

# 2012 Antigen Review for the New Zealand National Immunisation Schedule: Rotavirus

Auckland UniServices Limited

A wholly owned company of  
The University of Auckland

**Prepared for:**

New Zealand Ministry of Health

**Prepared by a scientific team incorporating the**  
Immunisation Advisory Centre, The University of Auckland  
Institute of Environmental Science and Research Ltd.

January 2013

uniservices



**Contact details:**

**Helen Petousis-Harris**

Immunisation Advisory Centre  
Tāmaki Innovation Campus  
The University of Auckland

Private Bag 92019,  
Auckland 1142, New Zealand

Phone: +64 9 923 2078

Fax: +64 9 373 7030

Mobile: +64 27 471 6749

Email: [h.petousis-harris@auckland.ac.nz](mailto:h.petousis-harris@auckland.ac.nz)

# Executive summary

Rotaviruses are the leading cause of severe diarrhoeal illness in infants worldwide affecting virtually every child either in infancy or early childhood. Infections are most severe in infants three months to 24 months of age. Universal infant rotavirus vaccination programmes for all countries are recommended by the World Health Organization (WHO).

Current rotavirus vaccines on the world market are live attenuated, and focused on the common human P and G serotypes. Two international vaccines are licensed in NZ: Rotarix® (RV1) is a live attenuated human rotavirus strain P1A[8]G1 and RotaTeq® (RV5) is a pentavalent human-bovine reassortment containing G types 1-4 (VP7) and P[8] (VP4). There are a range of other live attenuated rotavirus vaccines in the pipeline.

In New Zealand (NZ) the third largest cause of potentially avoidable paediatric admissions to hospital is gastroenteritis (from all causes), preceded only by respiratory infections and asthma. Rotavirus gastroenteritis represents approximately 40% of the overall gastroenteritis hospitalisation burden. Rotavirus gastroenteritis is more common in children aged 12-35 months, followed by those six to 11 months and is less common in infants under six months. There is clear seasonality, with over half of cases occurring in winter/spring. NZ data estimates of the burden of disease predict that by the age of five years, one in five children will have sought medical advice for rotavirus gastroenteritis, and one in 43 will have been hospitalised. Mortality is very rare.

The predominant NZ circulating strain is G1, followed by G4 which is similar to the European and United States (US) pattern. However, NZ has significant regional differences and rarer strains have been identified, highlighting the importance of on-going surveillance.

The individual studies and pooled data from all studies for RV1 and RV5 have not raised any significant safety concerns for either vaccine, except for rare case reports of Kawasaki disease post vaccination. Association does not necessarily mean causation. There are no extra safety concerns for preterm infants. Children with human immunodeficiency virus (HIV) do not appear to have any extra safety risks, with the possible exception of prolonged shedding. There is reportedly a possible increased risk of intussusception in day one to seven post the first dose for both vaccines, with an increased risk in the order of 1.9 to 2.6 times. It is unclear if this translates to an overall increase in number of cases. Contamination by pieces of porcine circovirus (PCV) genome has been found in both vaccines but is not expected to pose any safety problems. Prolonged shedding is possible- particularly for RV1. This is most likely to occur in those who are immunocompromised, and is then more likely to transmit to individuals who have not been vaccinated. To date this has not created any safety concerns. Occasional reassortants have been observed and potentially, may cause gastroenteritis symptoms.

Other potential vaccine safety issues include: higher rates of viral shedding leading to disease outside the gastrointestinal tract such as central nervous system (CNS), as seen occasionally with wild disease but not with vaccines; an excess of pneumonia cases over placebo was observed in one study but this has not been replicated elsewhere; the potential for autoimmunity is considered to be unlikely.

Immunogenicity measures are not clear correlates of protection, but faecal and serum IgA are reasonable surrogate markers. Both vaccines give good immunogenicity responses, although, there is significant heterogeneity in study results. Both vaccines show good effectiveness in preventing rotavirus diarrhoea. Vaccine effectiveness varies between settings, with estimates around 44% to 51% in low-income settings, 76% to 86% in middle income setting and 80% to 86% in middle to high income settings. A consistent finding is the decreased effectiveness for children from low and middle-income settings compared to high-income regions. Both vaccines are more effective against severe gastroenteritis than mild.

Both vaccines appear to offer reasonable protection even in partially vaccinated infants. Co-infection with other viruses may be common, but good vaccine effectiveness is still observed. There is a possible decline in effectiveness in the second year of life, particularly in low income countries. There are no significant differences in vaccine effectiveness (VE) by genotype.

For vulnerable groups the vaccine is expected to be effective in HIV-infected children, in malnourished children and probably effective in preterm infants. There are small, though probably not significant differences in immunogenicity and efficacy between breast fed and non-breast fed infants, and breast feeding may reduce slightly the efficacy in the second season.

Despite the potential for decreased efficacy for different strains not contained in the vaccines, both vaccines to date have provided good cross protection against the common circulating strains in Europe and the US. RV1 may provide lesser protection against G2P [4] in Latin America, though this is not clear. Both vaccines appear to have similar efficacy against a wide range of strains in Asia and Africa. The VE for RV1 requires further monitoring.

Early data in the US and Europe is showing good herd immunity effects.

The vaccines are orally delivered, and used in universal infant programmes either as a two-course (RV1) or a three-course (RV5), with recommended minimum age times of delivery and intervals to avoid the age range in which intussusception is most likely to occur. There is no international experience or recommendations for the use of targeted programmes, or catch up schedules. NZ epidemiology data shows that Pacific children and children from more socioeconomically deprived backgrounds bear a greater burden of hospitalisation from rotavirus, and there may be potential for introducing the vaccine in regions with higher rates of deprivation, and with Pacific populations. There is likely to be little gain from using approaches targeted just for high risk individuals as this would lose the gains from herd immunity.

There is no data to support vaccinating older children, further data is awaited for the possible 'off label' use in vulnerable older age groups.

There are no concerns with concomitant use of RV vaccines with other standard national schedule vaccines. Longitudinal surveillance needs to continue to watch for possible strain serotype shifts with the introduction of RV vaccines. Herd immunity effects add to the effectiveness of RV vaccines.

Anaphylaxis to latex is a contraindication to the use of RV1 but not RV5. Both vaccines are contraindicated in infants with severe combined immunodeficiency disease. It is recommended not to vaccinate infants with a previous history of intussusception. There is a potential risk of transmission to immunocompromised household members, so good hand hygiene is particularly important in these situations.

There is no data on interchangeability of RV1 and RV5. A complete course with one vaccine is preferable, but if necessary, a series that contains both vaccines is preferable to an incomplete series.

For a new vaccine introduction capacity issues for increased cold chain storage, new training and education for healthcare workers and social mobilisation need to be considered.

As of September 2011, rotavirus vaccine has been introduced into the national programmes of 28 countries, 16 using RV1, eight using RV5, and four using both. In all countries the schedule needs to be complete by 26 to 32 weeks. In the USA, RV vaccine is recommended at a minimum interval of four weeks between doses and a maximum age for the first dose of 14 weeks and 6 days and the last does by eight months. The UK introduced RV1 in July 2013 (1).

# 2012 Antigen Review for the New Zealand National Immunisation Schedule: Rotavirus

Prepared as part of a Ministry of Health contract

by

Dr Nikki Turner, Immunisation Advisory Centre (Lead Author)

Dr Helen Petousis-Harris, Immunisation Advisory Centre (PI)

Tracey Poole, Immunisation Advisory Centre

Dr Mary Nowlan, Immunisation Advisory Centre (Editor)

This review is one of a series of 18 antigen reviews presented in 15 individual reports.

January 2013 (edited July 2014)

# Contents

<b>Executive summary .....</b>	<b>iii</b>
<b>1. Background – Rotavirus vaccines.....</b>	<b>1</b>
<b>2. Methodology for review.....</b>	<b>3</b>
2.1 Objectives .....	3
2.2 Literature search strategy.....	3
2.2.1 Medline search terms and strategy .....	4
2.2.2 Cochrane Library search terms and strategy .....	4
2.2.3 Scopus search terms and strategy.....	4
2.2.4 Grey literature.....	4
2.2.5 Additional searches.....	4
2.2.6 Final library .....	4
2.3 Participants/populations .....	5
2.3.1 High risk groups cover identified in the literature cover.....	5
2.4 Interventions .....	5
2.5 Study designs.....	5
<b>3. Rotavirus epidemiology.....</b>	<b>6</b>
3.1 Serotype distribution.....	6
3.2 Overview of NZ epidemiology.....	6
3.3 Summary NZ epidemiology .....	7
<b>4. Safety .....</b>	<b>8</b>
4.1 Objective .....	8
4.2 Outcomes.....	8
4.3 Review .....	8
4.3.1 Cochrane review .....	8
4.3.2 Recently published individual safety studies of RV1.....	8
4.3.3 Recently published individual safety studies of RV5.....	8
4.3.4 Safety in population subgroups .....	9
4.3.5 Intussusception .....	9
4.3.6 Porcine circovirus (PCV) contamination .....	11
4.3.7 Other potential safety issues.....	11
4.4 Summary vaccine safety.....	12
<b>5. Immunogenicity, efficacy, effectiveness and vaccine impact.....</b>	<b>13</b>
5.1 Objective.....	13
5.2 Outcomes .....	13
5.3 Review.....	13
5.3.1 Immunogenicity.....	13
5.3.2 Recently published individual studies of RV1.....	14
5.3.3 Recently published individual studies of RV5.....	14
5.3.4 Surveillance data .....	16
5.3.5 Effectiveness of partial vaccination.....	16

5.3.6 Duration of effectiveness.....	17
5.3.7 Vulnerable groups .....	17
5.3.8 Cross-protection.....	18
5.3.9 Herd immunity .....	18
5.4 Summary of effectiveness .....	19
<b>6. Vaccine Options .....</b>	<b>20</b>
6.1 Objective.....	20
6.2 Review .....	20
<b>7. Options for scheduling .....</b>	<b>21</b>
7.1 Objective .....	21
7.2 Review .....	21
7.2.1 Schedule timing and placement .....	21
7.2.2 NZ context.....	21
7.3 Summary of options for scheduling.....	21
<b>8. Implementation issues .....</b>	<b>22</b>
8.1 Objective.....	22
8.2 Review .....	22
8.2.1 Concomitant use with other vaccines.....	22
8.2.2 Serotype shifts.....	22
8.2.3 Herd immunity effects .....	22
8.2.4 Targeted versus universal programme.....	22
8.2.5 Catch-up campaigns and vaccinating older children and adults .....	23
8.2.6 Contraindications/precautions .....	23
8.2.7 Serotype replacement.....	23
8.2.8 Interchangeability of RV1 and RV5 .....	23
8.2.9 Implementation of a new vaccine .....	23
8.3 Summary for implementation issues.....	24
<b>9. International policy and practice .....</b>	<b>25</b>
9.1 Objective.....	25
9.2 Review.....	25
9.2.1 United States .....	25
9.2.2 United Kingdom.....	25
9.2.3 Canada .....	25
9.2.4 Australia.....	25
9.3 Summary of international policy and practice .....	26
<b>References.....</b>	<b>27</b>
<b>Figures</b>	
Figure 1. Flow of selection of articles for review.....	4
<b>Tables</b>	
Table 1. Common Human Group A Rotavirus Serotypes in 2006.....	1
Table 2. Post-licensure VE for RV1 and RV5.....	16

## Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AEFI	Adverse Event Following Immunisation
CNS	Central Nervous System
EIP	Emerging Infections programme
EPI	Expanded Programme on Immunisation
FDA	Food and Drug Administration (US)
GMT	Geometric mean titres (the simple arithmetic mean of the logarithms of the last positive dilution of each serum)
HIV	Human immunodeficiency virus
NZ	New Zealand
PCV	Porcine circovirus
RCT	Randomised control trial
RST	Rotavirus Efficacy and Safety Trial
RV1	Rotarix® vaccine
RV5	RotaTeq® vaccine
SAE	Serious Adverse Event
UK	United Kingdom
US	United States
VE	Vaccine Effectiveness
VP4	Human-Bovine Reassortment Containing P-type 8
VP7	Human-Bovine Reassortment Containing G-Types 1-4
WHO	World Health Organization

## Acknowledgements

The Immunisation Advisory Centre (IMAC) and the University of Auckland appreciates the opportunity to undertake literature reviews of the specific vaccines under consideration for, or currently in use for the NZ national immunisation programme. This work was commissioned by the Ministry of Health, to inform decision-making for changes to the schedule and to enable up-to-date clinical guidelines to be incorporated into the NZ Immunisation Handbook 2014. These documents were prepared by IMAC, in collaboration with Environmental Science and Research (ESR), under contract to the Ministry of Health, and were reviewed by members of the Prescription and Therapeutics Advisory Committee (PTAC) immunisation subcommittee 2013 to Pharmac. The authors would also like to acknowledge Val Grey, Graphic Designer, Faculty of Medical and Health Sciences, the University of Auckland, for her assistance with design and layout of these documents.



# 1. Background – Rotavirus vaccines

Rotaviruses are the leading cause of severe diarrhoeal illness in infants worldwide (2). Virtually every child will have been infected through infancy and early childhood. Rotavirus infections are more likely to be severe in children three to 24 months of age than in younger infants or older children and adults. Improvements in water, sanitation and hygiene are unlikely to alter the incidence of the disease as faecally contaminated water or food is not thought to be the primary transmission route. Spread is most likely to occur by person-to-person contact or through exposure to aerosolized respiratory droplets. In temperate climates the disease has winter seasonality. Protection of young infants is probably mediated via passive transplacental maternal antibody transfer and breast-feeding also offers some protection against the disease (3).

Rotaviruses infect most common species of domestic animals and many wild mammals and birds. Human and animal rotaviruses share one set of antigens (group A) but they differ in their type-specific surface antigens. Animals are not thought to be a reservoir for human strains nor a source for direct transmission to humans. However, reassortant strains composed of genomic segments from both human and animal rotaviruses have been identified. Rotaviruses only replicate in mature villous epithelial cells in the mucosa of the small intestine. While antigen, RNA and live virus have been identified in blood during infection, the significance of this is unknown. First infections offer protection against severe disease on reinfection. Rotavirus disease is not more severe in HIV-infected children, although viral shedding may be longer (4).

The outer layer of rotavirus contains two distinct proteins: VP4 and VP7. Each bears type-specific antigenic determinants. The protein VP7 is encoded by gene segments 7, 8 or 9 in different rotavirus strains and VP4 by gene segment 4. The VP7 protein is glycosylated and serotypes determined by this protein are termed **G types**. Of the 14 G-types that have been identified, 12 of these are in humans. Serotypes that form the VP4 protein are termed **P types**. There have been 26 major P genotypes identified, 15 in humans. Since there is extensive cross-reactivity among different P types, it is not possible to classify all P types. While more than 60 G-P combinations have been found in humans, there are only five strains P[8]G1; P[4]G2; P[8]G3; P[8]G4; and P[8]G9 that are associated with 80 - 90% of all the childhood disease burden, globally. The most common types are listed in Table 1.

**Table 1. Common Human Group A Rotavirus Serotypes in 2006**

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

Adapted from Plotkin 6th Edition (4)

Rotavirus is capable of substantial genetic diversity because of its segmented genome, which can undergo gene reassortment. The ability of the virus to mutate and reassort allows the potential for new serotypes to emerge, and it is estimated that reassortment alone could lead to almost 200 different combinations (5). The relative importance of including all common human P and G types in a vaccine remains undetermined (4). The distribution of different strains varies by region and over time.

RotaShield®, a tetravalent rhesus-based rotavirus vaccine, was the first rotavirus vaccine to be licensed and introduced into the US immunisation programme in 1998. It was withdrawn a year later when it was found to be associated with an increased risk of intussusception. Following this the newer vaccines required very large Phase III trials in order to exclude an association with intussusception. RotaTeq® (RV5) and Rotarix® (TV1) underwent Phase III clinical trials in more than 70,000 and 60,000 infants, respectively, prior to US FDA approval. RotaTeq® was licensed as part of the US immunisation schedule in 2006. Rotarix® was licensed for use in the European Union and Latin America in 2006 and the US in October 2008.

The WHO recommends universal rotavirus vaccination programmes for all countries and numerous cost-effectiveness analyses have been conducted across a wide range of low and middle income countries which, despite varied data sources and assumptions, have all consistently shown that the introduction of the vaccine is expected to be cost effective (6). Analyses have been undertaken in higher income countries with similar conclusions (7, 8).

Rotavirus vaccine has been recommended to be introduced on the NZ childhood schedule, but is currently only available on the private market (9). When compared to current medical practices, the cost of introducing rotavirus vaccine in NZ can be considered to be cost effective (10).

This review evaluates the literature on vaccination against rotavirus published since the writing of the New Zealand (NZ) Immunisation 2011 Handbook from 2009 to 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

# 2. Methodology for review

## 2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for rotavirus vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around rotavirus vaccines for New Zealand.

- General specifications.
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake).
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination.
  - Different options of placement on the schedule, based on international findings and best practice.
  - Different vaccine options and comparisons between the options.
- Specific specifications for rotavirus.
  - Different vaccine options.
  - Implications offering the vaccine may have for herd immunity.
  - Different schedule options as described in the literature.
  - Examples of and considerations for targeted programmes, and placement of the programmes on the Schedule.
  - Evidence for administering the vaccine programme as a universal programme and evidence for administering it as a targeted programme.
  - Investigation of whether there should be a two or three dose schedule.
  - Duration of protection provided by vaccines.

## 2.2 Literature search strategy

The points below have formed the focus of the literature search.

1. Safety
2. Effectiveness in disease control.
  - a. Indirect effects/herd immunity.
  - b. Duration of protection.
3. Implementation issues
  - Different schedule options.
4. Differences that need to be considered for targeted programme.
  - a. Examples of and considerations for targeted programmes.
  - b. Placement of programmes on the Schedule.
5. Different dosage options for placement on the schedule, based on international findings and best practice.
  - Two or three dose including dose intervals/timing.
6. Different vaccine options.
  - Current available.
7. Current international research and evidence around use of vaccines.
  - Consider this point covered in 1-6.

### Other areas of special interest

- Consideration of the risk groups and whether the vaccine should be provided to them.
- Investigation of the implications for herd immunity.
- Investigation of suitable vaccines.
- Duration of protection provided by vaccines.

## 2.2.1 Medline search terms and strategy

### MeSH term: Rotavirus Vaccines

932

Limit to Humans, English, 2009 – current

409

NOT parent, physician, survey, qualitative

389

NOT Costs

314

### MeSH term: Adverse Effects

36

Safety as keyword

18 (keep and view)

### MeSH term: Effectiveness

58 (keep and view)

## 2.2.2 Cochrane Library search terms and strategy

Search term Rotavirus Vaccin\*

Limit to Cochrane Reviews, Other Reviews, Trials  
2009-present

1 result (keep and view)

## 2.2.3 Scopus search terms and strategy

Rotavirus AND Vaccin\* Published 2011 – present

795

Limit to: Medicine, humans, vaccination, Rotavirus  
vaccine, priority journals, English

Exclude Letter, Note, editorial, short survey and  
erratum

476

Reject social science articles. Veterinarian

364 (keep and view)

Delete duplicates

## Final Endnote Library 142 Articles

## 2.2.4 Grey literature

8

## 2.2.5 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. A further 11 articles were accessed.

## 2.2.6 Final library

The final library includes 153 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

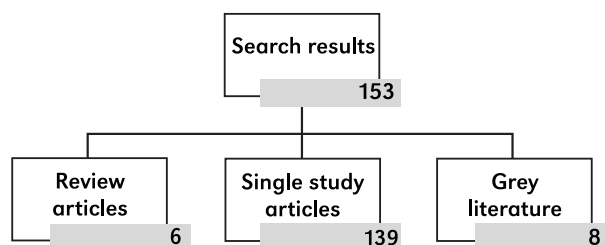


Figure 1. Flow of selection of articles for review

## 2.3 Participants/populations

The population for the universal programme are infants under six months of age.

### 2.3.1 High risk groups cover identified in the literature cover

- HIV infected infants
- Other immunocompromised infants
- Preterm infants
- Malnourished
- Breast feeding

## 2.4 Interventions

RotaTeq® (RV5) from Sanofi Pasteur is a pentavalent human-bovine reassortment containing G-types 1-4 (VP7) and P-type 8 (VP4). Four strains express human virus VP7 from serotypes G1, G2, G3, G4 and VP4 (P7[5]) from bovine strain WC3. The fifth reassortant contains VP4 (P1A[8]) from a human strain and VP7 (G6) from WC3. The reassortants were propagated in Vero cells. It is administered in a three-dose regimen, the first dose at six - 12 weeks of age and the last dose by 32 weeks of age.

Rotarix® (RV1) from GlaxoSmithKline is a live attenuated human rotavirus strain P1A[8]G1. The strain originated from a single wild strain circulating in Cincinnati, USA. It is administered in a two-dose regimen, the first at six - 14 weeks and the second by 10 - 24 weeks of age.

The interventions included are:

- RV1 in infants as a primary series
- RV5 in infants as a primary series
- Phase IV safety and effectiveness studies
- RV1 and RV5 in special groups at higher risk for disease
- Serotype analysis by region
- Case studies

## 2.5 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching. Conference abstracts have also been added.

# 3. Rotavirus epidemiology

The burden of rotavirus disease has been well established in many countries, including low and middle income and high income (7, 11). While the predominance of death and severe illness is carried in the low income countries, it causes significant morbidity and healthcare burden in all countries, particularly in early childhood (9).

## 3.1 Serotype distribution

Significant variability in circulating strains has been documented, geographically, annually and seasonally. Furthermore, within the same region, there can be multiple strains circulating at the same time. The most prevalent circulating strain in North America, Australia and Europe is G1, in approximately 70% of all the infections, but is less prevalent in South America, Asia and Africa where it is estimated to cover 20 – 30% of infections. More recently, G9 has emerged as an important strain, particularly in South America and Australia. Other emerging serotypes include G5, G8 and G12 strains (5).

## 3.2 Overview of NZ epidemiology

In NZ, almost 2500 children younger than three years of age are hospitalised annually with gastroenteritis, ranking it third among potentially avoidable paediatric admissions to hospital behind respiratory infections and asthma (12). A survey was undertaken, between May 1998 and April 2000, in eight hospitals in NZ for all children younger than three years of age admitted with infectious diarrhoea; a total of 2019 children were enrolled. Out of 1138 stool samples, 485 (42.5%) tested rotavirus positive. Rotavirus positivity varied with age: 26.8% of infants zero – five months, 42.5% of those six - 11 months, and 52.1% of those 12 – 35 months. There is clear seasonality with 51.2% occurring in winter/spring versus 24.5% in summer/autumn. The estimated national hospitalisation rate for rotavirus diarrhoea was 634/100 000 for children under three years in NZ (13).

Based on NZ data estimates of burden of disease, it is predicted that by the age of five years one in five children will have sought medical advice for rotavirus gastroenteritis, and one in 43 will have been hospitalised. Mortality is very rare (10).

Little is known about rotavirus strain diversity in the NZ setting. A study, undertaken between June 2005 and May 2006, analysed 416 stool samples from children less than 5 years of age admitted to five major hospitals throughout major cities in NZ, or at community medical laboratories in two cities. This showed that G1 was the dominant circulating strain (55.8%), followed by G4 (21.4%), G3 (3.4%), G9 (3.4%), G2 (1.0%) and mixed infection (1.0%). For 10% of samples containing the common G strains and all those containing unusual G types, P genotypes were determined. All of the samples tested contained P[8] bearing strains, except for G1P[4], G2P[4] and G8P[14] strains. There were significant differences between North and South Island samples: G1 was the most common strain in the North Island (81.9%), whereas G4 was the more common in the South Island (39.6%). Hospital and community samples did not show significant differences. The predominance of G1 is consistent with experience in North America, Europe and Australia, followed by the four other common global G-types, G2, 3, 4 and 9. Similarly the predominance of P[8] is consistent with other Western countries. However, there were two less common strains identified: G6, a bovine strain which is rarely seen in humans and G8, also a bovine strain which is more commonly associated with regions in Africa. The authors suggest the strong agricultural influenza in NZ may have an effect on interspecies transmission of Group A rotaviruses. The authors commented that the variation in regional strains highlights the importance of multicentre surveillance, which will be necessary to monitor programme effectiveness, when the rotavirus vaccines are introduced to the national childhood immunization schedule in NZ (14).

### 3.3 Summary NZ epidemiology

In NZ the third largest cause of potentially avoidable paediatric admissions to hospital is gastroenteritis, only preceded by respiratory infections and asthma. Based on limited NZ epidemiology data, over 40% of children less than three years of age who are admitted to hospital with diarrhoea, test positive for rotavirus. It is more common in children 12-35 months, followed by those six to 11 months and less common in infants under six months. There is clear seasonality, with over half of cases occurring in winter/spring. NZ data estimates of the burden of disease predict that by the age of five years one in five children will have sought medical advice for rotavirus gastroenteritis, and one in 43 will have been hospitalised. Mortality is very rare.

The predominant NZ circulating strain is G1, followed by G4 which is similar to the European and US pattern. However NZ has significant regional differences and rarer strains have identified highlighting the importance of on-going surveillance

# 4. Safety

## 4.1 Objective

The objective of this section is to review the most recent safety data for currently licensed rotavirus vaccines. The focus is on RV1 and RV5. Only Adverse Events Following Immunisation (AEFI) considered to have been subsequent to the pivotal clinical efficacy trials will be reviewed here.

## 4.2 Outcomes

Outcomes are vaccine safety including AEFI and serious adverse events (SAE).

## 4.3 Review

### 4.3.1 Cochrane review

A 2012 Cochrane review of vaccines for preventing rotavirus-related diarrhoea assessed 43 trials, which met the inclusion criteria and covered a total of 190, 551 enrolled participants (15). Of these, 31 trials assessed RV1 and 12 trials assessed RV5. Approximately half of the trials did not provide details of how adverse event data were collected. Out of the trials that did report the method of collecting adverse event data, nine trials used passive methods e.g. diary cards, two used an active method ('active surveillance system') and five used both passive and active methods.

Four trials were specifically safety trials, and eight trials were efficacy and safety outcomes. Length of follow up was variable, up to a maximum of three years.

#### 4.3.1.1 RV1

Serious adverse events were reported in 28 trials, and overall, fewer children allocated to RV1 had a serious adverse events compared with placebo (RR 0.89 95% CI 0.84-0.94 in 95,178 participants). Eleven trials reported the incidence of intussusception with 27 cases reported in 53,887 children who received RV1 compared with 23 cases in 44,560 who received placebo. Pooled results showed no increased risk for intussusception in those receiving the vaccine. There were two trials which reported three cases of Kawasaki disease among 3429 children allocated to RV1 compared to no cases in 1190 children in the placebo arm; this was not statistically significantly different (RR

1.4, 95% CI 0.16 – 12.43). Two trials reported SAEs requiring hospitalisation and found fewer events in the RV1 group than the placebo.

The occurrence of fever, diarrhoea and vomiting was evaluated after each dose and at the end of the follow-up period. There were similar results for RV1 and placebo at each time point. There was no significant difference in the number of adverse events leading to discontinuation of the schedule between vaccine and placebo.

#### 4.3.1.2 RV5

Pooled results showed no significant difference in the rate of serious adverse events following vaccination with RV5 compared with placebo in seven trials with 77,480 participants. Six trials recorded the incidence of intussusception: 12 cases were reported in 38,641 participants who received RV5 and 15 cases in 37,439 placebo participants; there were no statistical differences in the number of cases between vaccinated cases and placebo.

No statistical differences were observed for fever, diarrhoea and vomiting between vaccine and placebo groups. There was no significant difference between vaccine and placebo in the number of adverse events leading to discontinuation of the schedule.

### 4.3.2 Recently published individual safety studies of RV1

A Korean post-licensure study, which compared 318 healthy infants aged six -12 weeks who received RV1 with 114 infants who received placebo, showed no difference in solicited and unsolicited adverse events (16).

In a randomised control trial (RCT), 756 infants aged six-14 weeks were randomised 2:1 to two-dose RV1 vaccine or placebo across 20 centres in Japan. No differences in the solicited and unsolicited adverse events were seen between the two groups (17).

### 4.3.3 Recently published individual safety studies of RV5

A prospective evaluation of the risk of intussusception and other pre-specified adverse events among RV5 recipients was undertaken, based on the US Vaccine Safety Datalink data, for children from age four – 48 weeks who received the vaccine between May 2006



and May 2008. Adverse events over the subsequent 30 days were ascertained from inpatient, outpatient and emergency department files. There were 207,621 doses of RV5 administered to the study population, 42% were the first dose. Five children had diagnosed intussusception. Based on historical rates 6.75 cases were expected giving a relative risk of 0.74. The authors concluded there was no elevation in risk identified for intussusception or any other adverse event (18).

The European Rotavirus Efficacy and Safety Trial (RST) evaluated the safety of RV5 on 30,523 children in Europe. All infants were followed for SAE with active follow-up for 42 days after each dose. Comparing results from 15,278 participants with 15,207 placebo recipients there was no statistically significant differences for any of the safety outcomes (19). In the Finnish subcohort, investigating adverse events post-vaccination occurring within seven days of dose one, showed no significant difference between 1343 vaccine recipients and 1341 placebo recipients including diarrhoea, vomiting, irritability and high fever (19).

A double-blind, placebo-controlled, randomised clinical study in Bangladesh assessed the efficacy of RV5 in 1136 healthy infants in 2007 – 2009 given as part of an EPI schedule at six, 10 and 14 weeks of age. Of these infants, 1128 received a full course of three doses. During the study period, 39 serious adverse events (SAE) were reported and six deaths. There were no significant differences between the placebo and vaccine groups. The most common SAE was pneumonia. Follow-up was conducted at seven days, 14 days and then monthly for 12 – 24 months (20).

A Jamaican study was part of the international placebo-controlled RST. A total of 1804 Jamaican infants aged six – 12 weeks received at least one of three doses of RV5 vaccine with a placebo group of 809. Of the 1802 participants included in the safety analysis, intussusception was confirmed for one vaccine recipient 115 days after the third dose and three placebo recipients. There was no difference in other serious adverse events between the groups (21).

A double-blind controlled trial in Taiwan, which randomised 189 infants 1:1 to receive RV5 vaccine or placebo, showed no difference in adverse events between vaccine and placebo recipients within 42 days of receipt of vaccine (22).

#### 4.3.4 Safety in population subgroups

Two studies, conducted in five countries from March 2007 to March 2009, evaluated the safety of RV5 in Africa and Asia. In Kenya, 1308 participants, including HIV-infected and HIV-exposed, infants were randomised 1:1 RV5 to placebo. SAE were followed for 14 days and in a smaller group of 297 participants for 42 days: there were 21 HIV-infected infants in the vaccine group and 17 in the placebo group. No individual SAE was more common among vaccine versus placebo recipients (23).

A group of 100 HIV positive infants aged six-10 weeks were enrolled in a South African RCT with a 1: 1 randomisation RV1 versus placebo. All elicited and un-elicited symptoms monitored at day 15 and 31 occurred at a similar frequency in both groups. Of note was one infant who showed prolonged shedding beyond day 42 (24).

A European study evaluated using RV1 in 1009 preterm infants who were randomised 2:1 vaccine to placebo, and vaccinated according to recommended chronologic age for full term. Results showed that the frequency of serious adverse events was similar in both groups. Additionally, fever, diarrhoea and vomiting also occurred at a similar frequency in both groups (25).

A retrospective study in Australia reviewed the effects of RV5 rotavirus vaccination on weight gain and gastrointestinal losses in nine infants with functional short gut syndrome secondary to an ileostomy. Although one infant developed severe stomal losses after vaccination, the vaccination did not alter weight gain, temperature or urinary sodium, overall (26).

#### 4.3.5 Intussusception

Neither RV1 nor RV5 were associated with intussusception in the large pre-licensure trials. However, recent post-licensure data from international settings suggest the possibility of a low-level risk, primarily in the first week after the first vaccine dose (27).

To understand the baseline rates of intussusception prior to the introduction of Rotavirus vaccine a Japanese retrospective cross-sectional study was undertaken reviewing medical charts of all hospitals in one prefecture in Japan between January 2001 and December 2010. Over this 10 year period, 122 children were diagnosed with intussusception, an incidence of 158/100 000 person-years (28).

A cohort study, in infants aged four to 34 weeks enrolled in the US Vaccine Safety Datalink who received RV5 from May 2006 – February 2010, compared those who received RV5 concomitantly with other recommended vaccines, with those who received the other vaccines alone. During the study period, a total of 786,725 doses of RV5 were given, including 309,844 first doses. There was no statistically significant increase in risk of intussusception following any dose in either the one to seven day or one to 30 day risk window (27).

A serial cross-sectional analysis was conducted in the USA of hospital discharges for intussusception in children younger than one year of age, which evaluated changes since the reintroduction of rotavirus vaccine by comparing the four years prior to reintroduction with one year after. No detectable increase in the number of hospital discharges for intussusceptions amongst US infants was seen after reintroduction of rotavirus vaccination in 2008. The measured rate of hospital discharge post introduction of vaccine in 2009 was 33.3 per 100,000 (95% CI 29-37.6) and prior to introduction was 41.6 (95% CI 36.7-46.5) to 36.5 (95% CI 31.7-41.2) per 100,000 infants from 1997 to 2006 (29).

A case control study was conducted in Mexico and Brazil, using active surveillance of infants age-matched with controls in the same neighbourhood at 69 hospitals (16 in Mexico and 53 in Brazil). A total of 615 cases and 2050 controls were enrolled. An increased risk of intussusception 1-7 days after the first dose of RV1 was identified among infants in Mexico using both a case series method (IR 5.3; 95% CI 3.0-9.3) and case control (OR 5.8; 95% CI 2.6 – 13.0). No significant risk was found after the first dose in Brazil but a small increased risk was seen day 1-7 after the second dose, showing an increase by a factor of 1.9-2.6. This translated to a combined annual excess of 96 cases and 5 deaths, however, the vaccine prevented approximately 80,000 hospitalisations and 1300 deaths in these two countries (30).

In support of the findings in Mexico, Australian data has shown some evidence of an elevated risk following the first dose of both RV1 and RV5 vaccines. Two active surveillance mechanisms using hospital-based case ascertainment and monthly reports from paediatricians in Australia identified intussusception cases between July 2007 – December 2008 in four states, and linking to vaccination records. Overall, there was no evidence of an increased risk of intussusception following vaccination for either vaccine. However, in infants one to three months of age there was evidence of excess intussusception cases at 1-7 days (RV5 RR 5.3, 95% CI 1.1-15.4; RV1 RR 3.5, 95% CI 0.7-10.1) and one-21 days following dose one (RV5 RR 3.5, 95% CI 1.3-7.6; RV1 1.5, 95% CI 0.4-3.9). There was no evidence that clinical outcomes of intussusception occurring within 21 days of rotavirus vaccination differed from that in cases occurring late post-vaccination (31).

An analysis of the health benefits versus intussusception risk was undertaken for the 14 Latin American countries currently using rotavirus vaccines. The study used the post-licensure evaluation rates of a short term 4-6 fold elevated relative risk of intussusception in 1-7 days after dose one based on the Mexican experiences with RV1 and Australian experiences with RV1 and RV5, baseline estimates of intussusception rates from pooled global analysis and a range of conservative estimates. The study concluded that the vaccine would annually prevent 144,746 hospitalisations (90% CI 128,821-156,707) and 4124 deaths (90% CI 3740-4239), but could cause an additional 172 hospitalisations (90% CI 126-293) and 10 deaths (90% CI 6-17) (32).

Even when an age restriction is not imposed, the lives saved benefits were substantially greater than the risk, particularly in settings with high rotavirus mortality and delays in vaccination (32).

An expert review article summarising the data on intussusception post vaccination concluded that there is a low, albeit significant, temporal clustering of cases within one week post vaccination compared to controls. The studies do not allow the conclusion that intussusception will actually increase with vaccination, because they have not allowed for the possibility of a reduction of cases in vaccinated children later in life (33).

### 4.3.6 Porcine circovirus (PCV) contamination

In March 2010, the US Food and Drug Administration (FDA) temporarily suspended the use of RV1 after the presence of an extraneous porcine circovirus (PCV) was identified in commercial vaccine lots (34). Fragments of the genome of PCV were also later identified in RV5. The FDA later resumed the use of RV1 and continued to recommend both vaccines based on three considerations (4):

- Both vaccines have strong safety records, including clinical trials involving tens of thousands of patients as well as clinical post-licensure experience with millions of vaccine recipients.
- There is no evidence that PCV poses a safety risk in humans and they are not known to cause infection or illness in humans.
- The benefits of the vaccines are substantial.

There was no PCV virus or viral proteins detected in these vaccines. The contamination was restricted to viral nucleic acids. The technology (deep sequencing) used to detect these residual nucleic acids have been applied to a number of vaccines including MMR. The approach allows all nucleic acid material in the vaccine to be detected and sequenced as opposed to using specific probes against known genomic sequences of interest.

### 4.3.7 Other potential safety issues

An overview of other potential safety issues was covered by Bines et al. in 2009 (35) and summarised below:

Wild type rotavirus infection is not confined to the gut of infected patients; rotavirus has also been identified in the central nervous system, lymph nodes, liver, lung and myocardium. Infectious particles and non-infectious antigens have been identified in large proportion of serum samples from children hospitalised with severe gastroenteritis. The transmission of rotavirus infection via serum has been demonstrated in piglets. The ability of a rotavirus to cause viraemia may vary with specific strain of the rotavirus. To date, no data on viraemia after vaccination have been reported. CNS infection including seizures, meningitis and encephalitis have been rarely reported following wild type rotavirus infection and are likely to be associated with high rates of viral shedding or specific serotypes such as G1. To date there have been no reports of CNS disease associated with rotavirus vaccines.

In a phase III trial of the RV1, an excess of pneumonia-related deaths were observed in vaccine recipients (16 versus 6 who received placebo). This has not been consistent across studies and there was no significant difference in other potential pneumonia-related outcomes.

There have been a small number of reports of Kawasaki disease following vaccination with RV5 in the US, but a causal relationship has not been established.

Rotavirus contains peptide sequences similar to T cell epitopes in human islet autoantigens, hence there have been concerns that acute rotavirus infection may trigger or exacerbate islet cell autoimmunity, leading to the development of diabetes in genetically susceptible children. However, it is considered more likely that the development of type 1 diabetes is the result of a complex series of environmental and genetic factors.

The risk of coeliac disease is reported to be higher in children with a history of repeated rotavirus infection in infancy and early childhood. To date, post-marketing surveillance has not confirmed this with vaccines.

#### 4.3.7.1 Shedding

Specific characteristics of each vaccine strain determine the potential to infect intestinal cells and shed the vaccine virus in the stool. The RV1 vaccine replicates well within the intestine and live virus can be detected in more than 25% of patients after only one dose. RV5 does not replicate so well and is shed infrequently; as a result higher aggregate vaccine titres are required to achieve protection. US data reports shedding of rotavirus vaccine virus observed within two weeks of vaccination in approximate 9% - 21% of infants post RV5 vaccine and 35 - 80% of infants post RV1 vaccine (36).

Shedding does not appear to be a concern for immunocompetent individuals. However, since both of these vaccines contain live attenuated rotavirus, the safety for immunocompromised patients or contacts of immunocompromised people is an important consideration. To date, there is no clinical data to confirm the safety of these vaccines for patients with immunodeficiency.

Available evidence does not indicate that wild-type rotavirus infection is more severe in HIV infected infants than in non-infected suggesting that the risk from attenuated vaccine virus may be small or not at all (35).

### 4.3.7.2 Reassortant potential

Reassortants have been observed at low frequencies in several vaccinated populations with RV5 (36, 37). A case study of three patients in the US describes a vaccine-derived new G1P[8] human bovine double reassortant rotavirus, which represented 3.8% of the 79 rotavirus-positive cases of acute gastroenteritis detected during a two year period. The true rate of symptomatic or asymptomatic shedding due to vaccine-derived double reassortant may be higher as mild cases associated with vaccination and asymptomatic shedding would not be detected in hospital base surveys (38).

Of note, no reassortants have been detected among any healthy control subjects. Evidence regarding RV1 strain is more limited, but some transmission to unvaccinated subjects may occur (36). Human to human transmission of a reassortant appears possible and may cause gastroenteritis symptoms, although causality is not clear in the published reports to date (36).

## 4.4 Summary vaccine safety

The individual studies and pooled data from all studies have not raised any significant safety concerns for either vaccine. There appears to be no increased risk for fever, diarrhoea or vomiting. There have been three case reports of Kawasaki disease post vaccination.

Children with HIV do not appear to have any extra safety risks, with the possible exception of prolonged shedding. There are no extra safety concerns for preterm infants. There is a case report of an infant with functional short gut having diarrhoea in the stoma post vaccination. No increased risk of intussusception was identified in the US safety surveillance data. In contrast, studies in Brazil, Mexico and Australia have identified significant temporal clustering, particularly in day 1 - 7 post the first dose for both RV1 and RV5 vaccines, with an increased risk in the order of 1.9 - 2.6 times in this window period. It is unclear if this translates to an overall increase in number of total cases.

Contamination by pieces of PCV genome found in both vaccines is not considered to pose any safety problems.

Other potential vaccine safety issues include:

- Higher rates of viral shedding leading to disease outside the gastrointestinal tract such as CNS, seen occasionally with wild disease but not with vaccines.
- An excess of pneumonia cases over placebo was seen in one study, not replicated elsewhere.
- A small number of cases of Kawasaki disease noted after receipt of RV5.
- The potential for autoimmunity is considered to be unlikely.
- The possibility of coeliac disease, also not shown to date.

Prolonged shedding is possible, particularly for RV1 and more likely in immunocompromised patients, which is then more likely to be transmitted to those who are unvaccinated. Although no safety concerns have been highlighted to date, further monitoring is necessary.

Occasional new vaccine virus reassortants have been observed, which may cause gastroenteritis symptoms, although the importance of these is not yet clear.

# 5. Immunogenicity, efficacy, effectiveness and vaccine impact

## 5.1 Objective

The objective of this section is to review the most recent effectiveness data for the current internationally licensed rotavirus vaccines, RV1 and RV5. Considerations will be given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of rotavirus vaccines and evidence for the non-inferiority of alternative schedules.

## 5.2 Outcomes

The outcomes considered for this review include:

- Hospitalisation for all cause gastroenteritis.
- All medically-attended diarrhoea visits.
- Hospitalisation for rotavirus gastroenteritis: severe cases, and all cases.
- Rotavirus requiring medical visits.
- Immunogenicity measures: anti-rotavirus IgA.

## 5.3 Review

Review articles summarising developed and developing country data estimate the efficacy of both current rotavirus vaccines against rotavirus associated diarrhoea to be between 70-100% in some countries in Europe and Latin America, and close to 70% in developing countries in Africa and Asia (15, 39). Efficacy is recognised as generally being lower in low-income countries due to greater serotype diversity (40). Ecological studies in eight countries to date have shown a decline in protection within two years of vaccine introduction, ranging from 49% - 89% in hospital admission for laboratory-confirmed rotavirus (41). Vaccination effectiveness varies in settings with estimates around 44 - 51% in low-income settings, 76- 86% in middle income settings and 80 - 86% in middle to high income settings (41, 42). A consistent finding is decreased effectiveness among children from low and middle-income settings compared with the sustained protection seen in children in their first two to three years of life in high-income regions (41).

### 5.3.1 Immunogenicity

The immunological mechanism by which protection against disease occurs is still unknown, and this has made it difficult to understand the mechanism of protection in clinical trials. Most studies on immune responses have suggested that the presence of faecal IgA or serum antibodies serve as a good surrogate marker for protection, however, animal studies also point to the importance of CD4 and CD8 T cells (43).

The 2012 Cochrane review of vaccines for preventing rotavirus-related diarrhoea assessed 43 trials, which met the inclusion criteria and covered a total of 190, 551 enrolled participants (15). Of these, 31 trials assessed RV1 and 12 trials assessed RV5. This included 18 efficacy trials with RV1 and seven efficacy trials with RV5. Immunogenicity was measured by seroconversion following the third dose in seven trials, but data could not be pooled due to significant heterogeneity. For RV5, the vaccine schedules were all of three doses with intervals between doses of four and 10 weeks. RV1 was given as two doses in all except four trials.

RV1 was shown to be more immunogenic than placebo when immunogenicity was measured by vaccine virus shedding at the end of follow-up (RR = 10.34, 95% CI 4.76-22.44 in 2720 participants in 16 trials), however, the results were significantly heterogeneous. The immunogenicity of RV1 was greater than placebo as measured by seroconversion at all time-points. As seen previously with virus shedding, the pooled data were significantly heterogeneous after dose one and two.

#### 5.3.1.1 Cochrane review of RV1

Both vaccines prevent over 80% of rotavirus diarrhoea cases that require hospitalisation. The authors conclude that both vaccines are effective in preventing rotavirus diarrhoea; however, the potential for reduced vaccine efficacy in low-income countries needs to be investigated (15).

In infants under one year of age, RV1 prevented 70% of all cases of rotavirus diarrhoea compared to placebo in seven trials of moderate-quality evidence with 12,130 participants (RR 0.30, 95% CI 0.18 - 0.5), and 80% cases of severe rotavirus diarrhoea in seven trials of



moderate-quality evidence with 35,005 participants (RR 0.20, 95% CI 0.11 to 0.35). RV1 may reduce severe cases of all-cause diarrhoea by 42%, based on two multi-centred trials from South Africa, Malawi and Europe (RR 0.58, 95% CI 0.40 – 0.84, low quality evidence with 8291 participants).

In children during the second year of life, RV1 prevented 70% of all cases of rotavirus diarrhoea of any severity compared to placebo (RR 0.30, 95% CI 0.21- 0.43 in six trials of moderate quality evidence covering 8041 participants) and 84% of cases of severe rotavirus diarrhoea (RR 0.16, 95% CI 0.12 – 0.21 in eight trials of moderate quality with 32,854 participants). RV1 appeared to reduce all-cause diarrhoea cases by 51% (RR 0.49, 95% CI 0.4 – 0.6 in two trials of moderate quality with 6269 participants).

### 5.3.1.2 Cochrane review of RV5

In infants aged less than one year, RV5 prevented 73% of all rotavirus diarrhoea cases (RR 0.27, 95% CI 0.22-0.33 in four trials of high-quality evidence on 7614 participants) and 77% of cases of severe rotavirus diarrhoea (RR 0.23, 95% CI 0.08 to 0.71 in three trials of high-quality evidence with 6953 participants). Based on data from one trial from Finland, RV5 may reduce severe cases by 72% (RR 0.28, 95% CI 0.16-0.48 low quality evidence with 1029 participants).

During the second year of life, RV5 prevented 49% of all rotavirus diarrhoea cases of any severity (RR 0.51, 95% CI 0.36-0.72 in four trials of high quality with 9784 participants) and 56% of cases of severe rotavirus diarrhoea (RR 0.44, 95% CI 0.22- 0.88 in 4 trials of high quality evidence with 9783 participants). For all cause diarrhoea RV5 showed no difference with placebo (3 trials, 8533 participants) (15).

### 5.3.2 Recently published individual studies of RV1

A Korean post-licensure study, which compared 318 healthy infants aged six -12 weeks who received RV1 with 114 infants who received placebo, showed the anti-RV IgA seroconversion rates following one month post dose 2 were 88% (95% CI 84-91.4) with geometric mean titres (GMT)s of 208 U/ml (95% CI 174.2 – 249.5) (16).

In a randomised control trial (RCT), 756 infants aged six-14 weeks were randomised 2:1 to two-dose RV1 vaccine or placebo across 20 centres in Japan. The study showed vaccine efficacy, against any and severe rotavirus gastroenteritis leading to medical intervention until two years of age, was 79.3% (95%

CI 60.5-89.8%) and 91.6% (95% CI 62.4-99.1%), respectively (17).

A phase III RCT in South Africa and Malawi enrolled 4939 infants who were vaccinated with RV1 and 4417 placebo controls. Vaccine efficacy (VE) against severe rotavirus gastroenteritis caused by G1, G12 and G8 types were 64.1% (95% CI 29.9-82%), 51.5% (95% CI -6.5 – 77.9%) and 64.4% (95% CI 17.1-85.2%), respectively. Against the predominant circulating P type genotype P[8], VE was 59.1% (95% CI 32.8-75.3%). The authors concluded that this vaccine demonstrated efficacy against severe gastroenteritis caused by diverse circulating rotavirus types. This supports evidence that RV1 provides heterotypic protection (44).

A retrospective case-control analysis reviewed the medical records of indigenous children under five years of age who were hospitalised for acute gastroenteritis during an extensive outbreak caused by G9 rotavirus in Australia Northern Territories. Each case was matched up to four matched controls from the risk-set population. The analysis showed a VE following two-doses of RV1 of 84.5% (95% CI 23-97%) (45). A further study was undertaken during an outbreak of G2P[4] rotavirus infection in Central Australia in a remote population where 60% of the children were indigenous. A case-control analysis of children hospitalised for acute gastroenteritis up to 36 months of age matched by date of birth and indigenous status with four children in the risk set population showed no evidence of protection against hospitalisation for G2P[4] rotavirus following two-dose RV1 vaccination (95% CI -105 – 68). Although protection was observed against rotavirus-associated severe acidosis, for vaccinated children less than one year of age (OR 0.15; 95% CI 0.03-0.84), it was not for children aged 12 -35 months (46).

Refer to the studies in section 5.3.3 undertaken in Navarre, Spain and in Belgium.

### 5.3.3 Recently published individual studies of RV5

The European Rotavirus Efficacy and Safety Trial (RST) evaluated the safety of RV5 in 30, 523 children in Europe. All healthcare utilisation and rotavirus gastroenteritis was evaluated in a clinical efficacy cohort of 2686 children in Finland. RV5 was 98.3% and 68% efficacious against severe rotavirus gastroenteritis (95% CI 90.2-100) and all rotavirus gastroenteritis (95% CI 60.3-74.4), respectively, due to any serotype for two rotavirus seasons post-vaccination (19).

Rotavirus vaccine was introduced in Spain in 2006. A case-control test-negative study in Spain of children aged three-59 months demonstrated that effectiveness against rotavirus disease was 78% in preventing gastroenteritis (95% CI 68-85%) and 83% in preventing hospitalisation (95% CI 65-93%), when RV5 and RV1 vaccines were used (47). A prospective case-control study in Belgium of 215 children admitted to hospital with rotavirus gastroenteritis showed vaccine effectiveness for either RV1 or RV5 to be 85% against P[4]G2 (95% CI 64-94%) and 95% against P[8]G1 (95% CI 78-99%). Interestingly, in 25% of cases co-infection with adenovirus astrovirus and/or norovirus was reported. Vaccine effectiveness against co-infected cases was 86% (95% CI 52-96%). Effectiveness of at least one dose of any rotavirus vaccine was 91% (95% CI 82-95%) (48).

A US-based RCT, involving Navajo and White Mountain Apache infants, enrolled 509 infants who were vaccinated with three-doses of RV5 and 494 controls who received placebo. The vaccine was 77.1% effective against G1-G4 rotavirus disease (95% CI 59-7 - 87.6), 89.5% effective against severe and moderate rotavirus disease combined (95% CI 65.9-97.9) and 82.9% effective against outpatient visits for rotavirus disease (95% CI 61.1-93.6) (49).

Following the introduction of RV5 in 2007 in Puerto Rico, a study showed that rotavirus accounted for 22% of acute gastroenteritis prevaccination and only 8.5% post-vaccination during 2007-2009. A reduction of 68% in acute rotavirus gastroenteritis hospitalisations was seen after vaccination (50).

A double-blind clinical study evaluated the efficacy of RV5 in Bangladesh in 1136 healthy infants vaccinated in 2007 - 2009 as part of the Expanded Programme on Immunisation (EPI) schedule. Infants were randomised 1:1 to receive RV5 or placebo at six, 10 and 14 weeks of age alongside the routine schedule. Of these infants, 1128 received a full course of three doses. Efficacy against hospitalised (severe rotavirus gastroenteritis) was 42.7% for the study period which was 12 - 24 months for each participant. Serum anti-rotavirus IgA was 78.1% in a subset of 150 infants from whom blood samples were obtained pre and post vaccination (20).

A double-blind randomised controlled trial in Taiwan enrolled 189 infants and showed at least a three-fold rise in serum anti-RV IgA among 93% of infants (22).

In a Jamaican study, part of an international placebo-controlled Rotavirus Efficacy and Safety Trial, a total of 1804 infants aged six - 12 weeks received at least one of three doses of RV5 vaccine and 890 infants received placebo. During the first year, there was a rate reduction of 82.2% in infants hospitalised for rotavirus gastroenteritis (95% CI 15.15 - 98%) (21).

A case-control study compared 1016 children hospitalised with laboratory-confirmed rotavirus diarrhoea in five hospitals in Nicaragua with 4930 controls with non-rotavirus diarrhoea (test-negative controls). The study found that vaccination with RV5 vaccine was associated with a significantly lower rotavirus hospitalisation (OR 0.55, 95% CI 0.41-0.74). However of note, the risk of hospitalisation was two-fold lower among vaccinated children less than one year of age compared with those over one year (51).

As a higher risk population with a heavier burden of disease than the rest of the US population, concerns had been expressed that rotavirus vaccines may not work as well in Native American Indian populations in routine usage. RV5 was introduced in 2006 via the Indian Health Service to all American Indian and Alaska Native infants. A survey of diarrhoea-associated hospitalisation and outpatient visits, for all children under five years of age from 2001 to 2010, showed significant declines in illness. Observed rates of diarrhoea-associated hospitalisations were reduced by 24%, 37% and 44% from 2008, 2009 and 2010, respectively, compared with the pre-vaccine era across all populations (52).

In contrast to the studies above, a US retrospective cohort study of children, from February 2006 - 2008 across two rotavirus seasons, showed a significant reduction in outpatient acute gastroenteritis calls and episodes among immunised children for the 2007 season, but no difference detected between RV-immunised and non-immunised children for any outcome in the 2008 season. The authors postulate that these results, which contradicted their earlier findings, may be due to indirect protection through herd immunity leading to their inability to detect a difference between immunised and unimmunised. They also acknowledged multiple limitations in the case design (53).

### 5.3.4 Surveillance data

Data was presented at the Advisory Committee on Immunisation Practices (ACIP) meeting in October 2012 from the New Vaccine Surveillance Network (NVSN) in the USA (1). This network undertook active surveillance of children under five years of age hospitalised or visiting emergency departments with acute gastroenteritis from November to June in 2009 – 2011 in nine large hospitals. This showed a continued steep decline in rotavirus-related hospitalisations and emergency department visits. Case-control logistic regression models were undertaken using confirmed vaccination records and rotavirus-negative controls. Table 2 summarises the post-licensure data as of early 2013.

#### 5.3.4.1 NVSN Results

The point estimate Vaccine Effectiveness (VE) (1):

- For RV1 70% (95% CI 40-88%)
- For RV5 84% (95% CI 79-88%)

By rotavirus genotype, the VE of RV5 was 89% for G1P[8] (95% CI 40 – 99%), 87% for G2P[4] (95% CI 78-795%), 87% for G3P[8] (95% CI 80-91%). For RV1, VE for G3P[8] was 74% (95% CI 40-90%) and for G12P[8] was 83% (95% CI 58-95%).

By age:

- VE for RV1 was 56% for up to one year of age (with very wide confidence intervals) and 86% for two years.
- VE for RV5 was 85% for up to one year of age, 89% for two years, 83% for three years and 79% for four years.

#### 5.3.4.2 EIP Results

In the US, an Emerging Infections Program (EIP) was conducted in five hospitals in Georgia and Connecticut. Children who were age-eligible to have received vaccine and were hospitalised or visiting the ED with diarrhoea were enrolled through active surveillance from January – June 2010 and 2011. A case control regression analysis was conducted (54)

The point estimate:

- Ror RV1 was 91% for children  $\geq$  8 months (95% CI 75-94%)
- For RV5 was 92% for children  $\geq$  8 months (95% CI 75-95%)

By genotype, the VE of RV1 was 94% G2P[4] (95% CI 74% – 94%), for G1P[8] VE was 89% (95% CI 70%-96%). For RV5, has a VE against 95% and 98% against G2P[4] and G1P[8] (95% CI 74% - 94%; 74 – 100%), respectively.

**Table 2. Post-licensure VE for RV1 and RV5**

Study	RV1 (Rotarix®): 2 dose VE (95% CI)	RV5 (RotaTeq®) : 3 dose VE (95% CI)
Boom JA et al. 2010 (55)		89% (70-96)
Staat MA et al. 2011 (56)		87% (71-94)
Cortese MM et al. 2011 (57)		89% (81-94)
NVSM Payne DC et al. 2013 (58)	70% (39-86)	84% (78-88)
EIP Cortese MM et al. 2013 (54)	91% (75-94)	92% (75-95)
Castilla J et al. Spain 2012 (47)	75% (60-85)	81% (68-89)

The conclusions from this meeting were:

- High effectiveness is observed for both rotavirus vaccines.
- The VE for RV1 requires further monitoring. Although this data points to an overall lower VE for RV1, this data is not sufficient to be able to state that the VE for RV1 is lower than for RV5.
- There is no evidence of waning immunity, at the limits of the observed study power; for the duration of these studies, the data does not show signs of waning immunity, for either vaccine.
- There are no significant differences in VE by genotype.

### 5.3.5 Effectiveness of partial vaccination

Summary data, from studies conducted in a range of countries in infants who had not completed a full course of three doses of RV5 or two doses of RV1, showed that partial vaccination with either RV1 or RV5 vaccines provided protection ranging from 51-55% in low and middle income countries, and from 69-93% in high-income countries (41).



### 5.3.6 Duration of effectiveness

Duration of protection offered by these vaccines is difficult to measure due to the impact of herd immunity which follows implementation. The issue of serotype replacement is likely to have the greatest influence on decisions around vaccine and scheduling options.

A Brazilian case-controlled study evaluating the efficacy of the RV1 vaccine, enrolled 70 infants aged six months or older hospitalised for confirmed G2P[4] rotavirus who were compared with control groups of 484 children hospitalised with rotavirus-negative acute gastroenteritis and 416 children with acute respiratory illnesses. VE against rotavirus disease requiring hospitalisation surpassed 80% using either control, but effectiveness decreased for children  $\geq 12$  months reaching non-significant levels using both groups of controls. This apparent decrease in vaccine effectiveness with increasing age, although not conclusive in this study owing to low numbers of cases, raises the possibility of waning immunity (59). In contrast, a larger matched case-control study in Brazil found that vaccine effectiveness with two doses of RV1 remained high after 12 months of age. The study enrolled 538 children 12 weeks of age or older hospitalised with acute rotavirus gastroenteritis and matched with a neighbourhood control and a control hospitalised without acute gastroenteritis (60).

Data from developing countries indicate a decrease in protection after the first year of life. For example, a study in El Salvador vaccine effectiveness decreased from 82% during infancy to 59% among children over a year of age (61). However, despite this, the effect on the reduced protection on the total burden of disease was minimal (62).

In the US, alterations in the rotavirus season have been seen following the introduction of rotavirus vaccines with the onset of the season delayed by two to four months and duration shortened from 26 weeks to 14 weeks (63).

### 5.3.7 Vulnerable groups

#### 5.3.7.1 Preterm

The 2012 Cochrane review reported on one study that analysed data separately for 170 preterm infants which showed that RV5 was marginally better than placebo at one year follow-up in preventing rotavirus diarrhoea (RR 0.39, 95% CI 0.15-1.06) (15).

A European study with 1009 preterm infants randomised 2:1 vaccine to placebo and vaccinated according to recommended chronologic age for full term showed good immunogenicity responses with anti-rotavirus IgA seroconversion 86% following the second dose (64).

#### 5.3.7.2 Malnourished

The 2012 Cochrane review reported data on malnourished children and showed RV1 was significantly better than placebo in preventing rotavirus diarrhoea for this group at one year follow up in 287 participants (RR 0.39, 95% CI 0.19-0.79) (15).

#### 5.3.7.3 Children infected with HIV

A cohort of 100 HIV-positive infants aged six-10 weeks were equally randomised to receive RV1 or placebo in a South African RCT. Satisfactory immune responses were mounted with seroconversion rates at 57% in the RV1 group versus 18.2% in the placebo group two months after dose two (24).

#### 5.3.7.4 Other groups

Expert opinion recommends that rotavirus vaccine is to be given to children with chronic kidney disease, except for those on immunosuppressive treatment, although there is currently no data available on the response to this vaccine in these children (65).

#### 5.3.7.5 Breast Feeding

A Finnish RCT study followed 3994 healthy infants aged six to 14 weeks who received two doses of RV1 or placebo over two seasons. When comparing breast-fed infants to exclusively formula-fed infants, the IgA seroconversion rates were 85.5% in the breast-fed (95% CI 82.4-88.3) and 89.2% in formula-fed infants (95% CI 84.2 – 93). Geometric mean titres (GMT) tended to be lower in breast-fed infants at 185.8 U/ml (95% CI 161.4-213.0) and 231.5 U/ml (95% CI 185.9-288.2) in formula fed. Efficacy was equal in both groups in the first season, but fell in breast-fed infants in the second rotavirus season. Combined

two year efficacy from any rotavirus gastroenteritis was 76.2% for breast-fed (95% CI 68.7-82.1) and 89.8% for formula fed (95% CI 77.6-95.9), and against severe rotavirus gastroenteritis 88.4% (95% CI 81.6-93) and 98.15 (95% CI 88.2-100) in breast fed and exclusively formula fed infants, respectively. The authors concluded there were small differences in immunogenicity. However, vaccine efficacy was equal in both groups, although, breast feeding seemed to reduce slightly the efficacy in the second season (53).

Summary commentary, including earlier data from the pre-licensure studies, concludes that the efficacy of the vaccine is similar for breast fed and non-breast fed infants (4).

### 5.3.8 Cross-protection

RV vaccines need to provide cross-protection against multiple serotypes because circulating strains vary considerably and multiple strains can circulate simultaneously. RV1 does not directly cover G2P[4] strains. Although RV5 contains G and P antigens for all common strains, serotype-specific immune response vary by strain, with the lowest response against G3P[8]. A 2012 summary article concluded that, despite the potential for decreased efficacy, both vaccines to date have provided good cross protection against the common circulating strains in trials in Europe and the US. RV1 appears to provide less protection against G2P[4] in Latin America, although, at the time of the study the strain was not circulating so the study was underpowered. In contrast, in six European countries RV1 provided effective protection (85%) against severe rotavirus gastroenteritis from G2P[4]. In recent publications, both vaccines appear to have similar efficacy against a wide range of strains circulating in Asia and Africa, during the study periods. In both Brazil and Australia, RV1 appears to show good effectiveness against G2P[4]. In the US, RV5 was shown to have high effectiveness against severe disease caused by G3P[8]; and in a case control study in Mexico RV1 effectiveness was 94%, after the emergence of a novel G9P[4] strain (5)

### 5.3.9 Herd immunity

Rotavirus vaccine was introduced in the US in 2006. Data following the introduction of these vaccines showed marked reductions in rotavirus infections in both vaccinated and non-vaccinated individuals in all age groups. It was estimated that 15% of the total 66,000 averted hospitalisations and 20% of the US\$204 million in averted direct medical costs attributable to the vaccination programme were among the unvaccinated five-24 year olds reflecting herd immunity effects (66). Epidemiological data from Austria, which was the first European country to implement universal vaccination with rotavirus vaccine, showed that decreasing hospitalisation rates from rotavirus gastroenteritis was observed in children in all age groups, including in those age groups not vaccinated (67). Vaccine viruses are shed in the stool following vaccination and may be transmitted from vaccinated to unvaccinated children, one possible mechanism to herd immunity. This is likely to be more common with the RV1 vaccine than with the RV5 and occurs primarily after the first dose (68).

## 5.4 Summary of effectiveness

Immunogenicity measures are not clear correlates of protection, but faecal and serum IgA are reasonable surrogate markers. Both vaccines give good immunogenicity responses, although there is significant heterogeneity in study results. Both vaccines show good effectiveness in preventing rotavirus diarrhoea. Vaccine effectiveness varies in settings with estimates around 44 to 51% in low-income settings, 76 to 86% in middle income setting and 80 to 86% in middle to high income settings. A consistent finding is the decreased effectiveness for children from low and middle-income settings compared to high-income regions. Both vaccines are more effective against severe gastroenteritis than mild.

There is a possible decline in effectiveness in the second year of life, particularly in low income countries.

Both vaccines appear to offer reasonable protection even in partially vaccinated infants. Co-infection with other viruses may be common, but good vaccine effectiveness is still observed.

While there are some data suggesting the VE for RV1 may be lower than RV5, further monitoring is required. To date there are no significant differences in VE by genotype, and no evidence of waning immunity.

For vulnerable groups the vaccine is expected to be effective in HIV-infected children, in malnourished and probably effective in preterm infants.

There are small differences in immunogenicity and efficacy between breast fed and non-breast fed infants; vaccine efficacy was similar in both groups, although, breast feeding seemed to reduce slightly the efficacy in the second season.

Despite the potential for decreased efficacy for different strains not contained in the vaccines, both vaccines to date have provided good cross protection against the common circulating strains in Europe and the US. RV1 may provide lesser protection against G2P[4] in Latin America, though this has not been confirmed. Both vaccines appear to have similar efficacy against a wide range of strains in Asia and Africa.

Early data in the US and Europe is showing good herd immunity effects.

# 6. Vaccine Options

## 6.1 Objective

The objectives for this section are to consider the different vaccine options for NZ in terms of available vaccines and schedules.

## 6.2 Review

Both rotavirus vaccines are licensed in NZ: RV1 in a two-dose course and RV5 in a three-dose course. To date, data would suggest that either vaccine is expected to be effective with a good safety profile. There is some data suggesting that the RV1 may have lower VE than RV5, this is not currently seen as significant although worthy of further monitoring. As both vaccines appear to show similar efficacy against all genotypes, there is no obvious preferential vaccine based on NZ epidemiological patterns.

There are a range of other vaccine candidates in the pipeline. For example, a live oral attenuated G1P[8] derived from a child in Vietnam is in phase II trials in Israel (69). In low income countries the current rotavirus vaccines are less effective than in high income countries, primarily because the development of these vaccines was based predominantly on serotype spectrums in higher income countries. There are other vaccines in development from low income countries such as the 116E (Bharat Biotech) based on the human rotavirus G9P[11] in phase II trials in India (40). An RV3 vaccine, derived from a P2A[6]G3 strain in Australia, is being developed with BioPharma, Indonesia. Technically, it is feasible and straightforward to make any new type of reassortant vaccine as needed if the serotype match is poor (43).

Although orally administered live virus vaccines are the primary approach with rotavirus vaccines currently, other approaches and routes of administration are being evaluated in animal models, such as virus-like particles, cold-adapted strains, inactivated strains and DNA vaccines (43).

# 7. Options for scheduling

## 7.1 Objective

The objectives for this section are to summarise the available vaccines and present options of using rotavirus vaccines on the NZ Immunisation Schedule. The recommendations for the minimum age times of delivery and intervals are considered so as to avoid the age range in which intussusception is most likely to occur.

## 7.2 Review

### 7.2.1 Schedule timing and placement

In countries where rotavirus vaccine has been introduced, it is as a universal programme either for the entire country, or to a region. All introductions have been as part of an infant schedule. No countries have introduced a targeted vaccination campaign. Early data to date has shown the effectiveness of herd immunity based on the use of an infant schedule, with no catch-up schedule (66, 67).

The ACIP recommends the use of three doses of RV5 at two, four and six months of age, or two doses of RV1 at two and four months of age. The minimum age for the first dose is six weeks with subsequent doses given with an interval of at least four weeks. To avoid the age range in which intussusception is most likely to occur, the first dose is not recommended for infants more than 14 weeks and six days old, and due to insufficient safety data for the age group, no doses are to be given to infants over eight months of age (4).

Modelling has been conducted for responses to the lower vaccine efficacy seen in low income countries, and suggested strategies have included delaying administration of the RV1 schedule to 10 and 14 weeks to allow maternal antibody levels to wane for another four weeks, although this needs to be weighed against the risk of early natural infection and potential risk of intussusception with later vaccination. Another possibility is a three-dose schedule with RV1, for which an estimated gain of 9% in vaccine effectiveness has been predicted in these settings (42). This issue is likely to be less pertinent to NZ, but will require surveillance when rotavirus vaccine is introduced.

### 7.2.2 NZ context

The internationally recommended age ranges are suitable for the NZ schedule at six weeks and three months for RV1 or six weeks, three months and five months for RV5.

There may be gains in a two-dose RV1 regimen over a three-dose RV5; however, the primary course currently offers the same vaccines at each visit which allows simplicity, so it is equally valid to suggest a three-dose regimen for simplicity of schedule delivery.

There is a small difference in immunisation coverage between dose two and dose three which could theoretically reduce the uptake of a three dose vaccine over a two dose vaccine. However, there is also the potential that having to deliver the rotavirus vaccine within a tight time window will encourage better on-time vaccination.

## 7.3 Summary of options for scheduling

The vaccines are all recommended and used in universal infant programmes either as a two dose (RV1) or a three dose (RV5) regimen, with recommended minimum age times of delivery and intervals to avoid the age range in which intussusception is most likely to occur. Maternal antibody interference with the first dose may contribute to lower efficacy in developing countries, but is expected to be less pertinent to the NZ setting. There is no international experience of the use of targeted programmes, or catch up schedules. While a two-dose regimen may be more attractive in terms of less delivered vaccine and the possibility of lower coverage at the third visit, so long as NZ maintains high coverage for the five month visit, the advantages of a two dose regimen are not compelling.

# 8. Implementation issues

## 8.1 Objective

The objective of this section is to review the most recent data for currently licenced rotavirus vaccines with respect to potential implementation issues in the NZ context. This includes placement in the current schedule, co-administration (concomitant use) with other schedule vaccines, targeted programmes, and vulnerable groups.

## 8.2 Review

### 8.2.1 Concomitant use with other vaccines

The Cochrane review of rotavirus vaccines in 2012 reported that the use of all other national schedule vaccines did not affect the results for RV5 and placebo at a two-year follow-up (2). This would include schedules using oral and inactivated polio, whole cell and acellular pertussis, diphtheria, tetanus, Hib, pneumococcal conjugates and hepatitis B. When co-administered with oral polio vaccine (OPV), both RV1 and RV5 show a reduced immune response to the first dose, however, responses to subsequent doses were not affected. Hence, the WHO recommends that concomitant use is safe and effective with the EPI vaccines, including OPV (4).

### 8.2.2 Serotype shifts

To date, all studies suggest that a natural shift in strain, unrelated to vaccination, is commonly seen. However, these strain shifts also highlight the importance of robust, longitudinal surveillance to closely follow the long-term effect of rotavirus vaccination on strain ecology. The question remains as to whether high levels of immunity to vaccine serotypes could lead to evolution of strains that evade vaccine protection (5).

Current US and European studies suggest a good match between both RV1 and RV5 vaccines and the circulating strains (66). The match may not be so good for low income countries where there is more variety in circulating strains. Limited NZ epidemiological data suggests similar strains to Europe and US, but with occasional less common strains being identified. There is no compelling data to suggest either RV1 or RV5 would be preferable for the NZ epidemiology. Refer NZ epidemiology section 3.

### 8.2.3 Herd immunity effects

Herd immunity occurs as a result of decreased transmission of rotavirus in the community and provides indirect protection to unvaccinated individuals.

Post-market surveillance studies in the US and Australia have shown significant declines in rotavirus gastroenteritis among older child who were not age-eligible for vaccination, suggesting indirect benefits from reduced transmission in the community (4, 67, 70). Herd immunity effects have also been noted after routine vaccination in El Salvador, Panama, Mexico and Austria (5).

A comparative analysis of transmission dynamic models for rotavirus, based around the features of rotavirus epidemics in England and Wales, predicted that during the initial year after vaccine introduction, the incidence of severe rotavirus gastroenteritis would be reduced 1.8 - 2.9 times more than expected from the direct effects of vaccine alone, but over a five year period following vaccine introduction severe rotavirus gastroenteritis would reduce by only 1.1 - 1.7 times more than direct effects alone (68).

### 8.2.4 Targeted versus universal programme

Rotavirus vaccines are designed for universal infant vaccination programmes. There are no international programmes focused on targeted high risk groups, however, it could be feasible to introduce the vaccine into one region over another based on higher prevalence of rotavirus disease.

#### 8.2.4.1 Vulnerable groups

Rotavirus is a universal infection in young children. It is more severe in children aged three-24 months, in non-breast fed children, and in children with poor nutrition (4). There is a small socioeconomic gradient in NZ with children from lower socioeconomic groups up to twice as likely to be hospitalised and Pacific children 1.45 more likely to be hospitalisation than NZ European children (71). Surveillance data from the New Zealand Child and Youth Epidemiology Service shows that children aged 0-14 years from the most deprived decile by the NZDep scale have a twofold increased incidence of hospitalisation for gastroenteritis over the least deprived decile, and Pacifica children have a 1.45 increased incidence over NZ European (71).

It would be difficult to institute a programme just targeting low income and other high risk children such as Pacific peoples, unless it was a geographical based targeting. Furthermore, targeting just individuals would have the disadvantage of not utilising herd immunity effects.

### 8.2.5 Catch-up campaigns and vaccinating older children and adults

Catch-up campaigns or primary immunisation of older children is not recommended. There are three main reasons for this. Firstly, there are theoretical concerns regarding intussusception, secondly, there is currently no data in older infants or children, and thirdly, the major burden of disease is in infants. Older children and adults have usually acquired partial immunity from infection or vaccination earlier in life, and hence, are protected from severe disease.

There are no data regarding the use of the current rotavirus vaccines in older infants and children, although, it is likely that the safety profile will be similar to younger infants. Extensive post-marketing surveillance of rotavirus vaccines is being undertaken in studies in a number of countries and is expected to provide information regarding the 'off label' use of rotavirus vaccines.

### 8.2.6 Contraindications/precautions

Post-licensure safety data has not highlighted any unexpected areas of concern. Below are summary points from a recent review (4).

Anaphylaxis to latex is a contraindication to the use of RV1 as the oral applicator for this vaccine contains latex rubber. The dosing tube for RV5 is latex-free.

Both vaccines are contraindicated in infants with severe combined immunodeficiency disease (SCID); this is in response to reported cases of vaccine-acquired rotavirus infection in these infants.

The safety of these vaccines has not been established for infants with chronic gastrointestinal disease, such as congenital malabsorption syndromes, Hirshsprung's disease, short gut syndrome, or persistent vomiting of unknown cause.

It is recommended not to vaccinate infants with a history of intussusception, because they may be at greater risk of a repeat episode than other infants.

There is a small potential risk of transmitting vaccine virus to immunocompromised household members. However, protection of these household members afforded by immunisation of young infants is likely

to outweigh this risk. To minimise potential virus transmission, all household members should use good hand washing after contact with faeces of vaccinated infants.

### 8.2.7 Serotype replacement

There are theoretical concerns that the widespread use of rotavirus vaccines will introduce selective pressures on rotavirus serotypes by triggering genetic and antigenic changes that may alter the ecology and distribution of circulating strains, and thereby undermining the effectiveness of the vaccines (41). Although, there is no evidence of this to date, this issue remains uncertain and will require continued surveillance of serotypes (72). One hypothesis is that RV1 will protect more poorly against G2P[4] and G9P[4] with which it shares no common outer capsid proteins. There are theoretical concerns that the RV5 vaccine works less against G3, and therefore G3 viruses might emerge as breakthrough strains (41). Observational studies to date have not clearly shown any of these trends.

### 8.2.8 Interchangeability of RV1 and RV5

No current studies address the interchangeability of the two rotavirus vaccine products. However, the ACIP advises that "there are no theoretic reasons to expect that the risk for adverse events would be increased if the series included more than one product, compared with the risk for adverse events of a series containing only one product. Further, although it is possible that effectiveness of a series that contained both products could be reduced compared with a complete series with one product, the effectiveness of a series that contains both products is likely to be greater than an incomplete series with one product" (73).

### 8.2.9 Implementation of a new vaccine

A recent systematic review of the published literature around the impact of introducing new vaccines focused on systems issues. The full review analysed 130 relevant articles and concluded that the new vaccine introduction was most efficient when the vaccine was introduced into an existing delivery platform, and when introduced in combination with vaccines already in the routine immunisation schedule. New vaccine introduction did not impact on coverage of vaccines already included in the routine schedule. Capacity issues around the need for increased cold chain storage, new training and education for healthcare workers and social mobilisation were noted. Overall, the review concluded that there was evidence of reduced healthcare costs associated with introduction of the new vaccine in high income countries (74).



## 8.3 Summary for implementation issues

There are no concerns with concomitant use of RV vaccines with other standard national schedule vaccines. Longitudinal surveillance needs to continue to watch for possible strain serotype shifts with the introduction of RV vaccines. Herd immunity effects add to the effectiveness of RV vaccines.

RV vaccines are designed for universal, not targeted programmes; NZ epidemiology data shows that Pacific children and children from more socioeconomically deprived backgrounds bear a greater burden of hospitalisation from rotavirus, and there may be potential for introducing the vaccine in regions with higher rates of deprivation, and in Pacific populations. Little would be added from using a targeted approach to high risk individuals, as this would lose the gains from herd immunity.

The use of catch up campaigns is not recommended. There is no data to support vaccinating older children, further data is awaited for the possible 'off label' use in vulnerable older age groups.

Anaphylaxis to latex is a contraindication to the use of RV1 but not RV5. Both vaccines are contraindicated in infants with severe combined immunodeficiency disease. The safety in other rare high risk groups such as congenital malabsorption, short gut syndrome, persistent vomiting of unknown cause and Hirshsprung's disease is unknown. It is recommended not to vaccinate infants with a previous history of intussusception. There is a potential risk of transmission to immunocompromised household members so good hand hygiene is particularly important in these situations.

There is no data on interchangeability of RV1 and RV5. A complete course with one vaccine is preferable, but if necessary a series that contains both vaccines is preferable to an incomplete series.

For a new vaccine introduction capacity issues for increased cold chain storage, new training and education for healthcare workers and social mobilisation need to be considered.



# 9. International policy and practice

## 9.1 Objective

Summarise international experience on the use of rotavirus vaccines and position statements and policies from countries with comparable populations to NZ.

## 9.2 Review

As of September 2011, rotavirus vaccine had been introduced into the national programmes of 28 countries; 15 in Americas, four in Europe (Austria, Belgium, Finland and Luxembourg), four in Oceania, three in the Middle East, two in Africa (5). Of these 16 countries are using RV1, eight are using RV5 and four are using both.

To date, all countries have introduced a schedule to be complete by 26-32 weeks. There have been no catch-up vaccination programmes instituted in older children.

### 9.2.1 United States

The US Advisory Committee on Immunization Practice (ACIP) recommends universal rotavirus vaccination for all infants, with either the RV1 in a two dose schedule at two and four months of age or RV5 in a three-dose schedule at two, four and six months of age (73). ACIP advises a minimum interval between doses of four weeks and a maximum age for the first dose at 14 weeks and six days, and the maximum age for the last dose at eight months. Vaccination is recommended for infants who have already had an episode of rotavirus gastroenteritis, infants who are breastfed, preterm infants who are clinically stable and have been discharged from the 'nursery', and infants living with immunocompromised individuals or pregnant women.

### 9.2.2 United Kingdom

The United Kingdom (UK) Joint Committee on Vaccines and Immunisation (JCVI) reported that after reviewing all the data, the licensed rotavirus vaccines provided good protection in infants against rotavirus infection, and that the vaccines have good safety profiles. It recommended the introduction of rotavirus vaccines if the vaccine price enables them to be cost effective (75).

Starting in September 2013, a two-dose regimen of Rotarix™ (RV1) was added to the UK childhood immunisation schedule for three years for all infants between six and 24 weeks of age.

### 9.2.3 Canada

As of 2010, the National Advisory Committee on Immunization (NACI) in Canada recommends universal vaccination for infants starting at six weeks of age and up to the age of 14 weeks and six days. The vaccination series should be completed by eight months of age. RV1 and RV5 are both available. NACI recommends that based on the theoretical risk of live attenuated viral vaccines in immunocompromised infants, and very minimal data in this population, infants with suspected or known immunocompromising conditions should not receive RotaTeq® (RV5) or Rotarix™ (RV1) without consultation with a physician specialist or expert in these conditions. The NACI also recommends that rotavirus vaccines should not be given to infants with a history of intussusception (76).

### 9.2.4 Australia

Rotavirus vaccines are recommended and funded from 1 July 2007 in Australia under the National Immunisation Program (NIP) for routine immunisation of infants in the first year of life. RV1 is administered as a two-dose course at two and four months of age, and RV5 in a three dose course at two, four and six months of age. Immunisation of older children and adults is not recommended. The intervals separating the doses should be no less than four weeks. The upper age limit for receipt of the first dose of RV1 is 14.9 weeks, and for receipt of the second dose is 24.9 weeks. The upper age limit for receipt of the first dose of RV5 is 12.9 weeks, and for the third dose is 32.9 weeks. Rotavirus vaccination is not recommended for infants who have known or suspected immunodeficiency. However, infants who are household contacts of immunocompromised patients are recommended to be vaccinated. Vaccination of premature infants according to chronological age is recommended if they are at least six weeks of age and are clinically stable (77).

## 9.3 Summary of international policy and practice

As of September 2011, rotavirus vaccine has been introduced into the national programmes of 28 countries, 16 using RV1, eight using RV5, and four using both. In all countries the schedule needs to be completed between by 26 to 32 weeks of age. In the US, RV vaccine is recommended at a minimum interval of four weeks between doses and a maximum age for the first dose of 14 weeks and six days and the last does by eight months. RV1 was introduced in the UK in July 2013. In Canada and Australia rotavirus vaccine is not recommended for infants who have known or suspected immunodeficiency, but is recommended to infant household contacts of those with immunodeficiency.

# References

1. Payne DC, Boom JA, Staat MA, Edwards KM, Szilagyi PG, Klein EJ, et al. Effectiveness of pentavalent and monovalent rotavirus vaccines in concurrent use among US children <5 years of age, 2009-2011. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2013;57(1):13-20.
2. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: A systematic review and meta-analysis. *The Lancet Infectious Diseases*. 2012;12(2):136-41.
3. Loebermann M, Winkelmann A, Hartung HP, Hengel H, Reisinger EC, Zettl UK. Vaccination against infection in patients with multiple sclerosis. *Nature Reviews Neurology*. 2012;8(3):143-51.
4. Clark HF, Offit PA, Parashar UD. Rotavirus vaccines In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines: Expert Consult*. 6th ed: Elsevier Saunders; 2013.
5. Dennehy PH. Effects of vaccine on rotavirus disease in the pediatric population. *Current Opinion in Pediatrics*. 2012;24(1):76-84.
6. Plosker GL. Pharmacoeconomic spotlight on rotavirus vaccine RIX4414 (Rotarix™) in the prevention of rotavirus gastroenteritis in developing countries. *Pediatric Drugs*. 2012;14(6):429-33.
7. Marlow RD, Finn A. The promise of immunisation against rotavirus. *Archives of Disease in Childhood*. 2012;97(8):736-40.
8. Eibl MM. The effect of routine rotavirus vaccination on healthcare utilization for diarrhea in US children. *Immunotherapy*. 2012;4(3):269-72.
9. Reid S. The further and future evolution of the New Zealand immunisation schedule. *New Zealand Medical Journal*. 2012;125(1354):86-99.
10. Milne R, Grimwood K. Should rotavirus vaccines be included in the national immunization program of a small developed country? *Expert Review of Pharmacoeconomics & Outcomes Research*. 2009;9(5):401-4.
11. Plosker GL. Rotavirus vaccine RIX4414 (Rotarix™): A pharmacoeconomic review of its use in the prevention of rotavirus gastroenteritis in developing countries. *PharmacoEconomics*. 2011;29(11):989-1009.
12. Graham D, Leversha A, Vogel A. The Top 10 Report; Top 10 issues affecting the health and wellbeing of children and young people in Auckland and Waikato. Waikato District Health Board,, 2011.
13. Grimwood K, Huang QS, Cohet C, Gosling IA, Hook SM, Teele DW, et al. Rotavirus hospitalisation in New Zealand children under 3 years of age. *Journal of paediatrics and child health*. 2006;42(4):196-203.
14. Chandrasesan C, Grimwood K, Redshaw N, Rich FJ, Wood C, Stanley J, et al. Geographical differences in the proportion of human group A rotavirus strains within New Zealand during one epidemic season. *Journal of medical virology*. 2010;82(5):897-902.
15. Soares-Weiser K, Maclehorse H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst Rev*. 2012;2:CD008521.
16. Kim JS, Bae CW, Lee KY, Park MS, Choi YY, Kim KN, et al. Immunogenicity, reactogenicity and safety of a human rotavirus vaccine (RIX4414) in Korean infants: A randomized, double-blind, placebo-controlled, phase IV study. *Human Vaccines and Immunotherapeutics*. 2012;8(6):806-12.
17. Kawamura N, Tokoeda Y, Oshima M, Okahata H, Tsutsumi H, Van Doorn LJ, et al. Efficacy, safety and immunogenicity of RIX4414 in Japanese infants during the first two years of life. *Vaccine*. 2011;29(37):6335-41.
18. Belongia EA, Irving SA, Shui IM, Kulldorff M, Lewis E, Yin R, et al. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *Pediatr Infect Dis J*. 2010;29(1):1-5.
19. Vesikari T, Itzler R, Karvonen A, Korhonen T, Van Damme P, Behre U, et al. RotaTeq, a pentavalent rotavirus vaccine: efficacy and safety among infants in Europe. *Vaccine*. 2009;28(2):345-51.
20. Zaman K, Yunus M, El Arifeen S, Azim T, Faruque AS, Huq E, et al. Methodology and lessons-learned from the efficacy clinical trial of the pentavalent rotavirus vaccine in Bangladesh. *Vaccine*. 2012;30 Suppl 1:A94-100.

21. Christie CDC, Duncan ND, Thame KA, Onorato MT, Smith HD, Malcolm LG, et al. Pentavalent rotavirus vaccine in developing countries: safety and health care resource utilization. *Pediatrics*. 2010;126(6):e1499-506.
22. Chang CC, Chang MH, Lin TY, Lee HC, Hsieh WS, Lee PI. Experience of pentavalent human-bovine reassortant rotavirus vaccine among healthy infants in Taiwan. *J Formos Med Assoc*. 2009;108(4):280-5.
23. Laserson KF, Nyakundi D, Feikin DR, Nyambane G, Cook E, Oyioko J, et al. Safety of the pentavalent rotavirus vaccine (PRV), RotaTeq((R)), in Kenya, including among HIV-infected and HIV-exposed infants. *Vaccine*. 2012;30 Suppl 1:A61-70.
24. Steele AD, Madhi SA, Louw CE, Bos P, Tumbo JM, Werner CM, et al. Safety, Reactogenicity, and Immunogenicity of Human Rotavirus Vaccine RIX4414 in Human Immunodeficiency Virus-positive Infants in South Africa. *Pediatr Infect Dis J*. 2011;30(2):125-30.
25. Omenaca F, Sarlangue J, Szenborn L, Nogueira M, Suryakiran PV, Smolenov IV, et al. Safety, reactogenicity and immunogenicity of the human rotavirus vaccine in preterm European Infants: a randomized phase IIIb study. *Pediatr Infect Dis J*. 2012;31(5):487-93.
26. Fang AYW, Tingay DG. Early observations in the use of oral rotavirus vaccination in infants with functional short gut syndrome. *Journal of Paediatrics and Child Health*. 2012;48(6):512-6.
27. Shui IM, Baggs J, Patel M, Parashar UD, Rett M, Belongia EA, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA : the journal of the American Medical Association*. 2012;307(6):598-604.
28. Noguchi A, Nakagomi T, Kimura S, Takahashi Y, Matsuno K, Koizumi H, et al. Incidence of Intussusception as Studied from a Hospital-Based Retrospective Survey over a 10-Year Period (2001-2010) in Akita Prefecture, Japan. *Japanese Journal of Infectious Diseases*. 2012;65(4):301-5.
29. Zickafoose JS, Benneyworth BD, Riebschleger MP, Espinosa CM, Davis MM. Hospitalizations for intussusception before and after the reintroduction of rotavirus vaccine in the United States. *Archives of Pediatrics and Adolescent Medicine*. 2012;166(4):350-5.
30. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *The New England journal of medicine*. 2011;364(24):2283-92.
31. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011;29(16):3061-6.
32. Desai R, Parashar UD, Lopman B, De Oliveira LH, Clark AD, Sanderson CFB, et al. Potential intussusception risk versus health benefits from rotavirus vaccination in Latin America. *Clinical Infectious Diseases*. 2012;54(10):1397-405.
33. O'Ryan ML, Hermosilla G, Osorio G. Rotavirus vaccines for the developing world. *Curr Opin Infect Dis*. 2009;22(5):483-9.
34. Dore DD, Turnbull BR, Seeger JD. Vaccine discontinuation and switching following regulatory interventions in response to rotavirus vaccine contamination with porcine circovirus DNA fragments. *Pharmacoepidemiology and Drug Safety*. 2012;21(4):415-9.
35. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. *J Infect Dis*. 2009;200 Suppl 1:S282-90.
36. Boom JA, Sahni LC, Payne DC, Gautam R, Lyde F, Mijatovic-Rustempasic S, et al. Symptomatic infection and detection of vaccine and vaccine-reassortant rotavirus strains in 5 children: a case series. *J Infect Dis*. 2012;206(8):1275-9.
37. Donato CM, Ch'Ng LS, Boniface KF, Crawford NW, Buttery JP, Lyon M, et al. Identification of strains of rotateq rotavirus vaccine in infants with gastroenteritis following routine vaccination. *J Infect Dis*. 2012;206(3):377-83.
38. Hemming M, Vesikari T. Vaccine-derived human-bovine double reassortant rotavirus in infants with acute gastroenteritis. *Pediatr Infect Dis J*. 2012;31(9):992-4.
39. Goldman RD. Effectiveness of rotavirus vaccine in preventing severe acute gastroenteritis in children. *Can Fam Physician*. 2012;58(3):270-1.

40. Taneja DK, Malik A. Burden of rotavirus in India—is rotavirus vaccine an answer to it? *Indian J Public Health.* 2012;56(1):17-21.
41. Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *The Lancet Infectious Diseases.* 2012;12(7):561-70.
42. Lopman BA, Pitzer VE, Sarkar R, Gladstone B, Patel M, Glasser J, et al. Understanding reduced rotavirus vaccine efficacy in low socio-economic settings. *PLoS ONE.* 2012;7(8).
43. Chen SC, Tan LB, Huang LM, Chen KT. Rotavirus infection and the current status of rotavirus vaccines. *J Formos Med Assoc.* 2012;111(4):183-93.
44. Steele AD, Neuzil KM, Cunliffe NA, Madhi SA, Bos P, Ngwira B, et al. Human rotavirus vaccine Rotarix™ provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. *BMC Infectious Diseases.* 2012;12.
45. Snelling TL, Schultz R, Graham J, Roseby R, Barnes GL, Andrews RM, et al. Rotavirus and the indigenous children of the Australian outback: monovalent vaccine effective in a high-burden setting. *Clinical Infectious Diseases.* 2009;49(3):428-31.
46. Snelling TL, Andrews RM, Kirkwood CD, Culvenor S, Carapetis JR. Case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4] infection in central Australia. *Clinical Infectious Diseases.* 2011;52(2):191-9.
47. Castilla J, Beristain X, Martinez-Artola V, Navascues A, Garcia Cenoz M, Alvarez N, et al. Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. *Vaccine.* 2012;30(3):539-43.
48. Braeckman T, Van Herck K, Meyer N, Pircon JY, Soriano-Gabarro M, Heylen E, et al. Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study. *Bmj.* 2012;345(7872):e4752.
49. Grant LR, Watt JP, Weatherholtz RC, Moulton LH, Reid R, Santosham M, et al. Efficacy of a pentavalent human-bovine reassortant rotavirus vaccine against rotavirus gastroenteritis among American Indian children. *Pediatr Infect Dis J.* 2012;31(2):184-8.
50. García-Puebla A, García-Fragoso L. Acute rotavirus gastroenteritis in children younger than 5 years of age after initiation of rotavirus immunization schedule. *Boletín de la Asociación Médica de Puerto Rico.* 2012;104(1):4-7.
51. Patel M, Pedreira C, De Oliveira LH, Umaña J, Tate J, Lopman B, et al. Duration of protection of pentavalent rotavirus vaccination in Nicaragua. *Pediatrics.* 2012;130(2):e365-e72.
52. Desai R, Haberling D, Holman RC, Singleton RJ, Cheek JE, Groom AV, et al. Impact of rotavirus vaccine on diarrhea-associated disease burden among American Indian and Alaska native children. *Pediatrics.* 2012;129(4):e907-e13.
53. Nolan SM, Prasad P, Fiks AG, Zaoutis T, TenHave TR, Coffin SE. Effect of rotavirus vaccine on reducing acute gastroenteritis in a large outpatient pediatric network. *Archives of Pediatrics and Adolescent Medicine.* 2012;166(3):232-9.
54. Cortese MM, Immergluck LC, Held M, Jain S, Chan T, Grizas AP, et al. Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics.* 2013;132(1):e25-33.
55. Boom JA, Tate JE, Sahni LC, Rench MA, Quaye O, Mijatovic-Rustempasic S, et al. Sustained protection from pentavalent rotavirus vaccination during the second year of life at a large, urban United States pediatric hospital. *Pediatr Infect Dis J.* 2010;29(12):1133-5.
56. Staat MA, Payne DC, Donauer S, Weinberg GA, Edwards KM, Szilagyi PG, et al. Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics.* 2011;128(2):e267-e75.
57. Cortese MM, Leblanc J, White KE, Jerris RC, Stinchfield P, Preston KL, et al. Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. *Pediatrics.* 2011;128(6):e1474-81.
58. Payne DC, Humiston S, Opel D, Kennedy A, Wikswo M, Downing K, et al. A multi-center, qualitative assessment of pediatrician and maternal perspectives on rotavirus vaccines and the detection of Porcine circovirus. *BMC pediatrics.* 2011;11:83.

59. Correia JB, Patel MM, Nakagomi O, Montenegro FMU, Germano EM, Correia NB, et al. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. *J Infect Dis.* 2010;201(3):363-9.
60. Justino MCA, Linhares AC, Lanzieri TM, Miranda Y, Mascarenhas JDP, Abreu E, et al. Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belém, Brazil. *Pediatr Infect Dis J.* 2011;30(5):396-401.
61. Yen C, Figueroa JR, Uribe ES, Carmen-Hernandez LD, Tate JE, Parashar UD, et al. Monovalent rotavirus vaccine provides protection against an emerging fully heterotypic G9P[4] rotavirus strain in Mexico. *J Infect Dis.* 2011;204(5):783-6.
62. Yen C, Armero Guardado JA, Alberto P, Rodriguez Araujo DS, Mena C, Cuellar E, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. *Pediatr Infect Dis J.* 2011;30(1 Suppl):S6-S10.
63. Tate JE, Mutuc JD, Panozzo CA, Payne DC, Cortese MM, Cortes JE, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J.* 2011;30(1 Suppl):S30-4.
64. Omenaca F, Sarlangue J, Szenborn L, Nogueira M, Suryakiran PV, Smolenov IV, et al. Safety, reactogenicity and immunogenicity of the human rotavirus vaccine in preterm European infants: A randomized phase IIIb study. *Pediatr Infect Dis J.* 2012;31(5):487-93.
65. Neu AM. Immunizations in children with chronic kidney disease. *Pediatr Nephrol.* 2012;27(8):1257-63.
66. Laszlo B, Konya J, Dandar E, Deak J, Farkas A, Gray J, et al. Surveillance of human rotaviruses in 2007-2011, Hungary: exploring the genetic relatedness between vaccine and field strains. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology.* 2012;55(2):140-6.
67. Centers for Disease Control and Prevention. Recommended immunization schedules for persons aged 0 through 18 years-United States, 2012. *Jama-J Am Med Assoc.* 2012;12(5):1341-6.
68. Pitzer VE, Atkins KE, de Blasio BF, van Effelterre T, Atchison CJ, Harris JP, et al. Direct and indirect effects of rotavirus vaccination: Comparing predictions from transmission dynamic models. *PLoS ONE.* 2012;7(8).
69. Dang DA, Nguyen VT, Vu DT, Nguyen TH, Nguyen DM, Yuhuan W, et al. A dose-escalation safety and immunogenicity study of a new live attenuated human rotavirus vaccine (Rotavin-M1) in Vietnamese children. *Vaccine.* 2012;30 Suppl 1:A114-21.
70. Weinberg GA, Payne DC, Teel EN, Mijatovic-Rustempasic S, Bowen MD, Wikswa M, et al. First reports of human rotavirus G8P[4] gastroenteritis in the United States. *Journal of clinical microbiology.* 2012;50(3):1118-21.
71. Craig E, Jackson C, Han D, NZCYES Steering Committee. *Monitoring the Health of New Zealand Children and Young People.* Auckland, New Zealand: 2007.
72. Patton JT. Rotavirus diversity and evolution in the post-vaccine world. *Discov.* 2012;13(68):85-97.
73. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMRW.* 2009;58 (RR02):1-25.
74. Hyde TB, Dentz H, Wang SA, Burchett HE, Mounier-Jack S, Mantel CF, et al. The impact of new vaccine introduction on immunization and health systems: a review of the published literature. *Vaccine.* 2012;30(45):6347-58.
75. Joint Committee on Vaccination and Immunisation (JCVI). *JCVI Statement on rotavirus vaccines.* 2009.
76. (NACI) NACol. *Updated statement on the use of Rotavirus Vaccines.* Canada: 2010 July 2010. Report No.
77. National Centre for Immunisation Research and Surveillance. *NCIRS factsheet, Rotavirus vaccines for Australian Children: Information for Immunisation Providers.* Sydney, Australia 2009.



uniservices



Te Whare Wānanga o Tāmaki Makaurau



UNIVERSITY OF AUCKLAND