been identified as a potential correlate of protection. The role of serum IgG in immunity is unclear and was not evaluated in the reviewed literature.

The presence of maternal antibody appears to provide protection against rotavirus to the youngest infants (up to 3 months of age). However, high levels of rotavirus antibody and non-antibody components of breast milk can affect the infant immune response to rotavirus vaccines. These effects are most pronounced in infants from low and middle income countries where rotavirus infection is most prevalent. It is unlikely that withholding breast feeding improves the vaccine response in these high exposure situations.

Rotavirus-specific IgA seroconversion is non-inferior following mixed vaccine schedules compared with single vaccine schedules.

Effectiveness and impact

The effectiveness of rotavirus vaccines against severe rotavirus gastroenteritis is over 90% in high income countries. However, in low and middle income countries, effectiveness is lower (50-70%). Socioeconomic status potentially influences vaccine effectiveness, even in high income countries. Further studies are required.

Both vaccines (RV1 and RV5) have a broad spectrum of effectiveness against viral strains that match or partially match the vaccine-strain. The effectiveness of three doses with mixed vaccines schedules is similar to the effectiveness reported for schedules with single vaccines.

Rotavirus vaccination protects against seizures in young children. Vaccine effectiveness against febrile seizure hospitalisations was 38% in children aged 8 months to 2 years 7 months. Overall, fewer childhood seizures, including non-rotavirus gastroenteritis associated seizures and afebrile seizures, occur where rotavirus vaccination has been introduced.

In high income countries, significant decreases in rotavirus hospitalisations have been observed in both vaccinated (by 80-90%) and unvaccinated older children. Reductions have been reported in both community-acquired and nosocomial infections. The direct and indirect protection provided by rotavirus vaccination significantly reduces nosocomial rotavirus gastroenteritis in hospitalised children with comorbidities that put them at high risk. Another important outcome is a decrease in secondary bacterial blood infections associated with rotavirus disease.

Although there is an indirect protective effect of rotavirus vaccination, unvaccinated infants are still at risk of rotavirus gastroenteritis. High vaccine coverage provides greater indirect protection. Even with high vaccination rates, rotavirus infection remains in circulation in the community, as demonstrated by a temporary cessation of vaccination in Spain that resulted in a resurgence of disease.

On time rotavirus vaccination in neonatal units provides protection to preterm infants from rotavirus infection, particularly for those who will be too old to be vaccinated upon hospital discharge. Nosocomial rotavirus infections in intensive care units are very rare due to high standard hygiene practices.

Options for scheduling

Due to the age limitations of rotavirus vaccination, there are limited options for the scheduling of the vaccines, particularly for RV5 which requires three doses. Rotavirus vaccine is administered concurrently with the other scheduled vaccines. Consideration of the positioning of the rotavirus vaccination on the childhood immunisation schedule is required when making scheduling changes for the other primary series vaccinations.

No recent literature around considerations in terms of vaccine scheduling were identified for special groups.

Internationally, the timing of rotavirus schedules reflect the infant primary series immunisations of the each country.

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Figures and tables

Acknowledgements

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
AGE	Acute gastroenteritis
CDC	Centers for Disease Control and Prevention (United States)
CI	Confidence interval
CwG	Convulsions with gastroenteritis
ED	Emergency department
ESR	Institute for Environmental and Scientific Research Ltd
EU	European Union
GSK	GlaxoSmithKline
HIC	High income countries
IgA / IgG	Immunoglobulin A / immunoglobulin G
LMIC	Low and middle income countries
MMR	Combined measles, mumps, rubella vaccine
NICU	Neonatal intensive care unit
NREVSS	National Respiratory and Enteric Virus Surveillance System (United States)
NZ	New Zealand
RCT	Randomised controlled trial
RR	Relative risk
RV1 / RV5	Monovalent (Rotarix®) or pentavalent (RotaTeq®) rotavirus vaccine
RVGE	Rotavirus gastroenteritis
SCID	Severe combined immunodeficiency
SES	Socioeconomic status
UK	United Kingdom
US	United States of America
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine effectiveness / efficacy
VSD	Vaccine Safety Datalink
WHO	World Health Organization

1 Background – rotavirus infection and vaccination

Rotavirus infection is universal in young children and most children experience rotavirus gastroenteritis (RVGE) during their first 3 years of life, regardless of hygiene and water sanitation standards. However, the burden of disease is greater in low and middle income countries (LMIC) due to increased mortality through poor nutrition, dehydration and lack of access to health services. Rotavirus infection is often most severe when first exposed to the infection, particularly in infants from 3 months to 3 years of age. Immunity induced by natural rotavirus infection can protect from symptomatic disease and reduces severity, but does not protect against reinfection.[1]

Rotaviruses are icosahedral particles composed of three layers: the outer capsid layer consists of two proteins, a glycoprotein VP7, and protruding spikes formed by protease sensitive VP4. Following proteolytic cleavage, the head of VP4 interacts with host cell receptors to infect the cells. Genetic variability in these receptors are thought to result in susceptibility to different rotavirus strains.

Both VP7 and VP4 bear serotype-specific antigenic determinants that induce specific neutralising antibodies. Serotypes determined by the glycosylated VP7 protein are termed G types. Of the identified G-types, 12 out of 14 are found in humans. Serotypes that form the VP4 protein are termed P types. Further typing of P types by nucleic acid sequencing identified 26 genotypes, of which, 15 major P genotypes infect humans. It is not possible to classify all P types due to extensive cross-reactivity. While more than 60 G-P combinations have been found in humans, five strains - P[8]G1, P[4]G2, P[8]G3, P[8]G4 and P[8]G9 - are associated with 80 - 90% of all the childhood disease burden, globally. The most common types are listed in Table 1. [1, 2]

Vaccines have been developed using recombinant rotaviruses, consisting of a reassortant of both human and animal parental strains.

Table 1: Common human group A rotavirus serotypes in 2006 (adapted from Plotkin, Vaccines 6th Edition, 2013)

VP4 Serotypes (P types [genotype])	Associated VP7 types (G types)
P1A[8]	G1, G3, G4, G9 and G12
P1B[4]	G2
P2[6]	G9 and G12

The World Health Organization (WHO) recommended in 2013 that rotavirus vaccines be included in all national immunisation programmes as a priority and accompanied by measures to ensure high vaccination coverage and timely administration. The first dose is recommended as soon as possible after 6 weeks of age at the first vaccination event to provide protection prior to natural rotavirus infection.[3] The WHO also recommend that the epidemiological impact of rotavirus vaccination be monitored by high quality surveillance. The Global Rotavirus Surveillance Network was established in 2008 and a component of this

network is the Global Rotavirus Laboratory Network whose role is to characterise the most prevalent genotypes.[4]

1.1 Participants/populations

Rotavirus vaccine is only recommended for infants from 6 weeks to 6 to 8 months of age. However, the literature reviewed considers the effects of rotavirus vaccination on children up to the age of 5 years and the impact on the wider population.

1.2 Interventions

There are two rotavirus vaccines in common use around the world. These contain live recombinant reassortant rotaviruses using animal (bovine) viruses that express both human and animal proteins.[1] Only vaccines currently licensed in New Zealand vaccines are considered here, although there are other vaccines in clinical development.

1.2.1 Rotarix®

Rotarix® (RV1; GlaxoSmithKline) is a monovalent vaccine administered orally in a two dose schedule at 6 weeks and 3 months of age. Rotarix contains reassorted human P1A[8]G1 strain only (known as RIX4414), which is protective against this strain and also other non-G1 strains.

1.2.2 RotaTeq®

RotaTeq® (RV5, Merck Sharp and Dohme NZ) contains five reassortant rotaviruses, which are propagated in Vero cells. Four of the human-bovine (WC3) strains express VP7 serotypes G1, G2, G3 and G4 and the fifth expresses strain VP4 (P1A[8]). It is administered orally in a three dose schedule at 6 weeks, 3 and 5 months of age.

2 Epidemiology

2.1 New Zealand epidemiology

Prior to the introduction of a rotavirus vaccine to the universal childhood schedule, around one in 52 children were hospitalised due to rotavirus gastroenteritis by the age of 3 years. In 2006, it was reported that rotavirus represented approximately 40% of the total gastroenteritis hospitalisation burden. The peak age for infection is the second year of life with a clear pattern of seasonality - more than half of the cases occur from mid-winter to early spring.[5] As rotavirus was detected by enzyme-linked immunosorbent assay (ELISA) at that time, and not by the more sensitive reverse-transcription polymerase chain reaction (RT-PCR), it is likely to be an underestimation of the burden.[6]

Rotavirus is not a notifiable infection in NZ. Sentinel hospital-based surveillance was begun in 2014 at Kidz First Children's Hospital in Counties Manukau District Health Board and was extended to Wellington, Hutt and Christchurch Hospitals in 2016, with the aim of monitoring the impact of the vaccination programme on rotavirus hospitalisations in children aged under 5 years and viral genotypes.

Rotavirus vaccine (RV5, RotaTeq®) was introduced to the NZ schedule in July 2014. Very soon after its introduction significant reductions in hospitalised rotavirus and all-cause gastroenteritis cases were observed from national hospital discharge data in children under 5 years of age, as presented in Figure 1. In 2015, the usual late winter/early spring seasonal peak was not observed as shown in Figure 2. At that stage, only infants younger than one

year had been vaccinated, and therefore, such a dramatic decline in rates for all children under 5 years of age demonstrated herd protection.[6]

Figure 1: Rotavirus and all-cause gastroenteritis hospitalisation of children under 5 years of age, by year (Source: Institute of Environmental Science and Research)

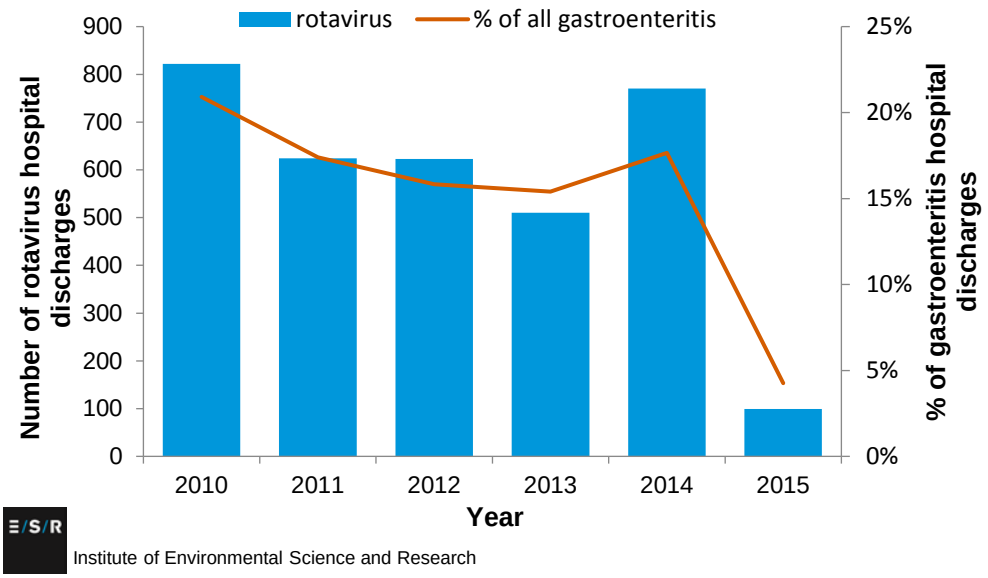
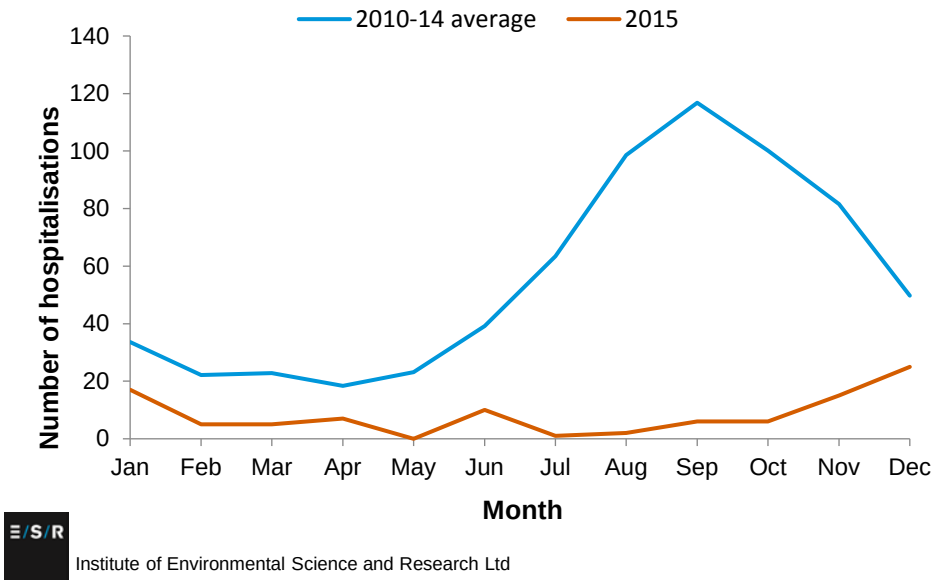


Figure 2: Rotavirus gastroenteritis hospitalisations in children under 5 years of age, by month



Data collected during December 2014 and December 2015 at the Kidz First sentinel site found that the most prevalent rotavirus genotypes were P[8], with G12 as the most predominant (9/19, 47.4% of samples), followed by G1 and G9 genotypes (4/19, 21.1% each). One case was vaccine-like P[8]G1 genotype.[6]

An Auckland-based study compared hospitalisation and laboratory testing rates for rotavirus infections prior to the introduction of RV5 (2009-2013), after (2015) and during the year of introduction (2014). Following RV5 introduction, there was a 68% decline in RVGE

hospitalisations in children aged under 5 years (from 258/100,000 to 83/100,000) and a 17% decline in all-cause gastroenteritis admissions (1815 to 1293 / 100,000), including in age-groups too old to have received vaccine. The study estimated that RV5 prevented 316 (range 289-349) acute gastroenteritis (AGE) admissions, including 180 (142-219) laboratory-confirmed RVGE for children under 5 years in the Auckland region during 2015. However, there was no change in number of rotavirus tests requested after the vaccine was introduced. Around one-third (19/58) of positive rotavirus tests were found to be false by confirmatory testing in the post vaccine period.[7]

3 Safety

3.1 Background

Although rotavirus vaccines are orally administered, they contain live viruses which have the potential to induce systemic responses following viral replication in the intestinal cells.

One severe adverse event that has been associated with rotavirus vaccination is a potentially enhanced risk of intussusception – a form of bowel obstruction in which the bowel folds in on itself. If untreated intussusception is usually fatal; mortality rises rapidly after the first 24 hours. The aetiology of intussusception is often unknown and approximately 90% of cases are idiopathic.[8] In 1998, a rotavirus vaccine called RotaShield was quickly withdrawn from the US immunisation programme after it was shown to significantly increase the incidence of intussusception.

Close scrutiny has been conducted of the newer vaccines, RV1 and RV5, to ensure that this risk is minimalised. The peak age of risk of intussusception is 6-8 months (60% of cases are younger than 1 year, 80% under 2 years of age).[8] Precautions are advised to reduce this risk and include adding a contraindication to rotavirus vaccine for children with congenital bowel defects or previous episodes of intussusception, and for no doses of these vaccines to be administered to infants older than 25 weeks.

The literature surrounding the safety of rotavirus vaccines is reviewed here to further gauge the risk of intussusception. Other safety factors are considered, these include the risk of infection with vaccine-derived reassortant strains and the use of the vaccine in hospitalised infants such as preterm infants.

Rotavirus vaccines are contraindicated for infants with severe combined immunodeficiency (SCID), those with a history of intussusception, or have had a severe allergic reaction to previous doses or components of the vaccine.[9, 10] Safety concerns around the use of rotavirus vaccine in severely immunocompromised infants was raised in 2010, when three infants with SCID were described as having vaccine-acquired disease.[11] Further details of safety in these groups is not reviewed. Since the first dose of rotavirus vaccine is often given from 6 weeks of age for some infants contraindicated indications may not have yet been identified and vigilance is required.[12]

An integrated analysis of the safety and reactogenicity data for 28 randomised controlled trials (RCT) found that RV1 had a similar safety profile to placebo.[13] Since reactogenicity has been characterised through clinical trials it is not considered further in this review.

3.2 Intussusception

3.2.1 Incidence of intussusception pre rotavirus vaccination

Before reviewing the potential for rotavirus vaccines to increase the risk of intussusception, the background of intussusception incidence is considered. In New Zealand, prior to the introduction of routine rotavirus vaccination in 2014, there were 794 cases of intussusception in children aged 0-36 months over the 16 years from 1998-2013, an average of 50 cases per year (range 39-62), and 56% of the cases occurred in the first year of life. The rate of incidence varied between years, the overall rate across all years for infants aged under 1 year was 56.1/100,000 child-years (95% CI 41.7-71.2), with seasonal peaks in spring and autumn months. An important consideration for the vaccine schedule is that, although there was no difference in incidence between ethnicities, cases occurred at a younger age in Māori and Pacific infants at median age of 7.8 months (interquartile range 5.9-11.6) and 7.5 months (5.5-12.3), respectively, compared with Asian (10.5 months [7.0-17.1]) and other ethnicities (10.2 months [8.2-12.3]), and for European at 9.2 months (5.8-15.8).[14]

The overall incidence rates of intussusception in Australia were very similar to NZ at 54 per 100,000 child-years in children aged ≤24 months during 2000-2006 based on national hospital discharge data.[15]

The annual incidence rates for hospitalised cases younger than 12 months of age in the UK and Republic of Ireland, as reported by clinicians through the British Paediatric Surveillance Unit, were 24.8 and 24.2 / 100,000 live births, respectively. The highest incidence rate was seen in the fifth month of life in England, at a rate of 50.3/100,000 live births (95% CI 33.4-72.7), with a significant seasonal trend of cases increasing in the winter and spring ($p=0.001$).[16]

Conclusions

In general, the overall incidence of intussusception is around 50/100,000 children particularly during the first year of life. Ethnicity appears to influence the age of onset, cases in Māori and Pacific children in NZ have occurred at a younger age than for European and other ethnicities and the highest incidence rate was seen in the fifth month of life in England. As with RVGE, intussusception also occurs seasonally.

3.2.2 Incidence of intussusception post-vaccination

In an Australian study, Carlin et al (2013) demonstrated by a self-controlled case-series analyses using age-adjusted regression models that there was a statistically significant increased risk of intussusception associated with both RV1 and RV5 vaccination during days 1-7 post vaccination following the first dose given (scheduled at 2 months of age), but not the second dose (at 4 months of age). Based on 306 confirmed cases, the relative incidence of intussusception days 1-7 post first vaccination with RV1 was 6.8 (95% CI 2.4-19.0) and RV5 was 9.9 (3.7-26.4) and statistically significant for both ($p<0.001$). For days 8-21 after RV1 the relative incidence was 3.5 (1.3-8.94; $p<0.01$) and for RV5 was 6.3 (2.8-14.4; $p<0.001$). The relative incidences were translated to attributable risks of 4.3 (0.8-23.3) cases per 100,000 RV1 vaccinated infants and 7.0 (1.5-33.1) cases per 100,000 RV5 vaccinated infants. Given the overlapping confidence intervals between the vaccines, the midrange estimate was 5.6 additional cases of intussusception per 100,000 vaccinated infants, which translated to an additional 14 cases nationally per year. It was estimated the rotavirus vaccination prevented 6500 cases AGE per year in children under 5 years of age, therefore, it was concluded that the risk of vaccination was outweighed by the benefit.[17, 18]

Another self-controlled case-series evaluation was conducted in the UK to investigate the risk of intussusception following vaccination of infants at 2 and 3 months of age with RV1. It found that the attributable risk after dose one and two was 1.91 and 1.49 per 100,000 doses, respectively. The peak incidence was 1-7 days after dose one, with an estimated 13.9 out of 15 cases (93%) being attributed to the vaccine using a historical age data model. A significantly elevated risk was also observed 8-21 days after the second dose (64%; 8.9/14). From these data, the RV1 programme in the UK was estimated to potentially cause 21 intussusception hospitalisations annually. However, since around 25,000 gastrointestinal infection admissions were prevented, the benefit was also found to outweigh the risk.[19]

A systematic review conducted by Velázquez et al in 2017 considered the safety of RV1 and RV5 in Latin American and the Caribbean and found them to be safe and well tolerated. Pooled analysis found no increase in risk of intussusception following receipt of RV1 (in three trials including 71,690 participants) and only one confirmed case was reported following RV5 compared with three placebo group cases (in 898 vaccine and 904 placebo recipients). The latter was the only study to consider severe adverse events for RV5, in which, one case of febrile infection and gastroenteritis was associated with RV5. No increased risk of severe outcomes was indicated by pooled analysis of the RV1 studies.[20]

During 28 international phase II and phase III double-blind RCTs, healthy infants aged 6-20 weeks received two or three doses of RV1 vaccine or placebo at 4-8 weekly intervals. Out of a sample size of over 100,000 subjects, 11 cases of intussusception received RV1 and seven cases received placebo (relative risk [RR] =1.39 [95% CI 0.49-4.27], p=0.66).[13]

A meta-analysis of post-licensure surveillance studies, conducted across different geographical regions, found that the overall estimated relative risk of intussusception during the 7 days following dose one was 5.4 (95% CI 3.9-4.3) for RV1 and for RV5 was 5.5 (3.3-9.3) across three studies for each vaccine; and following dose two the RR was 1.8 (1.3-2.4, four studies) for RV1 and 1.7 (1.1-2.6, three studies) for RV5. Hence, the risk of intussusception is similar between both vaccines, indicating this is expected to be a class effect of the currently available vaccines. The risk is approximately ten-fold lower than reported for RotaShield.[21]

No evidence was found of an increase in risk of intussusception in Canada following the introduction of rotavirus immunisation based on hospital discharge data for infants age less than 1 year from January 2003 to December 2013 (p=0.296). All jurisdictions used RV1 (Rotarix®) vaccine, which was introduced in staggered fashion over time by different regions during August 2011 to September 2015. The annual rate ranged from 20-30/100,000 infants, with the highest rate in infants aged 4 to less than 8 months and the lowest rates in those aged less than 2 months and 10 – less than 12 months of age. Males were at greater risk than females across and within all age groups. Prior to the immunisation programme, the rate of intussusception was 23.4/100,000 (95% CI 21.5-25.4) compared with 22.4/100,000 (18.3-27.4) after the rotavirus vaccination programme was introduced.[22]

An analysis of Vaccine Safety Datalink (VSD) data found that the incidence of intussusception among vaccinated children was not statistically different to those who had received no rotavirus vaccine (incidence risk ratio = 0.94 [95% CI 0.5-1.75]) and that rotavirus vaccination did not modify the risk of naturally occurring intussusception from 1 month to 1 year following vaccination. There were 50 cases of intussusception out of 186,488 (0.027%) vaccinated children and 22 cases out of 64,089 unvaccinated children (0.034%).[23]

Conclusions

Although the data are inconclusive in terms of demonstrating causality due to rotavirus vaccination, there is potentially a small increase in risk of intussusception clustered within a week following the first dose of rotavirus vaccine in infants aged 2-6 months. This is earlier than seen in unvaccinated infants for whom the peak incidence is around 6-8 months of age.

No overall increase in risk of intussusception has been observed. The benefit of rotavirus vaccination outweighs the potential risk of intussusception, which can be minimised by vaccinating within the maximum age limits and for parents to be made aware of the symptoms of intussusception and seek medical attention promptly.

3.3 Vaccine-derived rotavirus gastroenteritis

Cases have been reported of patients with severe RVGE related to RV5 vaccination. The potential incidence of vaccine-derived RVGE was reviewed by Aliabadi et al (2016). Vaccine-reassortant or derived strains were found in 5 out 106 cases severe RVGE during a case series study; four had been recently vaccinated. Although cases of severe RVGE have been identified to be potentially related to vaccine-derived rotavirus strains, the overall incidence appears to be small.[24]

Vaccine strain rotavirus was detected up to 43 days (median 12 days) after RV1 vaccination in 38 out 49 children hospitalised for gastroenteritis in Lothian, Scotland. Of these children, in 15 (39.5%) children were found to have other pathogens to account for their symptoms and 17 (44.7%) were assigned alternative diagnoses, including non-gastrointestinal diagnoses: unspecified viral illness, cow's milk allergy, congenital heart disease and issues related to prematurity, inguinal hernia, gastroesophageal reflux and issues related to congenital cytomegalovirus. It was concluded that, since vaccine virus is shed following vaccination, the possibility of an alternative diagnosis be considered to account for gastroenteritis in recently vaccinated children with a positive rotavirus result.[25]

3.4 Virus shedding and horizontal transmission

3.4.1 Virus shedding

Virus shedding was compared following vaccination with either RV1 or RV5 vaccine in stool samples from 87 Taiwanese infants. After the first vaccine dose, a peak in virus shedding occurred between days 4 and 7, and was detected from day 1 and up to 25-28 days post vaccination. Following the second dose of RV1 virus was detected for up to 15 days, and for 14 days after doses two and three of RV5. There was no significant difference in shedding rates between dose one and two: odds ratio 1.26 for both doses and vaccines. Infants who received RV1 shed significantly higher viral loads than RV5 after the first and second doses ($p=0.001$ and 0.039, respectively). The clinical significance of the difference was not investigated. The assays did not distinguish between circulating wild-type and vaccine-type rotavirus. Since the number of samples provided was small after day 14, it was not possible to determine if either vaccine resulted in more prolonged shedding.[26]

This study also demonstrated a marked difference in sensitivity between ELISA and RT-PCR. It found, for example, that in samples taken 4-7 days following dose one of RV1, only 7/31 (23%) were found to be positive for rotavirus by ELISA whereas 28/31 (90%) were positive by RT-PCR. However, it was noted that although RT-PCR is more sensitive, it may have detected RNA of degraded virus that is cannot be transmitted.[26]

3.4.2 Horizontal transmission

Horizontal transmission of vaccine-type rotavirus has previously been reported between twins. Each of twin pair was randomly selected to receive either two doses of RV1 or placebo. Although transmission was demonstrated in the 18% of the unvaccinated infants, none were associated with gastroenteritis.[27]

A study in Japan investigated the spread of vaccine-strain rotavirus from vaccinated infants to unvaccinated infants in a foster home. Although vaccine-strain virus was persistently detected in stools samples of all four vaccinated infants (160 samples), no virus was detected in 22/23 unvaccinated infants samples (766 samples). One apparently unvaccinated infant was proved to have been vaccinated prior to study enrolment. The study concluded that there was limited transmission of vaccine-strain rotavirus between infants in close contact.[28]

In the literature, one case of horizontal transmission resulting in severe RVGE has been described. A normally healthy two-year old girl was hospitalised with severe AGE that was positive for rotavirus during the non-endemic season. The child's younger sibling had been vaccinated with RV1, and remained healthy, nine days before disease onset in the child. The whole genome of this virus was sequenced and found to be very similar to RV1, with the exception of five amino acid mutations in genes associated with viral virulence, suggesting reverse reassortment of the vaccine virus. The article concluded that this was the first case reported of a RV1-associated secondary infection to result in severe RVGE in an infant without underlying disease.[29] No further cases have been reported.

Conclusions

Vaccine-strain virus can be detected in stools of infants following vaccination, peaking at 4-7 days following dose one, lasting up to 28 days and for up to 15 days following second dose of RV1 and RV5, and third dose of RV5.

There is a potential for horizontal transfer to occur, but good hygiene practices can minimise this risk. Only one case of RVGE associated with vaccine type transmission has been reported and in this case the virus had possibly reverted back to a virulent form.

3.5 Vaccine use in neonatal intensive care units

Preterm infants, particularly those with multiple comorbidities, are at increased risk from severe RVGE. Very-low-birth-weight infants have a 2.6-fold increase in rotavirus hospitalisation compared with full-term infants. However, there are concerns around using rotavirus vaccination in neonatal intensive care units (NICU), particularly around a theoretical risk of nosocomial transmission of vaccine-strain virus. In some areas due to this theoretical concern, infants are vaccinated upon hospital discharge, but frequently, age-restrictions mean that some infants remain unvaccinated. Internationally, recommendations vary around preterm infant eligibility.[30]

A retrospective study was conducted at the Children's Hospital of Philadelphia, US, where age-appropriate RV5 was routinely administered in NICU through enteral feeds. Gastrointestinal symptoms were investigated in unvaccinated infants matched to similar proximity within the NICU (located in the same 'pod') as 96 vaccinated infants within 15 days of vaccination. Most of these vaccinated and unvaccinated infants were preterm (mean gestational age 32.6 ± 5 weeks and 34.8 ± 5 weeks, respectively). By interrogating electronic medical records, 51 (out of a total of 801) unvaccinated infants were identified as having been prescribed bowel rest, abdominal imaging and antibiotics within 15 days of exposure to a vaccinated infant; of these, 40 had been admitted with pre-existing

gastrointestinal symptoms and the remainder had concomitant medical conditions to explain the development of their gastrointestinal symptoms; two for whom stools samples were tested were negative for rotavirus. Therefore, none of the unvaccinated infants appeared to have developed gastrointestinal symptoms as a result of exposure to vaccine-derived rotavirus. There were no documented cases of nosocomial RVGE in the NICU and the study did not find evidence of nosocomial transmission of rotavirus (vaccine-strain or wild-type) between infants within the NICU.[31]

In this study, symptoms in the vaccinated infants were monitored before and after vaccination. Of the vaccine recipients, 24/96 (25%) were asymptomatic post-vaccination and 49/96 (51%) were symptomatic, but unchanged from pre-vaccination baseline; symptoms that changed from baseline were frequently considered not vaccine associated (e.g. narcotic withdrawal, formula fortification or change). This study was unable to exclude the possibility that RV5 contributed to some of the clinical changes.[31]

The tolerability of at least one dose of RV5 vaccine and nosocomial rotavirus transmission were examined in a retrospective chart review of 102 hospitalised infants in two NICUs in Quebec, Canada. The mean gestational age of the infants was 31 weeks (95% CI 30-32). During July 2011-March 2013, as compared with 3 days prior to vaccination, no changes in the average risk of gastrointestinal complications or total daily feeding were detected overall, among participants for up to 4 weeks following RV5 administration: the difference in risk of gastrointestinal complications was 2% (95% CI −9% to 14%) following administration of any RV5 dose, and −3% (95% CI −17 to 11%) following administration of dose one. Overall, 18% (13-25%) of vaccine recipients had diarrhoea or vomiting following and RV5 dose and 40% (32-48) following dose one. These infants also received DTaP vaccination concurrently, and although exacerbation of apnoea and bradycardia symptoms were the most common adverse events following vaccination (18% of vaccinated infants experienced increase in the mean number of episodes of either of these symptoms following vaccination), the study was unable to determine the effect of RV5 on these symptoms alone.[32]

The rates of nosocomial rotavirus were similar and very low before and after NICU-based vaccination. However, the sample size was too small to detect small changes in the rate of nosocomial rotavirus between pre- and post-vaccination periods or low frequency adverse events. It was noted that, had they waited until discharge to vaccinate these infants, up to 40% of the vaccine recipients in this study would not have been vaccinated due to maximum age restrictions (age 104 days). Even with older age restrictions in Quebec of up to 139 days, 20% of infants would not have been vaccinated. The authors believe that, at the medical professionals' discretion, the benefits of vaccination outweigh the potential risk of viral transmission. Further studies are needed to evaluate RV5 safety, viral shedding and vaccine virus transmission.[32]

Conclusions

The risk of nosocomial transmission of vaccine-type rotavirus within NICU appears to be negligible. High standards of hygiene practices are required in NICUs, and therefore, the risk of nosocomial infections are significantly reduced.

In general, RV5 is to be well tolerated by premature infants, however, these infants frequently have multiple medical issues and the studies were unable to determine if rotavirus vaccination had a direct effect on any clinical changes observed in these unwell infants.

Rotavirus vaccination, given in NICU, provides protection to preterm infants outside of the hospital, particularly for those too old to receive the vaccine upon discharge.

3.6 Mixed vaccine schedule

The safety of administering mixed schedules of RV1 and RV5 vaccines was assessed in a randomised clinical trial. Two groups received two doses of one vaccine only (RV5-RV5 or RV1-RV1) and three groups received three doses of mixed schedules (RV5-RV1-RV1; RV5-RV5-RV1; RV1-RV5-RV5) from mean age of 9 weeks; doses given one month apart. No statistically significant difference in solicited symptoms were reported between single vaccine and mixed vaccine schedules. Although significantly higher proportion of cases of fever, vomiting and any solicited symptoms were observed in the RV1-RV5-RV5 groups overall compared with the RV1-RV1 reference groups, overall; no statistical difference was shown for the first and second doses when stratified by dose. Of the 33 cases of haematochezia (blood in faeces), 14 were vaccine attributable, half of which were in the RV1-RV5-RV5 group. All episodes were mild and resolved without sequelae. The most frequently reported adverse event was irritability across all groups. The study concluded that mixed schedules were safe and well tolerated.[33]

3.7 Summary of vaccine safety

Oral rotavirus vaccination is generally very safe and few adverse events are associated with receipt of the vaccines. There is a suggestion of an increased incidence of intussusception within a week following the first dose and two to three weeks after the second dose of the vaccines. However, due to the rarity of intussusception, a causal link or an overall increase in incidence have not been confirmed. Since the peak incidence of intussusception in infants is around 6-8 months of age in NZ, it is advised that the first dose of vaccine is administered prior to this high-risk period and that all doses are given before 8 months of age.

Viral shedding occurs for around a week and up to four weeks following vaccination. Horizontal transmission of vaccine-type rotavirus can occur but does not appear to result in gastroenteritis. It is unknown whether any protection is conferred.

Overall, rotavirus vaccination appears to be safe and well tolerated when given to premature infants in NICU and has the potential to provide protection upon hospital discharge, particularly for those who are older than the maximum age limit when discharged.

Mixed schedules with different rotavirus vaccines are safe and well tolerated. There may be a slightly increased risk of solicited symptoms such as fever and vomiting when RV1 is followed by RV5, compared with RV1 only.

4 Immunogenicity

4.1 Background

Immunity against rotavirus is primarily mucosal. VP7 and VP4 proteins in the outer capsid of rotavirus induce neutralising antibodies in the mucosal surfaces of the intestine and in the circulation. The rotavirus first infection is often most severe and reinfections are milder or asymptomatic. Since viral replication occurs in absorptive epithelial cells in small intestine, mucosal IgA is necessary for clearance of rotavirus infection and protection from re-infection. However, the presence of secretory IgA in the stools after infection is short-lived. Memory is likely to be due to the presence of rotavirus-specific memory B cells in the intestinal lymphoid tissue (lamina propria). In addition, there is evidence of roles for both cytotoxic and helper T cells. During rotavirus infection, virus antigens are also present in systemic circulation, although the significance of this is unknown.[1]

4.2 Immunoglobulin A correlate of efficacy

No immunological correlate of efficacy has been established for rotavirus vaccines. However, anti-rotavirus IgA seropositivity is associated with lower incidence of rotavirus gastroenteritis. Secretory IgA is considered to be an acceptable measure of responsiveness to RV vaccines in clinical trials. A meta-analysis of RV1 clinical trial data, measured the regression between clinical vaccine efficacy (VE) data against all and severe RVGE, and predicted VE based on immunogenicity data (designated VE1). The data supported the hypothesis that post vaccination serum levels of anti-RV IgA ≥20 U/ml may serve as a correlate of efficacy in clinical trials.[34]

4.3 Breastfeeding and maternal antibody

Analysis of breastmilk samples from mothers of infants aged 4-29 weeks found higher levels of rotavirus-specific IgA and the non-antibody components, lactoferrin and lactadherin, and greater neutralising activity in samples from India and South Africa than from the US against three rotavirus vaccine strains (Rotarix, RotaTeq G1 and 116E [a neonatal strain in development]). The inhibitory effect of lactoferrin was dose and species dependent. Rotavirus IgA titres were as much as four-fold higher in Indian and South Africa breastmilk samples than the US samples ($P<0.05$). The highest rotavirus neutralising activity titres were in Indian samples and lowest from the US. The study concluded that alternative vaccine strategies are required in breast feeding populations, particularly in developing countries.[35]

A study in Soweto, South Africa assessed the potential inhibitory effect of pre-existing anti-rotavirus antibodies on the immunogenicity of RV1 in 181 infants from a low-income background. It found that high levels of pre-existing serum IgG, including maternally acquired IgG, had a significantly inhibitory effect on RV1 immunogenicity and seroconversion to IgA in the infants ($p=0.004$). This effect may be associated with an observed reduction in vaccine efficacy among African children.[36]

The overall IgA seroconversion frequency in response to RV1 vaccination of 216 infants in Zambia was 60.2%. The study found that infants who were IgA seropositive at baseline for rotavirus-specific IgA were less likely to seroconvert following vaccination compared with seronegative infants ($p=0.04$). Around one quarter of infants were seropositive pre-vaccination, suggesting high exposure to rotavirus from birth. The study also found seasonally variable high titres of maternal IgA in breast milk. It concluded that low immunogenicity of RV1 vaccine could result, in part, from exposure to high antibody titres in breast milk and early exposure to wild-type rotavirus infections. Maternal IgG also showed a trend to affect seroconversion in infants, although this was not statistically significant in this study ($p=0.06$). The authors argue that although other studies have shown no benefit of withholding breastfeeding, the levels of antibodies reported in these mothers are greater than in those reported in other studies. Where infants have a high risk of exposure to rotavirus, the benefits of withholding breastfeeding are uncertain.[37]

An RCT conducted in Pakistan found that withholding breastfeeding an hour prior to RV1 administration does not increase anti-rotavirus IgA seroconversion. Conversely, IgA seroconversion in infants immediately breastfed tended to be higher. After two doses of RV1, seroconversion was 16.6% (95% CI 11.9-22.7; $n=181$) for the withholding arm and 29.1% (22.8-36.3; $n=172$; $p=0.005$) in the immediately breastfed group.[38]

Conclusion

Antibodies and non-antibody components of breast milk and maternal IgG can affect the immune response to rotavirus vaccines in infants. However, this effect is most pronounced when mothers have had high exposure to rotavirus, as seen in low income situations. In these circumstance, infants are also likely to be exposed to rotavirus from an early age, and therefore, the presence of maternal IgA and IgG antibodies are likely to provide protection for the youngest infants against RVGE.

4.4 Mixed vaccine schedules

An open-label multicentre study conducted in the US compared the immunogenicity of mixed schedules with different rotavirus vaccines. Infants aged 6-14 (mean 9.2) weeks of age were randomised to receive RV1 or RV5 in single vaccine or mixed vaccine regimes: group 1 RV5-RV5-RV5; group 2 RV5-RV1-RV1; group 3 RV5-RV5-RV1; group 4 RV1-RV1 and group 5 RV1-RV5-RV5. All sequential mixed schedules were shown non-inferior compared with the single vaccine groups. Group 5 showed significantly high proportion of infants with seropositive vaccine antigen-specific IgA (≥20 U/ml) than group 4 (single vaccine, RV1; $p<0.0001$) at 3-6 weeks after last dose of vaccine.[33]

4.5 Summary

The immunity against rotavirus is not fully understood and there is uncertainty around a reliable correlate of protection. Rotavirus vaccines induce serum IgA, which has been identified as a potential correlate of protection. No studies were identified that considered serum IgG levels.

The presence of maternal antibody probably provides protection to the youngest infants (up to 3 months of age) against rotavirus. However, high levels of rotavirus antibody and non-antibody components of breast milk also affect the immune response to rotavirus vaccines. These effects appear to be most pronounced in infants from LMIC where rotavirus infection is most prevalent. It is unlikely that withholding breast feeding will improve the vaccine response in these high exposure situations.

Mixed schedules are non-inferior to single vaccine schedules and induce adequate IgA seroconversion.

5 Effectiveness in disease control

5.1 Background

This section will consider literature reporting on the vaccine effectiveness of rotavirus vaccines in preventing rotavirus hospitalisations and severe rotavirus gastroenteritis in children younger than 5 years. Further details on the impact of vaccination programmes are given in section 6.

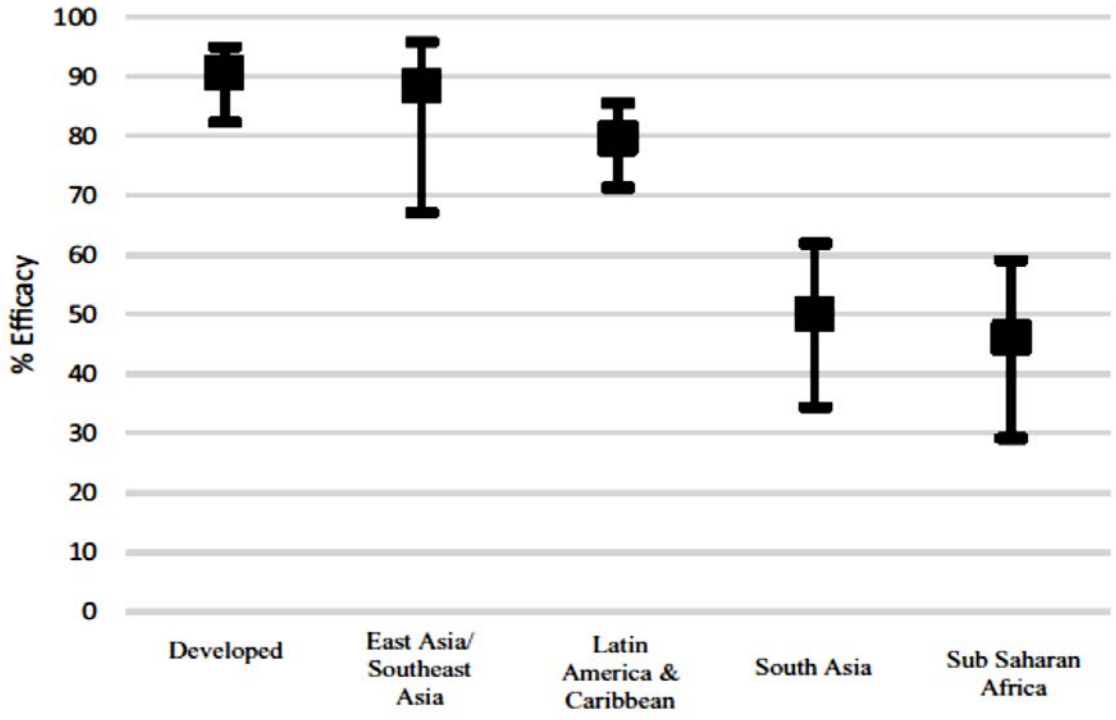
5.2 Reviews

Some of the published literature on rotavirus vaccine efficacy and effectiveness were specifically conducted in Latin America, Caribbean and LMIC settings. Since these regions have different rotavirus burden and prevalence than seen in high income countries (HIC), including NZ, these individual reviews are not presented here. However, systematic reviews of rotavirus vaccine effectiveness are considered to provide an overall picture worldwide.

A systematic review was conducted to investigate vaccine effectiveness (VE) during the first decade post-licensure of RV1 and RV5 from 2006 to 2016 (Jonesteller et al 2017). Overall VE against rotavirus hospitalisation, emergency department (ED) visits and outpatient encounters were stratified by child mortality rate in under 5 year-olds of the country where the study was conducted. Mean VE for RV1 from 13 studies was 84% (range 19-97) in countries with low child mortality [HIC], but decreased to 75% (range -2 to 94; eight studies) and 57% (range 18-69; nine studies) in countries with medium and high mortality [LMIC], respectively. VE of RV5 was 90% (range 63-100; 20 studies) and 45% in low and high child-mortality countries (seven studies), respectively. When disease severity was considered, VE tended to be greater against more severe rotavirus disease. The median VE estimates for hospitalisation were 88% (70-95) and 94% (83-100) for RV1 and RV5, respectively, and VE estimates for ED visits were 80% (78-89) for RV1 and 81% (74-91) for RV5 for low mortality countries.[17, 39] The study concluded that, across a range of mortality settings, both vaccines are effective against RVGE and that these data support the WHO recommendations and that good protection against severe rotavirus disease is provided during the first two years of life.[39]

The effectiveness of rotavirus vaccination globally in under 5-year old children was assessed in a systematic review of efficacy and effectiveness data published from 2011 to 2014 (Lamberti et al 2016). As shown in Figure 3, the efficacy against severe rotavirus diarrhoea was 90.6% (95% CI 82.3-95.0) and 94.3% (72.8-98.8) against rotavirus hospitalisation in HIC regions. The lowest efficacy was seen in Sub-Saharan Africa (50.0% [34.4-61.9] and 57.5% [7.2-80.8], respectively). The review concluded that rotavirus vaccination provides protection against rotavirus diarrhoeal outcomes in children younger than 5 years, globally.[40]

Figure 3: Efficacy of rotavirus vaccination on severe rotavirus by region (with permission, Lamberti 2016)



A pooled analysis of data from five studies found that the effectiveness of rotavirus vaccination against RVGE hospitalisation or ED presentation differed significantly depending on the season of a child's birth. For infants aged 6-12 months, the adjusted VE was 72% (95% CI 61-80) for infants born during the rotavirus season in Latin America and the US, and 84% (78-88) for those born in other months. No specific cause for this variation was identified.[41]

The effectiveness of rotavirus vaccines was 53% (95% CI 46-60) against rotavirus infection, 73% (66-78) against hospitalisation and 74% (68-78) against severe diarrhoea, according to a systematic review and meta-analysis of observational, post-licensure studies conducted across upper-middle and low income countries of South and Latin America.[42]

A Bayesian network meta-analysis, which reanalysed of data collected as part of an earlier Cochrane Database systematic review, found similar VE between RV1 and RV5 vaccines. No statistical difference was found in the effectiveness of the two vaccines for prevention of severe rotavirus disease for up to 2 years (odds ratio 2.23 [0.71-5.20]).[43]

Conclusion

The vaccine effectiveness of rotavirus vaccines varies between countries according to the disease burden and economic status. In HIC, VE of both RV1 and RV5 is more than 80% against severe rotavirus disease and higher (>90%) against rotavirus-associated hospitalisation. Whereas in LMIC effectiveness is lower (around 50-70% against severe disease).

5.3 Socioeconomic status

A retrospective cohort study was conducted in Québec, Canada to assess VE of RV1 in preventing RVGE and all-cause AGE among children younger than 3 years of age according to neighbourhood level socioeconomic status (SES). The study considered three cohorts of children: group 1 – vaccinated and born during post-universal vaccination period (2011-2013, n=5,033); group 2 – unvaccinated (born 2011-2013, n=1,239); and group 3 – unvaccinated, born pre-universal vaccination (2008-2010, n=6,436). The universal rotavirus programme was introduced in November 2011. As of January 2012, only 13.6% of one-year old children were immunised for rotavirus, and in 2014 vaccine coverage was 85.9% The adjusted VE of two RV1 doses in preventing AGE hospitalisation was 62% (95% CI 37-77) and RVGE hospitalisation was 94% (52-99). Stratified analyses showed that VE against AGE was significantly lower for children living in neighbourhoods with higher rates of low-income families compared with those with lower rates of low-income families, (30% versus 78%, p=0.027). The study concluded that although RV1 is highly effective in preventing severe gastroenteritis in young children, even in a HIC like Canada, VE is influenced by SES. Further studies based on individual SES and to determine factors that influence rotavirus VE are required.[44]

5.4 Rotavirus strain-specific effectiveness

The strain-specific effectiveness of RV1 and RV5 was assessed by a systematic review of literature published during 2006-2014 (Leshem et al 2014). Strains were classified as homotypic, partly heterotypic or fully heterotypic based on the amount of antigen-matching between the vaccine and the strain. The prevalence of rotavirus strains after vaccine introduction was also examined. RV1 pooled VE was 94% (95% CI 80-98), 71% (39-86) and 87% (76-93) against homotypic, partially and fully heterotypic strains, respectively, in high income settings. RV5 pooled VE was 83% (78-87) against homotypic strains, 82% (70-89)

against partly heterotypic strains, 82% (70-89) against single-antigen (G or P type) vaccine type strains and 75% (47-88) against single antigen non-vaccine type strains. There was no significant difference in VE noticed for either vaccines in any setting (all p>0.05). Although, no vaccine-induced selective pressure was identified, continued surveillance is important to identify emergent or changes to predominant strains.[45]

5.5 Mixed vaccine schedules

The effectiveness of mixed three-dose schedules with rotavirus vaccines was compared with single vaccine schedules in the US. Out of 2,425 fully vaccinated children, 75 (3.1%) had received mixed rotavirus vaccines; and 715 were unvaccinated. Of the children who visited hospital or ED with diarrhoea and/or vomiting, 578 tested negative for rotavirus and 212 tested positive. The study found that three-dose rotavirus vaccination with mixed RV1 and RV5 vaccines was statistically effective (adjusted VE 80%; 95% CI 51-92) against rotavirus gastroenteritis. These data were similar to previously published data for single vaccine schedules for the same population (three doses of RV5-only VE 80% [74-84]; complete two dose RV1-only VE 80% [68-88]). The authors reported that, by extrapolation based on National Immunization Survey findings in 2013, approximately 100,000 children in the US would be immunised with mixed rotavirus vaccines, annually.[46]

5.6 Childhood seizures

Rotavirus vaccine (RV5) was shown to be 35.8% (95% CI 26.0-44.2%) and 38.0% (20.1-51.9%) effective against febrile seizure-associated ED presentation and hospitalisation, respectively, in children aged 8 months to 2 years 7 months in Queensland, Australia. Protection against febrile seizures was maintained for up to 4 years after RV vaccination. It was noted that some RV-associated events will have been excluded since the analysis was limited to febrile seizures and did not include afebrile seizures, in which, rotavirus infection has been implicated.[47]

5.7 Summary of effectiveness

Rotavirus vaccines are 80 – over 90% effective in preventing rotavirus gastroenteritis in HICs. Both RV1 and RV5 have been shown to be highly effective against both vaccine and non-vaccine type rotavirus strains – although ongoing surveillance is recommended to watch for any emergent or new predominant strains.

Mixed schedules with RV1 and RV5 are as effective as single vaccine schedules when three doses are administered.

The effectiveness of rotavirus vaccines is less in LMIC with higher levels of circulating enteric pathogens and rotavirus. Coverage in these countries is also variable and has possible implications for herd immunity. However, even in HIC, low socioeconomic status has been shown to affect rotavirus vaccine effectiveness.

Rotavirus vaccination is moderately effective at preventing febrile seizures in young children for 2-4 years after vaccination.

6 Impact of rotavirus vaccination programmes in high income countries

6.1 Background

Based on clinical trial efficacy data and early vaccination impact data in the Americas, the World Health Organization (WHO) recommended that rotavirus vaccine be included on all national immunisation programmes, especially in countries with high mortality associated with gastroenteritis.[39]

This section will consider the impact that rotavirus immunisation programmes have had on the burden of rotavirus infections, RVGE and hospitalisations of young children. Focus will be on high income countries, such as NZ.

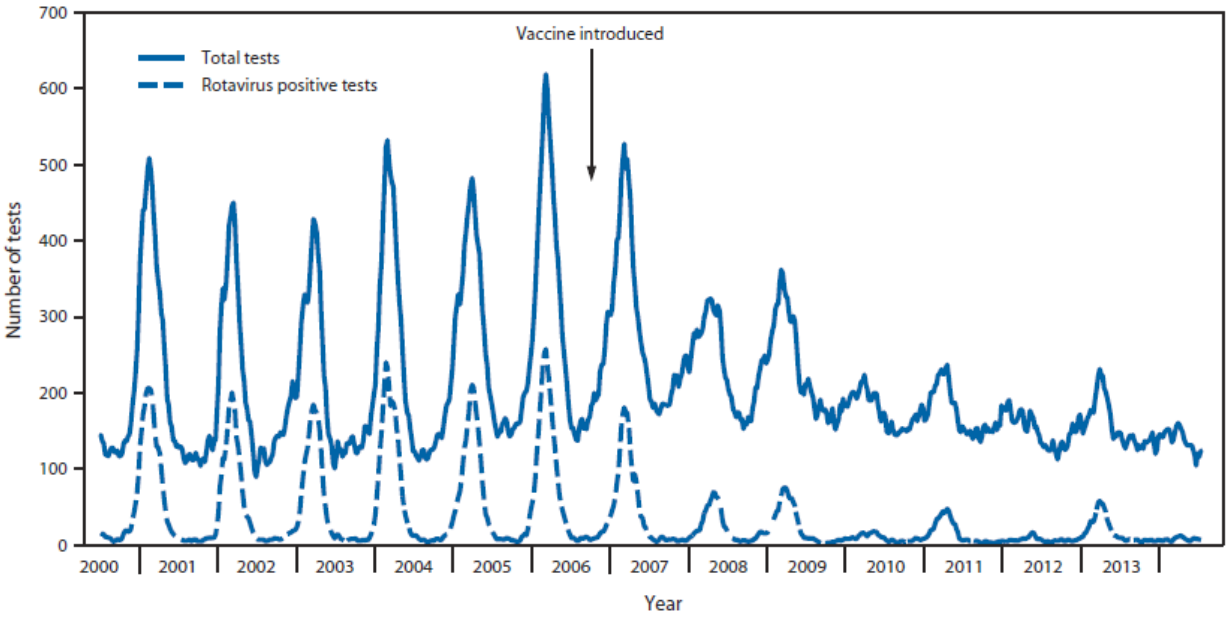
As shown in section 2, the introduction of rotavirus vaccination to NZ has resulted in a dramatic decline in RVGE and all cause gastroenteritis hospitalisations of under 5 year-old children, including for children not eligible for vaccination.

6.2 Review

A systematic review conducted by Burnett et al in 2017 examined the global impact of rotavirus vaccination on hospitalisations for all-cause AGE and RVGE. It found that RVGE was reduced by a median of 67% overall over the 10-year period since the vaccines became available, ranging from 59-71% in countries with medium, high and low child mortality. For all cause AGE, median reduction was 38% overall ranging from 30-46%.[48]

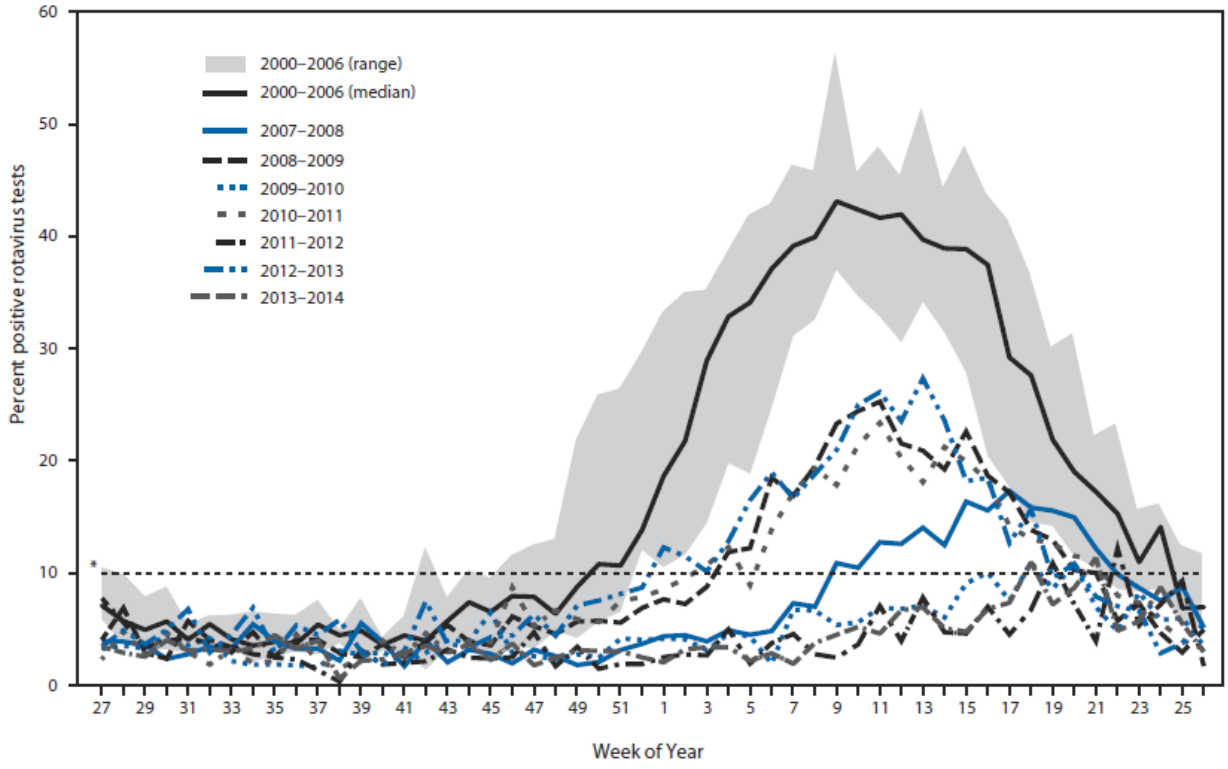
Rotavirus vaccination, with RV5, was first recommended by the Advisory Committee on Immunization Practices (ACIP) in the US in February 2006 and recommendations were expanded to include RV1 in June 2008. Three changes were noted from surveillance data reported by the National Respiratory and Enteric Virus Surveillance System (NREVSS) of the CDC. They showed national declines in rotavirus across seven reporting years (2007-2014).

Figure 4: Total and positive rotavirus tests - US 2000-2014. Source: CDC National Respiratory and Enteric Virus Surveillance System (NREVSS)



When compared with seven years prior to the vaccine introduction, in each of the post vaccination years, the proportion of tests that were positive for rotavirus declined from 57.8% to 89.9% as presented in Figure 4. Figure 5 shows that post-vaccination rotavirus seasons had later onset and shorter duration, including some years without a defined season that remained below threshold. A biennial pattern in rotavirus activity alternated between years of low activity and highly erratic seasonality with years of moderately increased activity and similar pre-vaccination seasonality is also seen in Figure 4. It was proposed that this biennial pattern in seasonality of rotavirus infection may be influenced by the accumulation of a sufficient number of unvaccinated, susceptible individuals as well as environmental factors like the weather.[49]

Figure 5: US rotavirus season duration and peak activity by reporting years (pre-vaccine 2000-2006 and post vaccine 2007-2011) Source: NREVSS



* Dashed line indicates the 10% threshold of numbers of positive test results, which is used to determine onset and offset of a rotavirus season.

When hospital discharge data was analysed from 62 paediatric hospitals, rotavirus-coded hospitalisations decreased dramatically during the rotavirus seasons post-vaccine, by 83% and 66% during 2007-2008 and 2008-2009, respectively, among children aged less than 5 years across all regions. During 2007-2008, a 50% reduction was observed and during 2008-2009, there was a 29% reduction in all-cause diarrhoea hospitalisations for children under 5 years of age. Coverage rates for ≥1 dose of rotavirus vaccine increased from 10% in 2007, 42% in 2008 to 67% in 2009.[17]

A seven-year follow-up study was conducted in Belgium to assess the medium to long-term impact of rotavirus vaccination on hospital care (RotaBIS study). The RotaBIS study retrospectively collected data on RV testing linked to hospitalisations of children under 5 years of age across 11 hospitals for the previous year. Following introduction of rotavirus vaccination in 2006, vaccine uptake was at least 85% from the start. Significant reductions in the number of rotavirus tests (-38%) and in the number of positive tests (-76.6%) were seen following the introduction of rotavirus vaccination.[50]

Two years following the introduction of rotavirus vaccination in Lothian, Scotland, the annual rate of paediatric admissions for RVGE declined by 84% (75.4-91.0; p<0.0001) and suspected hospital-acquired infections decreased by 95.7% (73.5-99.5), including non-vaccinated children aged up to 5 years. Vaccine uptake was 93-94%.[25]

During 2010, rotavirus vaccination was withheld for 5 months in Spain due to a vaccine quality control issue. A retrospective, observational study investigated the impact of this cessation on RVGE hospitalisation in children aged 5 years or younger in the region of Galicia. Prior to the introduction of the rotavirus vaccination programme, the median annual hospitalisation rate for RVGE was 297.7/100,000 from July 2003 – June 2007. Following the introduction of the vaccine, from July 2009 - June 2010 (mean coverage was 49%), the hospitalisation rate had dropped to 165.3/100,000 per year (44.5% reduction). During the period that included the five-month cessation of vaccination (July 2010-June 2011; mean coverage for year 22%), hospitalisation rates increased to 291.0/100,000 (76% increase from previous season). Rates of RVGE returned to pre-vaccination rates in the season following the resumption of rotavirus vaccination (285.6/100,000 during July 2011-June 2012, mean coverage in 2012 was 45%). The study estimated that during the period of vaccine cessation, approximately 497 RVGE hospitalisations were not avoided and 84,450 children were not vaccinated. It was concluded that the impact of rotavirus vaccines is only maintained while they are in use.[51]

Conclusion

The introduction of widespread rotavirus vaccination has dramatic effects on rotavirus gastroenteritis cases and significant reductions in the number of cases is observed in vaccine and vaccine-ineligible children younger than 5 years.

A cessation in the vaccination programme in Spain resulted in an increase in cases, suggesting that rotavirus remains in circulation in the population if vaccine coverage is moderate.

6.3 Direct protection

As would be anticipated, and demonstrated in section 5, rotavirus vaccines are effective in providing protection against rotavirus disease in those who have been vaccinated. Further literature detailing the impact of rotavirus vaccine programmes on direct protection against rotavirus disease is reviewed.

The impact of RV1 vaccination was assessed in a clinical study using commercial insurance claims data in the US from 2007 to 2011 (RV1 available from 2008). Within the study cohorts, a total of 34,928 children aged 5 years of age or younger completed two doses of vaccine (age 6-24 weeks), 8,390 were partially vaccinated (one dose) and 182,269 were unvaccinated (and aged 24 weeks of age on or after January 2008). The children in the unvaccinated cohort were significantly older than those in the other two cohorts. Excluded were children from states with universal vaccination programmes, since vaccination of these children will not have been recorded on insurance claim databases. When adjusted for gender, age and calendar year, the incident risk ratio for rotavirus episodes (rotavirus-coded visit) was 0.17 (95% CI 0.09-0.30; p<0.001) for complete vaccination and 0.19 (0.06-0.58; p<0.004) for incomplete vaccination compared with the unvaccinated cohort. Diarrhoea related inpatient and ED visits rates were significantly lower for the vaccinated versus unvaccinated children.[52]

Significant reductions in hospitalised RVGE cases were observed in Austria following the introduction of universal rotavirus vaccination programme. Between the pre-vaccination and

the fully funded vaccination periods (2002-2009 vs 2006-2007), there was an overall reduction of 73.9% in RVGE cases per year (p<0.001), which was pronounced in the children aged 0-11 months (87.8%). According to surveillance data in 2008, vaccination coverage was 72-87%.[53]

Conclusion

Rotavirus vaccination significantly reduces RVGE hospitalisation of vaccinated infants by up to 80-90%.

6.3.1 Premature infants

The impact of the rotavirus vaccination programme on RVGE in children less than 3 years of age born prematurely (before 37 weeks gestation) was evaluated as part of active hospital-based surveillance study (IVANHOE) during May 2007-May 2010 in Brest University Hospital, France. During this time period, 217 premature infants were vaccinated with at least one dose of RV5 (mean vaccine coverage for three doses was 41.9%; increasing from 23% to>50% during study). Following the introduction of the vaccination programme, there was a 2.6 fold (1.3-2.5) decrease in RVGE hospitalisations during the first two epidemic seasons (2007-08 and 2008-09) and an 11-fold (3.5-34.8) decrease during the third season (2009-2010). However, these findings are based on very low numbers of cases (three premature infants aged less than 3 years per season).[54]

6.4 Indirect protection

A reduced incidence in rotavirus diarrhoea has been reported for age groups that are ineligible for vaccination, including adults, demonstrating that rotavirus vaccination also provides indirect protection. Here literature is reviewed and the impact of vaccination programmes through indirect protection is examined further.

A systematic literature review was conducted by Pollard et al (2015) on literature published between 2008-2014 that measured the impact of rotavirus vaccination on gastroenteritis morbidity and mortality to estimate the herd immunity effect of the vaccine on children less than 1 year of age. The median herd effect against RVGE was 22% (19-25%) from five studies (four in the US, one in El Salvador) and against all-cause gastroenteritis was 24.9% (11-30%) in Latin American studies. The study concluded that rotavirus vaccination conferred herd immunity to children under 1 year of age in the US and Latin America, but too few studies had been conducted in countries with high mortality.[55]

Another study in the US demonstrated evidence of herd immunity in non-rotavirus vaccinated infants, although these infants were still at risk of RVGE. During the pre-vaccine availability period, the incidence of RVGE was 151 per 100,000 infants and following vaccine introduction the incidence of RVGE in unvaccinated infants was lower (110 per 100,000 infants). However, the direct effect of vaccination was greater in the vaccinated infant cohort and the mean peak in incidence of RV medical encounters was more than 95% lower than in infants who did not receive rotavirus vaccine. More than 91% of vaccinations were with RV5; coverage increased from 35% in July 2007 to 53% in July 2009.[56]

Following the introduction of RV1 to the infant immunisation schedule in England and Wales in July 2013, large reductions in rotavirus infections were observed in unvaccinated age-groups. Vaccination coverage level (two doses by 25 weeks of age) of 93% was achieved rapidly and maintained. As expected, the largest reductions were seen in infants less than 1 year of age (77% decline, p<0.0001). Significant reductions were also observed in older age groups (aged 5 years and older) with a 50% decline (p<0.0001) in laboratory-confirmed rotavirus infections (from July 2007 and June 2015). Across all age groups during 2013-

2014, it was estimated that 10,884 laboratory-confirmed rotavirus infections and 50,427 all-cause AGE-hospital admissions were averted. Of the latter, 90% (45,171/50,427) were averted in unvaccinated age groups and 42% (21,368/50,427) were in adults aged 65 years and older. For young children, there was an observed 80% reduction in RVGE admissions in children aged less than 1 year and a 63% reduction in those aged 1-4 years ($p<0.0001$ for both) from July 2007 to June 2014.[57]

In Austria, as described above, significant reductions in hospitalised RVGE cases were observed following the introduction of universal rotavirus vaccination programme, which were pronounced in the unvaccinated age groups as well as young infants: 84.5% reduction in children 6-10 years (from a mean of 19 per year [95% CI 15.1-22.9] to 3.0 (1.6-4.4) and 88.9% in those aged 11-18 years (from mean of 9.0 per year [4.1-13.9] to 1.0 [0.8-2.2]) from the pre-vaccination to the funded vaccination periods. [53]

In Chicago, US, the prevalence of rotavirus among stools samples from adults declined from 4.35% in 2006-2007 (pre-paediatric impact era) to 2.24% in 2008-2010 (paediatric impact era), which equated to a relative decline of 48.7% ($p=0.0007$) during the peak rotavirus season. The magnitude of the decline was similar between inpatient and outpatient samples. About 30% of the stool samples containing rotavirus were from immunocompromised adults and this remained constant. It was concluded that paediatric rotavirus vaccination provides indirect protection to some adults against rotavirus.[58]

Conclusions

Protection against RVGE provided by routine rotavirus vaccination extends to unvaccinated individuals, both children and adults, as well as those who receive the vaccine. However, unvaccinated infants remain at risk of infection if they are exposed to rotavirus. Greater levels of vaccine coverage allow for better herd immunity protection for unvaccinated individuals.

6.4.1 Nosocomial infection

The Belgian seven-year follow-up RotaBIS study assessed the impact of rotavirus vaccination on nosocomial infection and duration of hospital stay. The study found that, over a 6-year period following the introduction of rotavirus vaccination, that there was an 85% reduction in nosocomial infections from 221 in 2005 to 33 in 2012 ($p<0.001$). A shift in the distribution of nosocomial infection hospitalisations to the infants too young to be vaccinated (less than 2 months of age) was observed. The study concluded that children hospitalised for non-diarrhoea-related reasons were at a lower risk of a nosocomial rotavirus infection following the introduction of the vaccine.[59]

As mentioned above, significant reductions in hospitalised RVGE cases were observed in Austria following the introduction of universal rotavirus vaccination programme. Compared with the pre-vaccination (2002-2005), there was a 92.5% reduction in nosocomial RVGE cases per year during the fully funded vaccination period (2008-2009). In infants aged 0-11 months, there was a 96.5% total reduction in nosocomial RVGE. In hospitalised children, reductions of 90%, 100% and 100% were observed in nosocomial rotavirus infections in children aged 2-5 years, 6-10 years and 11-18 years, respectively. The study also found that the majority of secondary blood stream infections were linked to nosocomial RVGE. Blood-stream infection due to pathogens belonging to the intestinal microflora and *Enterobacteriaceae* family members have been associated with rotavirus infection. In this study, *Staphylococcus aureus* was detected in the blood of 12 out of 20 RVGE cases reported: 10/14 cases with nosocomial RVGE and 2/6 cases with community-acquired RVGE. Of the cases of blood-stream infection, 14 occurred during the pre-vaccination period, three cases during the recommended/early funding period (2006-2007) and three cases during

fully funded vaccine period. The study concluded that a reduction in nosocomial cases is an important outcome of vaccination, particularly when rotavirus infection in hospitalised patients with comorbidities are more likely to develop severe disease and are at increased risk of death due to complications of RVGE.[53]

Conclusions

Reductions in nosocomial infection help to protect hospitalised children at high risk from RVGE and reduce secondary blood infections.

6.5 Childhood seizures

Rotavirus infection has been linked to childhood seizures. The most characterised are benign convulsions with gastroenteritis (CwG), with or without fever, which occur between the age of 1 month and 6 years, peaking in the second year of life and are reported more frequently in East Asian (1% of all AGE cases) than European infants.[60, 61]

As described in section 5.6, an Australian study found that three doses of RV5 were associated with protection against febrile seizures for up to 4 years after rotavirus vaccination.[47]

A cohort study conducted in the Galicia region of Spain found that rotavirus vaccination was associated with a significant decrease in seizure-related hospitalisation during childhood, particularly in the youngest infants. The cohort consisted of 6149 children less than 5 years of age who were admitted to hospital during 2003 to 2013 with any kind of childhood seizure. The annual rate of seizure hospitalisations was negatively correlated with rotavirus vaccination coverage ($r = -0.673$; $p=0.033$) and positively correlated with RVGE admission rates ($\rho = 0.506$, $p=0.001$) for children aged less than 5 years. The most marked benefit was seen during the first 2 years of life. The largest decrease in seizure hospitalisations was observed at the age for peak incidence in febrile seizure hospitalisations – around 18 months of age. However, this study did not distinguish between febrile and afebrile seizures.[62]

Findings from a retrospective chart study of RVGE cases visiting the Department of Paediatrics, Gyeongsang National University, South Korea suggested that the clinical manifestations of rotavirus-associated seizures in unvaccinated children were modulated by the introduction of a rotavirus vaccination programme. The study examined the clinical features of rotavirus-associated seizures before and after the introduction of the vaccine. A total of 643 children (aged 6 months to 5 years) visited the department for RVGE during July 2002 to July 2013, of which, 55 out of the 62 who experienced rotavirus-associated seizures were included in the study (31 pre-introduction, 24 post-introduction, only one was rotavirus vaccinated). When the clinical characteristics were compared: fewer in the post-introduction had fever at the time of the seizure than pre-introduction group (20.8% vs 54.8%, $p<0.01$); the median interval between RVGE and seizure onset was longer (3 vs 2 days, $p<0.01$) and the post-introduction had a high median frequency of seizures during RVGE episode (2 vs 1, $p=0.02$). The authors proposed that potentially altered susceptibility to rotavirus enterotoxin, NSP4, linked to neurotoxicity and disruption of calcium homeostasis, could result in the clinical changes observed.[63]

Another study conducted in South Korea found that, although rotavirus vaccination reduced the incidence of rotavirus-associated CwG, the overall incidence of CwG increased due to an increase in norovirus. During period 1 (March 2005 - February 2010), the incidence of CwG was 8.5% (45 out of 531 patients admitted for first seizure attack) and during period 2 (March 2010 – February 2014) CwG incidence was 12.5% (57/456 patients; $p=0.018$). Of the patients for whom stool samples were collected, 15/37 (40.5%) during period 1 and

16.0% (8/50) during period 2 (p=0.01) were positive for rotavirus. Norovirus was the most common other virus and was more frequent in period 2 than period 1 (71.4% versus 22.2%, p=0.018; n=17/30 tested). Rotavirus vaccination was introduced in 2007 and in 2009 the vaccination rate was 50%.[64]

Although limited evidence is available, it has been suggested that rotavirus also plays a role in non-RVGE associated seizures.

A protective role for rotavirus vaccination against seizures was observed in a US-based retrospective cohort study. The study examined VSD data on 186,502 children fully vaccinated with rotavirus vaccine and 64,099 children not vaccinated (more than 90% of whom were aged between 8 – 18 months). An 18 to 21% reduction in risk of admission to ED or hospital with seizure (coded for convulsion, convulsion in newborn, myoclonus and epilepsy) was observed during the year following vaccination as compared with unvaccinated children (first time seizures RR 0.816 [95% CI 0.729-0.914] and all seizures RR 0.790 [0.714-0.875]). Significantly fewer seizures occurred during the rotavirus season (January to June) in vaccinated children than unvaccinated children (48-49% vs 55%; p=0.023).[65]

Conclusions

Rotavirus vaccination helps to protect infants and young children against both febrile and afebrile seizures.

6.6 Summary of impact

As has been seen in New Zealand (see section 2.1), in countries that have introduced a rotavirus vaccination significant reductions have been observed in RVGE hospitalisations and both direct and indirect effects on the incidence of rotavirus infections have been demonstrated. Reductions have been reported in both community-acquired and nosocomial infections.

Rotavirus vaccination provides protection to preterm infants from rotavirus infection. Fewer childhood seizures, including non-RVGE associated seizures, are reported when rotavirus vaccination has been introduced.

7 Vaccines and options for scheduling

7.1 Vaccine options

Since there are only two rotavirus vaccines available, currently, options for childhood immunisation schedules are limited. NZ introduced three-dose RV5 in July 2014 and in July 2017 switched to two-dose RV1. The impact of this change will not be known for months or years.

As of July 2017, the NZ National Immunisation Schedule provides rotavirus at 6 weeks and 3 months of age. This is earlier than many other countries and the potential effect of maternal antibody is unknown, particularly in low socioeconomic populations.

7.2 Routine rotavirus vaccination

There are very limited options for rotavirus vaccination timing. It is important, in order to reduce the risk of association with intussusception, to complete the immunisation course by 25 weeks of age.

In populations where rotavirus infection is abundant, such as in low income countries, the presence of maternal antibody may interfere with the immune response to the oral vaccines in breastfed infants. It is currently undetermined whether there is a greater amount of rotavirus in circulation in any NZ populations, particularly since the vaccination programme has successfully reduced rotavirus gastroenteritis in all children under the age of 5 years. Infections in adults can be subclinical, and potentially, some mothers may have higher quantities of anti-rotavirus antibody in their breastmilk. Although, there is currently no evidence of any interference.

The incidence of RVGE is highest in children aged 3 months to 3 years of age. A delay in vaccination may help to provide further protection to these ages without interference from maternal antibody. This potential increase in protection needs to be outweighed with the increasing risk of intussusception in older infants (from 6-8 months).

An important consideration for NZ, when balancing the risk of intussusception with maternal antibody interference, is that the peak age of incidence of intussusception in infants of Māori and Pacific ethnicity is younger than for NZ European or other ethnicities (at 7-8 months vs around 10 months of age).[14] These populations may also be exposed to higher rotavirus burden when living in more crowded housing and with greater socioeconomic deprivation.[66] However, there is evidence that community immunity reduces RVGE hospitalisations for under 5-year olds in New Zealand.[6] Therefore, high vaccination coverage of infants in low socioeconomic situations is advantageous.

The impact on rotavirus vaccination of infants needs to be considered when making any changes to the national immunisation schedule for other vaccines to ensure that there is a minimum of a four week space between doses and the course is completed within the maximum time limits.

7.3 Special groups

Apart from infants for whom the vaccine is contraindicated, no special considerations are provided for rotavirus vaccine scheduling. The two-dose or three-dose schedules are dependent of the vaccine types (RV1 vs RV5, respectively) and the maximum age limits are set so that doses are not administered during the periods of increased risk of intussusception.

Contraindications include infants with uncorrected congenital malformations of the gastrointestinal tract or other chronic intestinal disorders, those with a history of intussusception, with severe combined immunodeficiency disease or with hypersensitivity to a previous dose of the vaccine or vaccine components.

It is recommended that the risk to infants of acquiring rotavirus infection naturally be balanced with the risk from the vaccine. The risk of exposure to immunocompromised close-contacts with vaccine-strain RVGE also needs to be considered when making decisions around vaccinations. However, good hygiene practices when nappy changing minimise the risk of viral spread.

Age-appropriate immunisation of preterm infants, prior to hospital discharge, is indicated. Good hygiene practices prevents nosocomial transmission of vaccine virus.

No literature was identified that considered infants who have received intravenous immunoglobulin, for example, following surgery.

7.4 Surveillance

Ongoing surveillance is essential to ensure that the current rotavirus vaccines continue to provide good protection against RVGE in infants and minimise hospitalisations, and to maintain vigilance for emergent strains or changes in strain predominance.

However, continued requests for rotavirus tests in hospitals when there are low levels of rotavirus in circulation, risks the generation false positive results.[7]

Data is required to monitor the effect of the recent switch from RV5 to RV1 and the change from three to two doses. In some populations with higher rotavirus prevalence, in which there is potential for interference from maternal antibody to the 6 weeks dose, protection may only be afforded by one extra dose of RV1 rather than the two further doses provided by the three-dose schedule with RV5.

Further data is required around the effect of rotavirus vaccines and rotavirus infections on childhood seizures.

7.5 Summary

Due to the age limitations of rotavirus vaccination, there are limited options for the scheduling of the vaccines, particularly for RV5 which requires three doses. Rotavirus vaccine is administered concurrently with the other scheduled vaccines. Consideration of the positioning of the rotavirus vaccination on the childhood immunisation schedule is required when making scheduling changes for the other primary series vaccinations.

Apart from infants for whom the vaccine is contraindicated, the majority of infants are likely to benefit from rotavirus vaccination, since rotavirus is abundant in the community albeit asymptomatic, and the risks from RVGE are severe in young infants and infants with comorbidities.

Ongoing surveillance is essential to monitor disease incidence and to maintain vigilance of emergent or changes in rotavirus strain predominance. However, hospital testing of non-rotavirus severe diarrhoea cases for rotavirus can result in false positive test results.

8 International policy and practice

This section reviews the policy and practices for rotavirus vaccination internationally, with focus on HIC countries like New Zealand.

8.1 Review

Since there are few options for scheduling of rotavirus vaccines, due to the narrow time window to vaccinate, there is not much variability between countries and this variability is reflected by the other primary series vaccine given concurrently, such as combination vaccines containing diphtheria-tetanus-pertussis and pneumococcal vaccines. The major differences are in the use of RV1 or RV5, as to whether two or three doses are administered, and the age at which the primary series is commenced. The timing between the doses also varies according to the spacing of the primary series. According to the WHO, most countries worldwide have introduced rotavirus vaccine. However, some countries, including Canada, Sweden and Italy, do not have countrywide rotavirus vaccination programmes.[67]

8.1.1 United States

Since 2008, ACIP have recommended rotavirus vaccination, with either RV1 or RV5 vaccines, from 6 weeks of age to 14 weeks and 6 days for dose one with a minimum interval of 4 weeks between doses which may be given simultaneously with other age-appropriate schedule vaccinations. All doses should be administered by 8 months 0 days of age. The vaccine is contraindicated for infants with severe combined immunodeficiency and those who have previously had intussusception.

8.1.2 Canada

The routine schedule in Canada includes two or three doses of rotavirus vaccine (depending on vaccine brand) to be completed by 8 months of age. According to the public health service website, as of May 2017, most provinces and territories provide two doses given at 2 and 4 months of age.[68]

8.1.3 Australia

Rotavirus vaccination is recommended in all states and territories in Australia. As of July 2017, following advice from the Australian Technical Advisory Group on Immunisation, RV1 replaced RV5 in the states of Western Australia, South Australia, Victoria and Queensland to be given as a two dose schedule from 6 weeks to 2 months and 4 months of age. The first dose should be given prior to 15 weeks and the second dose prior to 25 weeks of age.[69]

8.1.4 United Kingdom

Rotavirus vaccine, RV1, was introduced in the UK in July 2013. Two doses are given alongside other routine vaccines at 8 weeks and 12 weeks of age (minimum of 4 weeks apart).[70] The vaccine is contraindicated for infants who are severely immunosuppressed, with predisposition to intussusception, severe allergy to vaccine components or rare hereditary sugar malabsorption or insufficiencies.[71]

8.1.5 European Union

The two rotavirus vaccines were available in Europe from 2006 and by 2014, Austria, Belgium, Finland, Greece, Luxembourg, Norway and the UK had begun national universal rotavirus vaccination. Some other countries were also recommending and reimbursing the vaccines, as of 2014.[72]

8.2 Summary

It appears that many countries have opted for RV1 vaccination or a choice of RV1 or RV5. The advantage of RV1 is that only two doses are required and infants are less likely to be administered the vaccines at an age older than 6 months, thereby, potentially avoiding the peak age of incidence and reducing the risk of intussusception.

International recommendations are summarised in Table 2.

Table 2: Summary of international immunisation recommendations for rotavirus vaccines, as of 2017 (adapted from European Centre for Disease Control and WHO)

Country	Age of rotavirus vaccination	Vaccine
USA	2, 4 (6) months	RV1 or RV5
Canada	2, 4 months	RV1
Australia†	6 weeks/2, 4, (6) months	RV1 (or RV5)
NZ	6 weeks, 3 months	RV1
Austria	6, 10, 14 weeks	RV5
Czech Republic	6 weeks, 2, 3 months	RV5
Finland	2, 3, 4 months	RV5
Germany	6 weeks, 3-4 months	RV1 or RV5
Greece	2, 4, 6 months	RV5
Ireland	2, 4 months	RV1
Italy	3-7 months	RV1
Norway	6 weeks, 3 months	RV1
UK	2, 3 months	RV1
† Start age and vaccine used varies between states. National immunisation schedule starts at 2 months.		

9 Methodology for review

9.1 Objectives

9.2 Literature search strategy

9.2.1 Ovid Medline search terms and strategy

1. Keyword rotavirus vaccines (MeSH focused) = 1582
2. Limit English, human, 2013-2017 = 543

- 2 AND immunogenicity = 54, 27 selected and removed duplications, excluded developing country specific studies
- 2 AND Vaccine safety = 19, selected 12, removed duplicates
- 2 AND Vaccine effectiveness = 6, removed duplicates = 1

9.2.2 Cochrane Library search terms and strategy

No recent Cochrane reviews found, since 2013.

9.2.3 Scopus search terms and strategy

(TITLE-ABS-KEY (rotavirus AND vaccin*) AND DOCTYPE (ar OR re) AND PUBYEAR > 2012 AND PUBYEAR < 2018) AND (effectiveness)) AND (safety) AND (LIMIT-TO (SRCTYPE , "j ")) AND (EXCLUDE (SUBJAREA , "VETE ") OR EXCLUDE (SUBJAREA , "AGRI ") OR EXCLUDE (SUBJAREA , "ARTS ") OR EXCLUDE (SUBJAREA , "NURS ") OR EXCLUDE (SUBJAREA , "MATH ") OR EXCLUDE (SUBJAREA , "CENG ")) AND (LIMIT-TO (LANGUAGE , "English ")) = 295

119 selected 98 after duplicates removed

9.2.4 Grey literature

No grey literature was identified.

9.2.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. All duplicates were removed from the final library.

9.2.6 Final Endnote Library 237 Articles

Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review, unless further information was required to clarify review.

9.3 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, case-control studies, case reports and observational studies using database matching. Cost-effectiveness and cost-benefit analyses were not included.

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