Rotavirus Vaccination in New Zealand: NHC Assessment 2012

In 2014 the National Health Committee (NHC) received a request for a copy of the NHC’s assessment report on varicella (chicken pox) vaccination. This report was part of early assessment work the NHC undertook in both varicella and rotavirus vaccination in 2011/12, before responsibility for the management and purchasing of vaccines (including considering any changes to the National Immunisation Schedule) transferred from the Ministry of Health to New Zealand’s Pharmaceutical management Agency (PHARMAC). The NHC provided PHARMAC copies of the vaccine assessment reports and recommendations papers in 2013 and formal NHC recommendations on this work were never provided to the Minister of Health. Following the principal of open disclosure the Committee has decided to release the package of NHC vaccination assessments and recommendations on their website (www.nhc.health.govt.nz).

In mid-2012 the NHC executive became aware of a national collections coding change for gastroenteritis and other issues that affected a Ministry of Health contracted rotavirus economic evaluation which was an input into the NHC’s assessment. An analysis of the potential consequences by the NHC executive indicated that the changes wouldn’t significantly affect the overall findings of the NHC’s rotavirus assessment report or the recommendations made by the Committee. However, it should be noted that a fully corrected economic evaluation was never completed for updating figures in the attached NHC rotavirus assessment report.
Table of Contents

List of Tables ......................................................................................................................... 4

1. Summary .............................................................................................................................. 5

2. Policy Question .................................................................................................................... 6
   2.1. Who initiated or commissioned the report? .................................................................. 6
   2.2. Why is an assessment needed right now? ...................................................................... 6
   2.3. Which decision is it going to support? .......................................................................... 6
   2.4. Who represents the primary target audience for the report? ....................................... 6

3. Background .......................................................................................................................... 6
   3.1. Condition & target group .............................................................................................. 7
       3.1.1. Nature of the health problem or disease ................................................................. 7
       3.1.2. Epidemiology and burden of the disease ................................................................. 8
       3.1.3. Treatments for the disease & current practice ......................................................... 9
   3.2. Technology status .......................................................................................................... 9
       3.2.1. Requirements for its use ........................................................................................ 10
       3.2.2. Current technology status ..................................................................................... 10

4. Research Questions ............................................................................................................. 11
   4.1. Clinical safety & effectiveness ...................................................................................... 11
   4.2. Societal & ethical considerations ................................................................................... 11
   4.3. Value for money ........................................................................................................... 12
   4.4. Feasibility of adoption in the health system ................................................................. 12
       4.4.1. Policy congruence ................................................................................................ 12
       4.4.2. Organisational issues ............................................................................................ 12
       4.4.3. Legal considerations ............................................................................................. 12
       4.4.4. Budget impact .................................................................................................... 13

5. Methodology ....................................................................................................................... 14
   5.1. Narrative literature review ............................................................................................ 14
   5.2. Internet ........................................................................................................................ 15
   5.3. Ministry of Health knowledge systems ......................................................................... 15
   5.4. Summary of latest New Zealand evaluation report ...................................................... 15

6. Results & Discussion .......................................................................................................... 16
   6.1. Clinical safety & effectiveness ..................................................................................... 16
       6.1.2. Safety ................................................................................................................... 16
       6.1.3. Effectiveness ....................................................................................................... 18
       6.1.4. Outstanding uncertainty ....................................................................................... 20
   6.2. Societal & ethical.......................................................................................................... 21
6.2.1. Acceptability ........................................................................................................21
6.2.2. Equity & Ethics ......................................................................................................23
6.2.3. Psychological considerations .................................................................................24
6.3. Value for money .........................................................................................................24

6.3.1. What non-financial benefits are expected? .............................................................26
6.3.2. What is the cost-effectiveness of adding the rotavirus vaccine to the existing childhood immunisation schedule as three separate shots for infants aged between 6 and 32 weeks (Option 1), relative to a counterfactual scenario where the rotavirus vaccine is not available at all (Option 2)? .................................................................26

6.4. Feasibility of adoption in the health system ..............................................................30

6.4.1. Policy congruence ..................................................................................................30
6.4.2. Organisational issues .............................................................................................31
6.4.3. Legal issues ...........................................................................................................33
6.4.4. Budget impact .........................................................................................................33
6.4.5. Funding ..................................................................................................................36

7. Conclusion ....................................................................................................................37

8. Options ..........................................................................................................................38

Glossary of Terms ..............................................................................................................40

9. References .....................................................................................................................43

10. Appendix 1: Immunisation Programme ......................................................................51

11. Appendix 2: HTA repositories searched .....................................................................52

12. Appendix 3: Search strategies .....................................................................................55
List of Tables

Table 1 Summary of the different quality of life weights for rotavirus in the literature ...................................................... 8
Table 2: Registration status of NZ Rotavirus Vaccines ........................................................................................................... 10
Table 3: Costs included in the economic evaluation of universal rotavirus vaccination .......................................................................................................................... 24
Table 4: Estimated annual costs of delivering a universal rotavirus vaccination programme with 100% uptake ................................................................................................. 33
Table 5: Strengths and weakness of different options for publicly funding rotavirus vaccination in New Zealand ........................................................................................................... 38
1. Summary

Aim/Objective

The Immunisation Technical Forum has recommended that that a two dose rotavirus vaccine be added to the immunisation schedule. To support advice to the Minister in September 2012 on whether or not to add the vaccine to the Schedule in 2014, this report examines the evidence for and against its inclusion across the National Health Committee's five domains for assessment: Clinical, societal, ethical, economic and financial.

Method

The policy question, background and research questions have been developed according to best-practice methods for Health Technology Assessment (HTA). In order to answer the research questions in each domain a systematic search of the scientific literature published after 2009 and reports held by HTA agencies and repositories was undertaken. Abstracts were sifted through and categorised on the basis of their content into four domains and relevant papers were used to provide a narrative summary of the issues relevant to each domain. No formal critical appraisal of studies was undertaken. The use of Ministry of Health knowledge systems and targeted internet searches was also used to obtain context-specific information to address questions in the 'societal & ethical' and 'feasibility of adoption' domains.

Results & Discussion

Evidence suggests that both vaccines currently available for rotavirus are clinically safe and effective for most infants. Universal vaccination (3 doses) for rotavirus is not cost-saving from a societal or health payer's perspective and while decreasing the number of doses is likely to increase the cost-effectiveness of the vaccine, it is still unlikely to be cost-saving to the health payer, particularly once the costs of a surveillance system are included. However, there is some evidence that targeting vaccination to patients at high risk of nosocomial infection may be a cost-effective alternative to universal vaccination. The acceptability of the rotavirus vaccine to the New Zealand public is uncertain, but evidence from overseas suggests that the rotavirus vaccine is prioritised lower than all other childhood vaccines.

Conclusion

While there is evidence that rotavirus vaccination is clinically safe and effective in most circumstances, it is rarely deemed cost-effective. Furthermore, when the societal, ethical, and feasibility of adoption domains are considered, it becomes clear that universal vaccination of infants for rotavirus in New Zealand may not be the best use of public funding at present, and that there are higher priorities for funding in vaccination and child health more generally. There are a number of alternative options to 'universal vaccination', which may be preferable depending on the priorities of decision-makers.

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1 Note that to ease analysis and include the decision criteria, in the report these domains are covered under the headings of Clinical safety & effectiveness, Societal & ethical, Value for Money (ie 'Economic) and Feasibility of adoption within the system (includes financial).
2. Policy Question

The goal of this assessment is to answer the policy question: Should the Ministry of Health fund the universal vaccination of infants against rotavirus gastroenteritis? It follows a recommendation by the Immunisation Technical Forum (ITF) that a two dose rotavirus vaccine be added to the immunisation schedule. No preference for either the Merck Sharp & Dohme (MSD) or GlaxoSmithKline (GSK) vaccines was expressed by the ITF.

2.1. Who initiated or commissioned the report?

The Ministry of Health’s (‘the Ministry’) Immunisation team in the Sector Capability & Implementation business unit have commissioned the National Health Committee (‘the NHC’) to assess the addition of the rotavirus vaccine to the National Immunisation Schedule (‘the Schedule’) following a clinical recommendation by the ITF.

A brief overview of the Ministry of Health’s immunisation programme and the role of the ITF and the Immunisation team are provided in Appendix 1 (page 51).

2.2. Why is an assessment needed right now?

The Immunisation Technical Forum (ITF), appointed by the Director-General of Health, reviews the Schedule every three years and makes recommendations on the use of current vaccines and new vaccines (or new combinations of vaccines) to be added to the Schedule. The ITF bases its advice on technical evidence on effectiveness of new vaccines, epidemiology, availability of new types of vaccines and sector capability. Historically, a full assessment of a vaccine has not been undertaken, and the other domains (such as value for money, societal & ethical, and feasibility of adoption in the system) have only been considered on an ad-hoc basis.

A full assessment of the addition of rotavirus to the vaccine schedule is needed now because the:

1. Immunisation team needs to show it is taking account of value for money in vaccines prioritisation
2. NHC wants to signal its intent to work in the area of vaccines in the future.

2.3. Which decision is it going to support?

The assessment will support advice to the Minister on a budget bid in September 2012 on whether or not to add the rotavirus vaccine to the Schedule at its next revision in 2014.

2.4. Who represents the primary target audience for the report?

The primary audience for this report are political decision-makers. However, as a policy review of the management of vaccines in New Zealand is currently underway, it is unclear whether the review will affect the audience for the report or when the audience for the report will be known. Until this is clarified, the assessment will proceed on the basis that the audience comprises: the Immunisation team, National Health Committee Board, and the Minister of Health.

3. Background

This section of the report provides background information on Rotavirus and the population it affects. It includes a description of the nature of the disease, its burden in the population and
currently available treatments. Following the description of the condition and target group, this section of the report concludes by detailing the current status of the available rotavirus vaccines, and their requirements for use.

3.1. Condition & target group
Rotavirus gastroenteritis is a significant cause of infant diarrhoea worldwide, both in developed and developing countries. Virtually all children are infected by the age of five (Ministry of Health, 2011a). Further details on the mechanisms of disease, course and prognosis, and epidemiological burden are provided below. Current interventions for Rotavirus include preventative measures such as good hygiene, breastfeeding, vaccination, and treatment with oral rehydration therapy.

3.1.1. Nature of the health problem or disease

3.1.1.1. What are the mechanisms of disease?
There are seven major groups of rotavirus (A through G); human illness is caused primarily by group A and, to a much lesser extent, by groups B and C (Parashar & Glass, 2011). Two outer-capsid proteins, VP7 (G-protein) and VP4 (P-protein), determine serotype specificity, induce neutralizing antibodies, and form the basis for binary classification of rotaviruses (G and P types).

The virus is spread from person to person through the faecal-oral route (Ministry of Health, 2008).

3.1.1.2. What is the course and prognosis of the condition?
The clinical spectrum of rotavirus infection ranges from subclinical infection to severe gastroenteritis leading to life-threatening dehydration. After an incubation period of 1–3 days, the illness has an abrupt onset, with vomiting frequently preceding the onset of diarrhoea. Gastrointestinal symptoms generally resolve in 3–7 days. Illness caused by rotavirus is difficult to distinguish clinically from that caused by other enteric viruses. Because large quantities of virus are shed in faeces, the diagnosis can usually be confirmed by a wide variety of commercially available enzyme immunoassays (EIAs) or by techniques for detecting viral RNA (ribonucleic acid), such as gel electrophoresis, probe hybridization, or polymerase chain reaction (PCR) (Umesh D Parashar & Glass, 2011).

3.1.1.3. What are the consequences following infection?
Dehydration can be very severe and may require hospitalisation. If untreated, the virus can cause death but this is extremely rare in New Zealand (Ministry of Health, 2008). Studies overseas have shown that rotavirus-associated gastroenteritis adversely impacts the health-related quality of life of children and parents (Brisson, Senecal, Drolet, & Mansi, 2010).

3.1.1.4. What is the quality of life following infection?
The quality adjusted life year (QALY) is a summary measure of health gain that takes into account not only length of life but also quality of life. When QALYs are calculated, the number of life years over which an individual will experience a particular condition is combined with the quality of life during those years. Quality of life in the calculation of QALYs is measured on a 0 to 1 scale where 0 is equated to ‘being dead’ and 1 is ‘full/normal health’. Values between 0 and 1 are known as ‘health state utilities’. Essentially reflecting different degrees of impairment across different dimensions of health, these utilities can be interpreted as judgements of how ‘good’ or ‘bad’ different conditions are.
For example, in Table 1 Zomer et al (2008) note that infants with rotavirus who are treated at home by caregivers have a better quality of life (0.93) compared with infants with rotavirus requiring admission to hospital (0.61).

### Table 1 Summary of the different quality of life weights for rotavirus in the literature

<table>
<thead>
<tr>
<th>Quality of life with infection</th>
<th>Quality of life lost per day</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93</td>
<td>0.07</td>
<td>Rotavirus treated at home by caregivers</td>
<td>(Zomer et al., 2008)</td>
</tr>
<tr>
<td>0.61</td>
<td>0.39</td>
<td>Rotavirus requiring visit to general practice</td>
<td>(Zomer et al., 2008)</td>
</tr>
<tr>
<td>0.61</td>
<td>0.39</td>
<td>Rotavirus requiring visit to emergency department</td>
<td>(Zomer et al., 2008)</td>
</tr>
<tr>
<td>0.61</td>
<td>0.39</td>
<td>Rotavirus requiring admission to hospital</td>
<td>(Zomer et al., 2008)</td>
</tr>
</tbody>
</table>

Source: Rosevear & Urlich (2012a)

### 3.1.2. Epidemiology and burden of the disease

#### 3.1.2.1. How many people are affected?

In New Zealand, rotavirus is not currently a notifiable disease so there are no national surveillance data available. However, it has been estimated that approximately 90% of New Zealand children will contract the virus by 3 years of age and that rotavirus is responsible for 25-50% of gastroenteritis in New Zealand (Ministry of Health, 2008).

Of the 2500 children less than 3 years of age hospitalised each year in New Zealand with acute gastroenteritis, approximately 43% of cases are rotavirus-related. Data collected prospectively on children admitted to eight hospitals in New Zealand from 1 May 1998 to 30 April 2000 provided the basis for an estimate of the national hospitalisation rate for rotavirus diarrhoea in children aged less than three years, standardised for age and season, of 634 per 100,000 (95% CI: 597–672) (Grimwood K et al., 2006).

#### 3.1.2.2. Who is affected?

Worldwide, nearly all children are infected with rotavirus by 3–5 years of age. Neonatal infections are common but are often asymptomatic or mild, presumably because of protection from maternal antibody or breast-feeding. First infections after 3 months of age are likely to be symptomatic, and the incidence of disease peaks among children 4–23 months of age. Reinfections are common, but the severity of disease decreases with each repeat infection. Therefore, severe rotavirus infections are relatively uncommon among older children and adults. Nevertheless, rotavirus can cause illness in parents and caretakers of children with rotavirus diarrhoea, immunocompromised persons, travellers, and elderly individuals and should be considered in the differential diagnosis of gastroenteritis among adults.

In New Zealand rotavirus infection is more prevalent in the winter and spring months, primarily among children aged 12 to 35 months (Grimwood K et al., 2006).

Rotavirus does not appear to be a major opportunistic pathogen in children with HIV infection. In severely immunodeficient children, rotavirus can cause protracted diarrhoea.
with prolonged viral excretion and, in rare instances, can disseminate systemically. Persons who are immunosuppressed for bone marrow transplantation are also at risk for severe or even fatal rotavirus disease (Umesh D Parashar & Glass, 2011).

3.1.3. Treatments for the disease & current practice
Rotavirus gastroenteritis can lead to severe dehydration. Standard oral rehydration therapy is successful in most children who can take oral fluids, but IV fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting (Umesh D Parashar & Glass, 2011). Despite a greater likelihood of dehydration, children with rotavirus diarrhoea on average spend less time (1-2 days) in hospital than those with other enteric infections (Grimwood K et al., 2006).

Rotavirus cannot be diagnosed solely on clinical presentation; stool antigen testing is required and the preferred oral rehydration solution in New Zealand is Pedialyte (Ministry of Health, 2011a).

The therapeutic role of probiotics, bismuth subsalicylate, enkephalinase inhibitors, and nitazoxanide has been evaluated in clinical studies but is not clearly defined. Antibiotics and antimitotility agents should be avoided. In immunocompromised children with chronic symptomatic rotavirus disease, orally administered immunoglobulins or colostrum may result in the resolution of symptoms, but the best choices regarding agents and their doses have not been well studied, and treatment decisions are often empirical (Umesh D Parashar & Glass, 2011).

Good hygiene (handwashing) and cleanliness are important for preventing the spread of rotavirus but they are not enough to control the spread of the disease (CDC, 2010). The Centers for Disease Control and Prevention (CDC) note that rotavirus vaccines are effective in preventing rotavirus gastroenteritis (inflammation of the stomach and intestines) and the accompanying diarrhoea and other symptoms. Breastfeeding has also been shown to be a protective factor against rotavirus gastroenteritis (Andreas et al., 2009; Gimenez-Sanchez, Delgado-Rubio, Martinon-Torres, Bernaola-Iturbe, & Rotascore Research, 2010; Keith Grimwood & Forbes, 2009; Plenge-Bonig et al., 2010).

3.2. Technology status
Efforts to develop rotavirus vaccines were pursued because it was apparent—that given the similar rates in less-developed and industrialized nations—that improvements in hygiene and sanitation were unlikely to reduce disease incidence (Umesh D Parashar & Glass, 2011). In 2006, two live oral attenuated rotavirus vaccines—RotaTeq® (a pentavalent vaccine, RV5) and Rotarix®—demonstrated efficacy of 85–98% against severe disease in trials conducted primarily in middle- and high-income nations (Barlam & Kasper, 2009; Gimenez-Sanchez, Delgado-Rubio, Martinon-Torres, Bernaola-Iturbe, & Rotascore Research, 2010; Keith Grimwood & Forbes, 2009; Plenge-Bonig et al., 2010).

RotaTeq® contains five bovine-human reassortants representing the common viral protein types, G1, G2, G3, G4 and P(8). The vaccine is administered as a three-dose oral course at the same time as the routine Schedule. Each 2 mL dose contains at least 20.0 x 10^6 infectious units (IU) per dose, depending on serotype. RotaTeq® vaccine virus is only shed in the stool after the first dose (in up to 13 percent of recipients) (Ministry of Health, 2011a).

Rotarix® is a monovalent G1 rotavirus vaccine derived from a human G1 strain. The vaccine is given in two oral doses at the same time as the routine Schedule. Each 1.5mL dose contains at least 10^6 median cell culture infective dose after reconstitution. Vaccine virus is detectable in the stool a week after vaccination in up to 80 percent of first-dose, and up to 30 percent of second-dose recipients.
3.2.1. Requirements for its use

Vaccines are prescription medicines, so they can only be administrated by medical practitioners, registered midwives, designated prescribers (including registered nurses), and people authorised to administer the medicine in accordance with a standing order. The use of the rotavirus vaccine may also require the education of personnel in health centres, monitoring of adverse events, and post-marketing monitoring of intussusception (a problem with the intestine where one portion of the bowel slides into the next) and Kawasaki disease (an autoimmune disease in which the medium-sized blood vessels throughout the body become inflamed) (Zomer et al., 2008).

Rotarix is recommended to be stored at 2°C-8°C for optimal immunogenicity, but it has shown similar immunogenicity when stored at 37°C for 7 days (Kerdpanich et al., 2011). No evidence was retrieved suggesting that RotaTeq had similar efficacy at warmer temperatures.

3.2.2. Current technology status

The United States, Australia, and parts of Europe (including Austria, Belgium & Finland) (World Health Organization, 2011), have all adopted recommendations to routinely immunize children for rotavirus. However in England it is currently felt that the public health risks posed by rotavirus do not warrant routine vaccination\(^2\) and in Canada decisions around public funding are awaiting the results of cost-effectiveness analyses\(^3\).

In New Zealand, as noted in the Immunisation Handbook 2011 (Ministry of Health, 2011a, p. 326), the rotavirus vaccine is recommended, but not currently publicly funded, for all infants (the first dose must be received by age 15 weeks) and especially infants who will be regularly attending early childhood services or where there is an immune-compromised individual living in the household (Ministry of Health, 2011a). Both Rotarix® (manufactured by GlaxoSmithKlein) and RotaTeq® (manufactured by Merck Sharp & Dohme Corp) vaccines are currently available in New Zealand (Table 2).

**Table 2: Registration status of NZ Rotavirus Vaccines**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Registration situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix Oral Vaccine Oral suspension, 1000000CCID50 (Prescription)</td>
<td>Consent given, and approved: 26/03/2009</td>
</tr>
<tr>
<td>Rotarix Powder with diluent for oral suspension, 1000000CCID50 (Prescription)</td>
<td>Not marketed, but approved: 11/04/2008</td>
</tr>
<tr>
<td>RotaTeq Oral suspension, 2mL (Prescription)</td>
<td>Consent given, and approved: 22/03/2007</td>
</tr>
</tbody>
</table>

Source: Medsafe (http://www.medsafe.govt.nz/regulatory/ <date accessed: 28/02/12>)

Rotarix® is approved for use in infants in the first six months of life and should not be administered to children older than 24 weeks of age. It is administered in two oral doses at the same time as the routine schedule (6 weeks and 3 months). In contrast, RotaTeq is approved for use for infants aged 6-32 weeks of age. The first dose of the RotaTeq vaccine should be administered by 12 weeks of age, and the vaccination course should be completed by 32 weeks of age.

The main supplier of the rotavirus vaccine in New Zealand is GlaxoSmithKline (Rotarix; 2-dose, oral rotavirus vaccine). A second vaccine (RotaTeq; 3 dose, oral rotavirus vaccine) produced by Merck Sharp and Dohme is registered but not available for private purchase in New Zealand. The RotaTeq brand of vaccine was only available in New Zealand in a small quantity (21 doses) during an error in the manufacturing process that affected both the

\(^2\) http://www.nhs.uk/Conditions/Rotavirus-gastroenteritis/Pages/Prevention.aspx

RotaTeq and Rotarix vaccines. The number of children being vaccinated with Rotarix has increased by 140% since 2010, from 610 children to 1,461 children. The increase in uptake over the last 18 months has been attributed to a patient access programme, medical education, advertising, consumer support material such as brochures and a website. Previously this vaccine was not promoted.

The wholesale price for Rotarix is $80 per dose for a 2-dose course (excluding GST), while RotaTeq is $55 per dose for a 3-dose course. Rotarix is currently available to New Zealand parents through a patient access programme that reduces the cost of the vaccine to $50 per dose. Prior to the introduction of this patient access programme, it was estimated that the price paid by consumers ranged from $170–$180 per dose due to significant practice charges being added to the cost of vaccination.

Based on the 2011 sales and using the 2011 birth cohort of 61,400, approximately 2.4% of infants were vaccinated against rotavirus in 2011. Since the patient access programme was launched in February, this has increased to 6.2% of the monthly birth cohort babies (April 2012)\(^4\).

4. **Research Questions**

The research question/s outlined below have been formulated with reference to the policy question and in terms of the domains for assessment\(^5\). Various assessment frameworks specific to vaccines have been developed and the questions under each of the domains below have been formulated with reference to a selection of these (Boot, de Melker, Stolk, de Wit, \& Kimman, 2006) in addition to those detailed in the Busse et al's (2002) paper detailing 'best practice' for undertaking Health Technology Assessments (HTAs).

4.1. **Clinical safety & effectiveness**

What is the clinical safety and efficacy of vaccines for rotavirus in infants?

What is the mortality and morbidity directly related to the use of the vaccine?

What is the morbidity/disability directly related to the use of the vaccine?

What is the overall change in condition-specific mortality?

What is the overall change in morbidity/disability/disease-free interval?

What is the change in quality-/disability-adjusted-life-years (QALYs/DALYs)?

4.2. **Societal & ethical considerations**

What proportion of the target population will accept the vaccine, or has already been vaccinated? (Acceptability)

Will reduced pathogen transmission lead to enhanced vulnerability of specific sub-populations? (Ethics)

Are the benefits of vaccination, or costs of not vaccinating, experienced disproportionately by different groups and if so, which ones? (Equity)

Are there any psychological issues associated with rotavirus or the vaccine?

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\(^{5}\) The HTA Core Model Handbook by EUnetHTA provides good definitions of each of the domains (EUnetHTA, 2011)
4.3. Value for money
In this domain of the Health Technology Assessment the cost-effectiveness and value for money from adding the vaccine to the New Zealand immunisation schedule is addressed. It looks at what are the costs and changes in cost compared to current practice using the appropriate form of economic evaluation (cost-effectiveness\(^6\), cost-utility, cost-benefit, cost minimisation etc).

The objective of this domain is to determine whether the recommendation of the Immunisation Technical Forum (ITF), for the addition of rotavirus vaccination to the immunisation schedule, is cost-effective from both a health payer’s and societal perspective. The specific question to be addressed is thus:

What is the cost-effectiveness of adding the rotavirus vaccine to the existing childhood immunisation schedule (Option 1), relative to a counterfactual scenario where the rotavirus vaccine is not available at all (Option 2)? The costs of vaccination and illness should be considered from a health payer’s perspective and a societal perspective.

Other questions for consideration are:

- How does reducing the number of doses affect the cost-effectiveness of the vaccine?
- Would the vaccine be more cost-effective if it were targeted to different population groups? If so, which groups?
- Do caregivers associate their children getting rotavirus with a significant loss of income?
- Do employers believe the productivity of their business is significantly affected by caregivers taking sick days to care for children with rotavirus?

4.4. Feasibility of adoption in the health system
What additional health sector factors would need to be addressed to ensure successful implementation of the proposed vaccination programme in New Zealand?

4.4.1. Policy congruence
How does the addition of this vaccine fit with other policy and practices in immunisation and the wider health sector?

4.4.2. Organisational issues
How would the addition of the vaccine fit with the existing Immunisation Schedule?

How would universal vaccination affect the use of other health services (ie, GP visits, hospitalisations, pharmaceutical consumption etc)?

What are the health workforce implications of introducing universal vaccination for rotavirus?

4.4.3. Legal considerations
Are there any legal considerations around continuing not to vaccinate, or around the decision to vaccinate?

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\(^6\) For a quick explanation of what cost-effectiveness is and how the analysis is done, check out the briefing by Phillips (2009).
4.4.4. **Budget impact**

What impact would the introduction of universal vaccination have on the available budget for vaccines and the total budget of Vote: Health?

Is the universal public funding of rotavirus vaccination affordable and sustainable?

How difficult would it be to disinvest in this vaccination programme in the future?
5. Methodology

The latest review of the clinical safety & effectiveness, and cost-effectiveness, of introducing rotavirus immunisation in New Zealand were published in 2011 (Ministry of Health) and 2009 (R. J. Milne & K. Grimwood, 2009), respectively. The review of the vaccine’s clinical safety & effectiveness was undertaken by the Immunisation Technical Forum (ITF) and published in the Ministry of Health’s Immunisation Handbook 2011. No formal systematic review or critical appraisal of the clinical evidence was undertaken as part of this review. The cost-effectiveness of introducing the vaccine was determined through a cost-utility analysis based on three doses delivered at 6 weeks, 3 months and 5 months of age alongside the vaccines for DTaP-IPV-HepB/Hib and PCV10 (R. J. Milne & K. Grimwood, 2009).

In order to compare the cost-effectiveness of rotavirus vaccination with varicella vaccination and to take into account not only clinical and economic factors, but also social, ethical and financial, an updated and broader assessment of rotavirus vaccination was required. This assessment achieves this in a number of ways: Firstly, through reviewing the literature from 2009 onwards; secondly, targeted searches of the internet, thirdly, use of the Ministry of Health’s existing knowledge systems (national collections and Health Report database), and finally, through summarising the findings of a recent evaluation report commissioned by the Ministry of Health’s immunisation team.

5.1. Narrative literature review

On the 26 September 2011 the Ministry of Health reference librarians searched the sites of key Health Technology Assessment (HTA) agencies and repositories using the following search terms: Rotavirus. A full list of the repositories and agencies searched is attached in Appendix 2. No time or language constraints were used. Three publications were retrieved from this search, the first was a cost-effectiveness analysis of rotavirus vaccination of Belgian infants published by the Belgian Health Care Knowledge Centre in 2007, the second was the Economics of Childhood Immunizations in Canada: Data Book published in 2007 by the Institute of Health Economics Canada, and the third was a cost-effectiveness analysis of childhood vaccination against rotavirus in Norway published in 2009 by Norwegian Knowledge Centre for the Health Services.

Following this initial search of HTA agencies and repositories, Ovid MEDLINE® and Cochrane Library were searched for scientific journal papers published between 1 January 2009 and 28 October 2011. The search terms used were: cost-effectiveness, cost-benefit, cost-utility, economic evaluation, economic model, decision analysis, rotavirus vaccination. Results were limited to either systematic reviews OR studies based in the United States, Europe, Canada, Australia, or New Zealand. No language limits were applied. A subsequent search of EMBASE for papers published between 1 January 2009 and 11 November 2011, using the same inclusion and exclusion criteria was also undertaken. The reference lists of identified publications were not searched. The full search strategy is provided in Appendix 3.

In addition to papers identified in this search, three papers included in the Ministry of Health’s tender for the economic evaluation were also retrieved (K. Grimwood, Lambert, & Milne, 2010; R. Milne & K. Grimwood, 2009; R. J. Milne & K. Grimwood, 2009; Zomer et al., 2008).

Abstracts were sifted through and categorised, on the basis of their content, into one of four domains: Economic, Clinical, Social & Ethical, and Feasibility of adoption within the system. Most abstracts were included (regardless of position on evidence hierarchy) but only the full text of relevant studies where further detail was required were retrieved. Studies focussing on developing countries were excluded. No formal critical appraisal of studies was
undertaken. Abstracts and full papers retrieved were used to create a narrative summary of the issues relevant to each domain and answer the specific research questions.

5.2. Internet

If, after producing the narrative summaries for each domain the key research questions had not been addressed, further targeted searches using Google and Google scholar were undertaken. This strategy was used primarily to identify context-specific information required to answer questions in the ‘societal and ethical’ and ‘feasibility of adoption within the system’ domains and included New Zealand-specific information on immunisation coverage, as well as an investigation of other vaccines on the horizon.

5.3. Ministry of Health knowledge systems

The Ministry of Health’s filing cabinets were used to obtain contextual information, particularly around the amount of money spent on promoting new vaccines. Data collected by Medsafe on adverse reactions to the rotavirus vaccines currently available in New Zealand was also reviewed.

5.4. Summary of latest New Zealand evaluation report

In 2009 Milne & Grimwood published a study investigating the budget impact and cost-effectiveness of including a rotavirus vaccine in the New Zealand childhood immunization schedule (Milne R & Grimwood K, 2009). The incremental cost was $2.99 million and the break-even price per vaccine dose was $32.39 at 2006 prices. Their results indicate that from a health payer’s perspective rotavirus vaccination would result in a cost of $67,007 per QALY gained, while from a societal perspective it would be $46,092 per QALY gained.

In June 2011 the Ministry of Health put out a request for tender (RFT) for an updated economic assessment of the introduction of the rotavirus vaccine into the national immunisation schedule according to the details provided in the Immunisation Handbook (Ministry of Health, 2011a). A literature search regarding the diseases and vaccines and an appraisal of the evidence was not expected of the contractor. Estimates of vaccine effectiveness were based on the Immunisation Technical Forum’s assessment of the literature, and were to be taken from the Immunisation Handbook 2011. The cost-effectiveness of the programme was to be determined via a cost-utility analysis consistent with PHARMAC’s analytical guidelines. A member of the NHC executive and PHARMAC were part of the steering panel for the contract. The results from the analysis were provided to the Ministry of Health as a report on 20 January 2012 (Rosevear & Urlich, 2012a). The report was critically appraised using the checklist for economic evaluations constructed by Drummond et al (2005), and the results of the evaluation and findings from the critical appraisal are presented in section 6.3 alongside those of other cost effectiveness analyses identified in the initial literature search described in section 5.1. The report by Rosevear and Urlich is used to provide contextualised answers to the research questions posed in the ‘value for money’ domain.

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7 Ministry of Health, PHARMAC, and direct caregiver costs including hospitalisations, ED visits, GP visits, and the standard subsidy for oral rehydration therapy.
6. Results & Discussion
The results from each of the processes described above are presented below under the headings of clinical safety & effectiveness, societal & ethical, value for money, and feasibility of adoption within the system. A summary of the key findings under each of these domains is provided at the beginning of the section and is followed by a more detailed discussion of the evidence.

6.1. Clinical safety & effectiveness
Internationally, it is evident that countries that have introduced universal rotavirus vaccination have seen declines in the number of cases and hospitalisations associated with the disease and that there may be indirect benefits for the unvaccinated population through herd immunity. While there were initial concerns around the clinical safety of early rotavirus vaccines related to the heightened risk of intussusception (Rotashield), large phase III pre-licensure clinical trials of Rotarix and RotaTeq vaccines have not detected an increased risk (though postmarketing surveillance indicates the possibility of an increased risk shortly after the first dose in some populations). The most common adverse effects from vaccination are fever and vomiting. While there is evidence supporting the co-administration of both Rotarix and RotaTeq vaccines alongside DTaP-IPV-HepB/Hib, only evidence supporting the co-administration of Rotarix alongside PCV10 was retrieved. Following the introduction of routine rotavirus vaccination, the United States, Australia and parts of Europe have all observed changes in the predominant strains of rotavirus circulating in the population, and in some instances, away from the strains targeted by the vaccine.

6.1.1. What is the clinical safety and efficacy of vaccines for rotavirus in infants aged 6 to 32 weeks?
To ensure that the evidence around the safety and efficacy of the vaccines available has not changed since the Immunisation Technical Forum (ITF) recommendation, a narrative review of the literature from 2009 onwards investigating the experience with the vaccine to date was undertaken. This section highlights the main issues arising from this review.

An initial systematic review conducted in 2004 concluded that while rotavirus vaccines could prevent diarrhoea caused by rotavirus, the safety of the available vaccines and their impact on mortality remained unclear. They also noted that the benefits of the vaccine were different depending on the type of vaccine and the reviewers were unable to make conclusive recommendations regarding the use of rotavirus vaccines (Soares-Weiser, Goldberg, Tamimi, Leibovici, & Pitan, 2004). However, the authors updated this review in 2010, focussing on Rotarix, RotaTeq and Lanzhou Lamb Rotavirus (LLR) brands. None of the identified trials used LLR or compared rotavirus vaccines, but Rotarix and RotaTeq were shown to be effective vaccines for the prevention of rotavirus diarrhoea, and the authors concluded that the balance between benefit and harm favoured benefit; advising that ongoing safety monitoring should be continued and that a trial comparing LLR with placebo should be conducted (Soares-Weiser et al., 2010).

6.1.2. Safety
While there are instances of morbidity directly related to the use of both brands of rotavirus vaccine, vaccine trials have not measured the effect of vaccines on diarrhoea mortality (Fischer Walker & Black, 2011). Experience internationally suggests the following adverse reactions are possible:

- Intussusception 3-14 days after the first dose of the vaccine in children as young as 49 days (Chen, Heyse, Heaton, & Kuter, 2010). The risk of intussusception was also observed in the roll-out of vaccination in Latin America (Butler, 2011). However, other large pre- and postmarketing studies have shown no increased risk of intussusception
with the current rotavirus vaccines (Bortolussi et al., 2010) and WHO and national regulators who reviewed the data say that the benefits far outweigh the slightly elevated intussusception risk of 1-2 in 100,000 vaccinated children (Butler, 2011).

- A review of RotaTeq clinical trial data revealed higher, though not statistically significantly, Kawasaki disease (KD) rates among RotaTeq vaccines than placebo recipients, however subsequent reviews do not suggest an elevated risk but continue to recommend postmarketing monitoring of KD (Hua et al., 2009; Oberle, Ponisch, Weier, Keller-Stanislawski, & Mentzer, 2010).

- A Rotarix trial conducted in Latin America showed an increased risk of seizures, but no similar association was evident in the European trial (Ministry of Health, 2011a).

- Fever and vomiting (Hale & Brown, 2009; Reyna-Figueroa et al., 2010).

The New Zealand adverse reactions database contains few events reported to be associated with rotavirus vaccination; as with any vaccine there are a number of reports of vaccine failure8.

The rotavirus vaccine is contraindicated for:

- infants with acute moderate or severe gastroenteritis until the condition improves
- infants with a history of a severe allergic reaction after a previous dose or to a vaccine component
- children with a history of an uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant to intussusceptions (eg, a Meckel’s diverticulum)
- children with severe combined immune-deficiency syndrome (SCID) (Ministry of Health, 2011a)

Studies addressing the safety, reactogenicity, and immunogenicity of rotavirus vaccines in an HIV-infected population are urgently needed (Steele et al., 2009).

For infants with a severe latex allergy, or those at risk of such an allergy (eg, with spina bifida or bladder extrophy) RotaTeq over Rotarix is preferred as latex is present in the Rotarix oral applicator but not in the RotaTeq oral applicator (Ministry of Health, 2011a). It is recommended that the same brand of vaccine be used for the entire course (Department of Health and Ageing, 2011).

There is an upper age limit for the administration of rotavirus vaccine so it is very important to give each dose on time, as late (“catch-up”) doses cannot be given. The safety of the vaccine has not been tested in older babies or children (Department of Health and Ageing, 2011; Umesh D. Parashar & Glass, 2009).

Co-administration

No information was provided in the New Zealand immunisation handbook around which other vaccines the rotavirus vaccines could be administered alongside. The handbook notes that “Rotavirus vaccine is recommended by the WHO but is not yet on the Schedule” (Ministry of Health, 2011a). However, a search of studies from 2009 onwards found some evidence suggesting that both RotaTeq and Rotarix can be co-administered with most routine childhood vaccines, including diphtheria, tetanus, pertussis, hepatitis B-Haemophilus influenza type b-vaccines (Ciarlet et al., 2009; Timo Vesikari et al., 2011). However, supportive evidence for the co-administration with pneumococcal conjugate (PCV10) vaccine could only be found for Rotarix (T. Vesikari et al., 2011).

Recent findings from a randomised controlled trial also support the coadministration of RotaTeq and Rotarix vaccines with meningococcal serogroup C conjugate vaccine to healthy

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8 Pers comm. – Manager, Clinical Risk Assessment at Medsafe (Email dated: 1 February 2012).
infants without impairing the protective immune response to MenC (Timo Vesikari et al., 2011; T. Vesikari et al., 2011).

Parashar & Glass (2009) have suggested that the concurrent administration of oral polio vaccine could affect the processing of vaccine in the infant gut and impair infant’s ability to generate an effective immune response. In response to this the Canadian National Advisory Committee on Immunisation has recommended that OPV should be given at least 2 weeks apart from Rotarix™.

6.1.3. Effectiveness

As noted previously, the United States, Australia, and parts of Europe (including Austria, Belgium & Finland) (World Health Organization, 2011), have all adopted recommendations to routinely immunize children for rotavirus. A systematic review of all publicly available data from vaccine-effectiveness and vaccination-impact studies in the USA, Europe and Australia between 2006 and February 2010 has demonstrated significant reductions in the burden of disease on healthcare services, and provides evidence for the effect of herd immunity (Giaquinto et al., 2011).

Most specialist groups do not formerly express a preference for a particular brand of vaccine (American Academy of Pediatrics, 2009) and while RotaTeq and Rotarix differ in virological characteristics, clinical trials indicate similar efficacy and safety (Hale & Brown, 2009). Each vaccine is more than 70% effective in preventing any severity of rotavirus gastroenteritis and more than 98% effective in preventing severe disease through one full season of rotavirus exposure post vaccination. Efficacy begins to wane during the second season of rotavirus exposure (Hale & Brown, 2009).

6.1.3.1. United States

Routine vaccination of infants with pentavalent rotavirus vaccine (RV5) (RotaTeq) began in 2006 (Cortes et al., 2011). By December 31, 2008, at least one dose of RotaTeq had been administered in 73% of children under 1 year of age, 64% of children 1 year of age, and 8% of children 2 to 4 years of age. Following vaccination the rotavirus burden in 2007-2008 was markedly reduced in all US regions (Cortese, Tate, Simonsen, Edelman, & Parashar, 2010; Curns et al., 2010). Rates of hospitalisation for diarrhea decreased by 33% between 2001-2006 and 2007-2008 and by 25% in 2008-2009. Rates of hospitalisation specifically coded for rotavirus infection declined by 75% between 2001-2006 and 2007-2008 and 60% in 2008-2009. Nationally, for the 2007-2009 period, there was an estimated reduction of 64, 855 hospitalisations, saving approximately $278 million in treatment costs (Cortes et al., 2011). Other studies have also suggested a herd-immunity effect (Begue & Perrin, 2010; Clark, Lawley, Mallette, DiNubile, & Hodinka, 2009; Eberly, Gorman, Eide, Olsen, & Rajnik, 2011; Jacqueline E. Tate et al., 2011) and substantial reductions in the costs of hospitalisation (Chang et al., 2010).

Another study in the United States has estimated that the completion of the three doses of RotaTeq conferred 100% protection against severe rotavirus disease requiring hospitalization and 96% protection against disease requiring intravenous hydration (Boom, Tate, Sahni, Rench, Hull et al., 2010). Vaccine effectiveness of 1 and 2 doses against hospitalisation and emergency department visits was 69% and 81%, respectively, suggesting that even partial immunization also conferred substantial protection (Boom, Tate, Sahni, Rench, Hull et al., 2010). These results were sustained for the first 2 years of the programme; for children 6 to 11 months of age, 3-dose effectiveness was 92% to 93%, whereas it was 78% to 84% among children 12 months or older (Boom, Tate, Sahni, Rench, Hull et al., 2010).

10 This particular systematic review focussed on RotaTeq but there is similar evidence for Rotarix.
Quaye et al., 2010). Wang et al (2010) has also shown that RotaTeq demonstrated effectiveness against rotavirus gastroenteritis, when the 3-dose regimen was incomplete.

6.1.3.2. Australia

Since July 2007, Australia has publicly funded rotavirus vaccine for all children born on or after 1 May 2007 (Department of Health and Ageing, 2011). Doses of vaccine are given at 2 and 4 months of age, or 2, 4 and 6 months of age, depending on the brand of vaccine (individual states and territories chose different brands as a result of different purchasing arrangements (Jim P. Buttery et al., 2011)). By 2009 approximately 87% of infants received at least one dose (Belshaw, Muscatello, Ferson, & Nurkic, 2009; Jim P. Buttery et al., 2011). Hospital admissions for both rotavirus gastroenteritis and non-rotavirus-coded gastroenteritis were reduced following vaccine introduction in all states (Jim P. Buttery et al., 2011), not only for the age group eligible for public funding, but also those born prior, indicating herd immunity (Jim P. Buttery et al., 2011; Clarke, Davidson, Gold, & Marshall, 2011; Macartney et al., 2011; J. E. Tate et al., 2010). A substantial decline has also been seen in nosocomial rotavirus gastroenteritis between 2007 and 2009, suggesting a reduction in virus transmission in the hospital setting (Macartney et al., 2011).

However, a case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine (Rotarix) during an outbreak of rotavirus G2P[4] infection in central Australia found that there was no overall protective effect against hospitalisation, raising concerns over the durability of vaccine protection against heterotypic strains (T. L. Snelling, Andrews, Kirkwood, Culvenor, & Carapetis, 2011). However, Rotarix exhibited efficacy of 84.5% against confirmed cases of rotavirus infection in a widespread outbreak of G9 strain (Thomas L. Snelling et al., 2009).

Post-marketing surveillance for intussusception following vaccination through both hospital-based case ascertainment and monthly reports from paediatricians has thus far shown no overall increase in intussusception in Australia following receipt of rotavirus vaccine. However, there was some evidence of an elevated risk following the first dose of both vaccines. Larger population-based studies using linked databases are required to provide more definitive evidence (J. P. Buttery et al., 2011). Annual adverse events surveillance reporting for immunisations in 2008 showed reports for infant immunisation increased, and were mainly related to gastrointestinal system events temporally associated with receipt of rotavirus vaccine in the first full year of the rotavirus immunisation program (Menzies et al., 2009).

6.1.3.3. Europe

Austria, Belgium, and Ireland have all implemented routine vaccination of infants for rotavirus. A study investigating at the efficacy and safety of RotaTeq among infants in Europe found that it was 98.3% and 68.0% efficacious against severe rotavirus gastroenteritis and all rotavirus gastroenteritis due to any serotype for two rotavirus seasons post-vaccination. It also found that there were no statistically significant differences between RotaTeq and placebo for any of the safety outcomes (Vesikari et al., 2009).

Austria was the first country in Europe to implement a universal mass vaccination program against rotavirus gastroenteritis for all infants nationwide (Paulke-Korinek et al., 2011). Since July 2007, rotavirus vaccinations have been subsidised for all children from the seventh week up to the sixth month of life. The coverage for the whole period was about 72%, increasing to 87% in 2008, and the field effectiveness of the vaccine was estimated between 61% and 98%, depending on assumptions about the vaccination status (Paulke-Korinek, Rendi-Wagner, Kundi, Kronik, & Kollaritsch, 2010). In 2009, decreasing hospitalisation rates from rotavirus gastroenteritis were observed in children of all age groups, even in those not eligible for vaccination according to their age, suggesting herd immunity induced by universal mass vaccination (Paulke-Korinek et al., 2011).
Rotavirus vaccines were introduced in Belgium in 2006 and recommended in the universal schedule in January 2007, with coverage quickly reaching 85% (Zeller et al., 2010). In 2008, the number of laboratory confirmed rotavirus cases declined by 61.4% compared to the 2005-2006 pre-vaccination period, with the highest decline in children <1 year (Hanquet et al., 2011). A further study showed that rotavirus-related hospitalisations significantly reduced in the first and second years after introduction (Raes, Strens, Vergison, Verghote, & Standaert, 2011).

Rotavirus vaccines have also shown outstanding effectiveness in Spain, regardless of the brand of vaccine used (Martinon-Torres et al., 2011). However, in France rotavirus vaccination has not yet been introduced into the routine immunisation program in infants less than 6 months (Kohli & Huet, 2011) and in the United Kingdom and Germany the application of the two available vaccines is not generally recommended (Stock, 2011).

6.1.4. Outstanding uncertainty
Several questions remain including whether current vaccines can maintain their effectiveness against the diverse range of rotavirus genotypes, especially in impoverished settings with high diarrheal burden (K. Grimwood, 2010). The two current attenuated oral vaccines contain the globally most common human G1, G2, G3, G4 and P[8] genotypes but other genotypes, such as G9 and G12 have emerged worldwide and spread throughout the world in a short period of time (Laszlo, 2011). It is important to see whether introduction of a vaccine might eventually change the genotype of the locally prevalent disease-causing genotypes in the community by post marketing surveillance. If this change does occur, the vaccine formulation either needs changing or adding to – which can be done reasonably easily.

There is evidence that the predominant genotypes of rotavirus in the population have changed following the introduction of routine vaccination for rotavirus in the United States, Australia and Europe. A shift from the G1P strain towards a higher proportion of the other G strains (including G3P and G9P) has been observed. It also appears the shift may depend on which rotavirus vaccine was introduced. However, it is still unclear whether these changes can be attributed to vaccine pressure or are simply due to normal fluctuations. In either case, these changes are important to monitor to ensure vaccination continues to protect against commonly circulating serotypes.

At the Children’s Hospital of Philadelphia in the United States, the remaining cases of rotavirus gastroenteritis presenting now appear to be the G9 serotype which is not included in either rotavirus vaccine (Clark, Lawley, Matthijnssens, DiNubile, & Hodinka, 2010). A different study of three counties in the United States found that the predominant genotypes varied annually following implementation of the vaccination program. In 2006 the dominant strain was G1P[8] (91%), shifting to G1P[8] (45%) and G12P[8] (36%) in 2007, and then G1P[8] (89%) in 2008, and G3P[8] (43%), G2P[4] (34%), and G9P[8] (27%) in 2009 (Payne et al., 2011). This dominance of the G3 genotype following RotaTeq introduction is also consistent with Australian reports (J. J. Hull et al., 2011).

Furthermore, there have been remarkable spatiotemporal changes in rotavirus activity, with the post vaccine introduction years failing to demonstrate the typical South west to Northeast spread of rotavirus activity (Curns et al., 2011).

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11 In the absence of a national rotavirus vaccination program in France, the IVANOE study was initiated to determine the real-world impact and effectiveness of rotavirus vaccine following introduction in a limited geographic area. The study found a twofold reduction rotavirus hospitalisations among children <2 years, and 98% effectiveness.

12 http://www.nhs.uk/Conditions/Rotavirus-gastroenteritis/Pages/Prevention.aspx
Following introduction in the Australian national Immunization Program, there have been differences in the rotavirus genotypes observed across Australia, suggesting that different immune pressures are exerted by the different vaccines. For instance, G2P[4] genotypes were more prevalent in states using Rotarix, whereas G3P[8] genotypes were more prevalent in states using RotaTeq (Kirkwood, Boniface, Barnes, & Bishop, 2011). Overall, G1P[8] was the dominant genotype nationally (52%), followed by G2P[3] (19.8%), G9P[8] (12.2%) and G3P[8] (11%) (Kirkwood et al., 2011). The identification of uncommon rotavirus genotype combinations has also increased since vaccine introduction (Kirkwood, Boniface, Bishop, & Barnes, 2010).

In Belgium, the prevalence of the G2 genotype sharply increased in the 2006-2007 rotavirus seasons compared to the previous seasons and remained high (30-40%) in the 2007-2008 and 2008-2009 seasons. However, it is unclear if the predominance of G2 genotypes is related to the vaccine introduction, or if this is attributable to normal genotype fluctuations (Zeller et al., 2010). It has been suggested in Ireland that the increase in novel G and P type combinations, as well as changes seen in G6 samples could have an impact on rotavirus vaccination programmes as the current vaccine available may not offer protection against all of the circulating types (Cashman et al., 2010).

Currently, in New Zealand G1 has been shown to be the dominant circulating genotype (55.8%) followed by G4 (21.4%), G3 (3.4%), G9 (3.4%), G2 (1.0%), and mixed infection. Two less common genotypes, G6 and G8, have also been identified. The frequency of these genotypes showed significant regional variation, with G1 being the most commonly identified genotype in the North Island (81.9%), and G4 predominating in the South Island (39.6%) (Chandrahasen et al., 2010). Despite these differences in the proportions of circulating genotypes, both available vaccines will protect equally well in either island.

6.2. Societal & ethical
This section of the assessment describes some of the social and ethical issues that need to be considered with respect to adding a rotavirus vaccine to the New Zealand immunisation schedule. These include: acceptability of the intervention to the public and health practitioners, the equitable distribution of benefits and costs, and any ethical and psychological issues associated with the decision to vaccinate or not. Overall, there is insufficient evidence to say whether health practitioners and individuals would support a universal vaccination programme in New Zealand. However, evidence from overseas and the coverage rates for existing vaccines on the schedule suggest that rotavirus vaccination may not be seen as a high priority or acceptable use of public funding at a societal level – particularly in the context of disparities in coverage for existing publicly-funded immunisations.

6.2.1. Acceptability
Diffusion of innovation theory predicts a >80% implementation if approximately 50% of a given population support an innovation (Agyeman et al., 2009). Evidence internationally suggests that if the vaccination was publicly funded, around 50% of caregivers and health practitioners would support rotavirus vaccination. However, when prioritised against other vaccinations, it ranked lowest and in countries that have adopted it, coverage remains lower than that for other vaccinations.

6.2.1.1. What proportion of the target population will accept the vaccine, or has already been vaccinated?
Perceptions and acceptability of rotavirus vaccination in a population are important indicators of the coverage levels achieved, and thus the likelihood the programme will achieve its desired outcome. Perceptions and acceptability of vaccination are influenced by a number of factors including: the opinions of health practitioners, availability of public funding, and
information on, or previous experience of, the disease and vaccine. Experiences overseas may be able to provide some indication of the expected acceptability of rotavirus vaccination (and therefore coverage) in New Zealand and how this might change over time.

Health practitioner support & public funding

In the United States, the rotavirus vaccine has been widely accepted by paediatricians and vaccine coverage is steadily increasing, though remains lower than coverage levels of other routine infant immunizations (Jacqueline E. Tate et al., 2011). However, an earlier study found that while rates of offering the new rotavirus vaccine were high among paediatricians (85%), less than 50% of family medicine physicians offered the new rotavirus vaccine, citing concerns about safety and adding another vaccine to the vaccinations schedule (Kempe et al., 2009).

A Swiss study found that routine rotavirus immunisation was only supported by 15% of primary care physicians, with 64% dismissing it outright and 21% undecided (Agyeman et al., 2009). However, when asked whether they would recommend vaccination to parents if it were officially recommended by the federal authorities and reimbursed, 48% agreed to recommend it.

In Canada, where the rotavirus vaccination is recommended, but not publicly funded, a survey of Canadian paediatricians’ knowledge, attitudes and beliefs regarding rotavirus disease and its prevention, was undertaken (Dube et al., 2011). Sixty-nine percent of respondents considered rotavirus vaccines to be safe and 61% to be effective. The reduction of severe gastroenteritis cases was seen as the main benefit of rotavirus vaccination, while the risk of adverse events was the principal perceived barrier. However, while more than half of surveyed paediatricians were willing to recommend rotavirus vaccines to their patients, the proportion of respondents who had a strong intention to do so remains low when compared to several other new vaccines (Dube et al., 2011). A different study of physicians in British Columbia found that 77% of physicians believed the vaccine should be publicly funded and 94% indicated they would recommend the vaccine if it was (Chan, Sahni, Donovan, & Naus, 2010). The most common perceived barriers to uptake were parental reluctance to pay (97%), parental concern about vaccine safety (90%), and parental belief that rotavirus infection was not severe (89%) (Chan et al., 2010).

A Canadian study of priorities for new vaccination program implementation found that when compared with other vaccination priorities, rotavirus vaccination ranked lowest, below MMRV, DTaP-Polio-Hib-Hepatitis B, PCV-10, quadrivalent meningococcal vaccine, combined hepatitis A & B vaccine, and HPV vaccines (Dube et al., 2010). Similar findings were observed in Italy where a group of public health officers and gynaecologists were requested to express their opinion on whether immunization for HPV in girls older than 12 years, rotavirus, and varicella with combined MMRV vaccine should be included in the National Immunization Plan. Overall, only 52.4% agreed that rotavirus should be introduced, compared with 83.5% for HPV and 77.9% for varicella (Marchetti & Morelli, 2009).

Information on vaccine safety

In 1997, the first rotavirus (Rotashield) vaccine was withdrawn due to an increased incidence in intussusception (Bissantz et al., 2011). This may make the population hesitant about taking up this vaccine and have adverse effects on the vaccine’s acceptability (Samad et al., 2010). In 2010 there were also reports that procine circovirus type 9 (PCV-1) DNA was present in US-licensed rotavirus vaccines, and Rotarix and RotaTeq appeared to have been affected (McClenahan, Krause, & Uhlenhaut, 2011). This concern prompted at least one international health agency to temporarily withdraw rotavirus vaccines; between 29 March 2010 and 4 November 2010 the release of Rotarix and RotaTeq onto the Spanish market was not authorised due to problems of good manufacturing practice (Alejandro, Domingo, & Torres, 2011). The author’s suggest that the impact of the temporary withdrawal of rotavirus vaccines in Spain may have been outstanding and that the influence of this event on rotavirus vaccination trust may have been even more important (Alejandro et al., 2011).
Perceived seriousness

A survey of mothers in France found that acute gastroenteritis in children below 2 years was considered to be a grave (43.1%) or very grave (51.3%) pathology due to the symptoms and complications associated with the disease (Haas, Olives, Virey, & Klein, 2010). In particular, the symptoms were well understood and mothers believed that hospitalisation was frequent. Most (86.3%) mothers favoured a drinkable vaccine to prevent acute gastroenteritis due to Rotavirus, and 88.1% said that they would intend to protect their child with this vaccine (Haas et al., 2010). However, this contrasts with the stance taken by the National Health Service in England, where rotavirus vaccination is not given as part of the routine childhood immunisation schedule, and is not usually available free of charge on the NHS because it is currently felt that the public health risks posed by the rotavirus are not serious enough to justify routine immunisation. The majority of respondents to a Canadian survey of physicians rated the consequences of rotavirus infection for young patients as moderate, but most (62%) believed it generated a significant economic burden (Dube et al., 2011).

Coverage rates achieved overseas

Coverage rates for rotavirus vaccination remain lower than for other vaccinations in most countries. In Belgium, where both vaccines are offered through partial reimbursement, estimates of vaccine uptake range between 85% (Zeller et al., 2010) and 90% (Braecman et al., 2011). Similar estimates were made in Austria (72-85%) (Paulke-Korinek et al., 2010) and Australia (83%-87%) (Belshaw et al., 2009; Jim P. Buttery et al., 2011; Hull, Dey, Mahajan, Menzies, & McIntyre, 2011).

However, these estimates are significantly higher than the coverage achieved in the United States where full coverage for rotavirus vaccine was 43.9% among children born within 2 years of licensure. This is significantly lower than the coverage observed for poliovirus (92.8%), MMR (90.0%), Hep B (92.4%), and varicella (89.6%) (Centers for Disease & Prevention, 2010). It is also evident that one dose or more rotavirus coverage among infants aged 5 months was 13% lower than the average coverage with one or more doses of DTaP and PCV7 at current sentinel sites (Centers for Disease Control & Prevention, 2010). The CDC suggested that this could reflect typical new-vaccine coverage dynamics, the presence of rotavirus-specific barriers, or both and emphasised the importance of identifying and reducing barriers and educating parents and providers about the health benefits (Centers for Disease Control & Prevention, 2010). In 2010, the coverage rates in the United States increased from 43.9% to 59.2% (Centers for Disease & Prevention, 2011).

6.2.2. Equity & Ethics

6.2.2.1. Will reduced pathogen transmission lead to enhanced vulnerability of specific sub-populations?

No evidence was retrieved suggesting that reduced pathogen transmission might lead to enhanced vulnerability of specific sub-populations.

6.2.2.2. Are the benefits and costs of vaccination, or benefits and costs of not vaccinating, experienced disproportionately by different groups and if so, which ones?

In England hospital admissions with gastroenteritis of all causes increases as deprivation increases (Pockett, Adlard, Carroll, & Rajoriya, 2011), and similar patterns are observed in New Zealand (The New Zealand Child and Youth Epidemiology Service, 2010). In Ireland it has also been observed that children of non-Irish ancestry suffer a more severe illness from rotavirus gastroenteritis than those of Irish ancestry (Nosherwan et al., 2010).

13 http://www.nhs.uk/Conditions/Rotavirus-gastroenteritis/Pages/Prevention.aspx
Implementation of a rotavirus vaccination programme may prevent some elements of health and social inequality (Pickett et al., 2011). However, while there is evidence that racial disparities in the United States for children 12-35 months resolved following rotavirus vaccination, higher hospitalisation rates among African American infants < 6 months persisted, highlighting that the impact of vaccination on decreasing ethnic disparities relies heavily on timely vaccination (Yen et al., 2010).

6.2.2.3. Could the vaccine be targeted to specific groups?
The vaccine could be targeted to vulnerable infants. In the Canadian hospital setting, nosocomial rotavirus gastroenteritis affects mainly patients with underlying chronic medical conditions requiring frequent and prolonged hospitalisations and targeting vaccination to these groups, as well as infants with congenital pathology and low birth weight (Verhagen, Moore, Manges, & Quach, 2011) has been suggested as an alternative to universal vaccination (Verhagen et al., 2010).

6.2.3. Psychological considerations

6.2.3.1. Are there any psychological issues associated with rotavirus or the vaccine?
Paediatric rotavirus gastroenteritis results in high levels of infant and parental stress (Van der Wielen et al., 2010). While the addition of another vaccine to the infant immunisation schedule may appear daunting, the oral delivery of the rotavirus vaccine, in contrast to injection, may address these concerns to an extent. However, further engagement with parents and caregivers is required to confirm this.

6.3. Value for money
Rosevear & Ulrich (2012a) determined that each year, rotavirus costs the New Zealand economy approximately $8.3 million\(^{14}\) through lost productivity as a result of parental time spent caring for sick children instead of working, and loss of future earnings through death (Table 3). In addition to lost productivity, the annual medical costs incurred were estimated to be around $3 million, bringing the overall cost of rotavirus to around $11 million. Rosevear & Ulrich (2012a pgs 30-31) suggest that, if their assumptions are correct, spending $7.9 million on a universal rotavirus vaccination programme for infants could save $2.3 million in medical costs (75% of total medical costs) and $6 million in lost productivity (72% of total productivity costs).

Table 3: Costs included in the economic evaluation of universal rotavirus vaccination

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (NZ$2011)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination Programme</td>
<td>Per dose</td>
<td>Per person(^{15})</td>
</tr>
<tr>
<td>NZ wholesale vaccine cost (unclear whether excl GST + excl freight) no volume discount(^{17}).</td>
<td>$ 35.50</td>
<td>$ 106.50</td>
</tr>
</tbody>
</table>

\(^{14}\) Assumes 60,000 cases of rotavirus per annum  
\(^{15}\) Assumes 3 doses  
\(^{16}\) Based on 60,000 cases of rotavirus  
\(^{17}\) Note: This contrasts with the NZ wholesale vaccine cost for varicella which excl freight and GST, and had an 85% volume discount.
### Administration cost based on 15 min time to administer, $32/hour for nurse and 50% practice overhead costs; $12 = 0.25 × $32 × 1.5

<table>
<thead>
<tr>
<th></th>
<th>Average per case</th>
<th>Per year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$ 12.00</td>
<td>$ 36.00</td>
<td>($2,160,000.00) (Milne, 2009)</td>
</tr>
</tbody>
</table>

### Ministry procurement/management costs (5% of the cost of the vaccine)

<table>
<thead>
<tr>
<th></th>
<th>Average per case</th>
<th>Per year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$ 2.50</td>
<td>$ 7.50</td>
<td>($450,000.00) (Milne, 2009)</td>
</tr>
</tbody>
</table>

### Total cost of programme

<table>
<thead>
<tr>
<th></th>
<th>Average per case</th>
<th>Per year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$ 50.00</td>
<td>$ 150.00</td>
<td>($9,000,000.00) Assumes 100% uptake</td>
</tr>
</tbody>
</table>

### Productivity costs

<table>
<thead>
<tr>
<th>Productivity costs</th>
<th>Average per case</th>
<th>Per year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver taking care of sick child with rotavirus (1.2 days (in France) × 0.31 (NZ participation in ECE)) = 0.4 days. 0.4 days × 26.3/hr × 8 hrs = 84.16 (84.16 × 0.837 incidence of caregiver taking time off)</td>
<td><strong>$70.00</strong></td>
<td><strong>$4,200,000.00</strong></td>
<td>Estimate based on Fau 2008 and ECE 2011</td>
</tr>
<tr>
<td>Lost working days - GP (1.5 days lost) × 0.117 (% required) × 8 hours</td>
<td><strong>$37.00</strong></td>
<td><strong>$2,220,000.00</strong></td>
<td>Milne 2009 (hosp/GP ratio) + Milne 2009 (days)</td>
</tr>
<tr>
<td>Lost working days - ED (1.6 days lost × 0.031 × $26.3 × 8 hrs)</td>
<td><strong>$10.00</strong></td>
<td><strong>$600,000.00</strong></td>
<td>Milne 2009 (hosp/GP ratio) + Milne 2009 (days)</td>
</tr>
<tr>
<td>Lost working days - Hospitalisation (3.6 days lost × 0.015 × $26.3 × 8 hrs)</td>
<td><strong>$11.00</strong></td>
<td><strong>$660,000.00</strong></td>
<td>See Burden of Disease + Milne 2009 (days)</td>
</tr>
<tr>
<td>Future productivity due to mortality from rotavirus (45 working years lost) × 0.68 (workforce participation) × $55k (avg wage) × 0.4</td>
<td><strong>$11.00</strong></td>
<td><strong>$660,000.00</strong></td>
<td>Estimate</td>
</tr>
</tbody>
</table>

**Total productivity costs from rotavirus** | **$139.00** | **$8,340,000.00** |

### Medical costs

<table>
<thead>
<tr>
<th>Medical costs</th>
<th>Average per case</th>
<th>Per year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP visit due to rotavirus</td>
<td><strong>$5.90</strong></td>
<td><strong>$354,000.00</strong></td>
<td>Assumes 11.7% cases go, at $50 per visit</td>
</tr>
<tr>
<td>Pharmaceuticals for rotavirus</td>
<td><strong>$6.20</strong></td>
<td><strong>$372,000.00</strong></td>
<td>Community pharmacist</td>
</tr>
<tr>
<td>Emergency department for rotavirus</td>
<td><strong>$10.50</strong></td>
<td><strong>$630,000.00</strong></td>
<td>Assumes 3.1% cases, $340 per visit</td>
</tr>
</tbody>
</table>

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18 If only 91% uptake of first dose and 98% and 96% uptake the second and third doses following the first dose, this total may reduce to $7,973,780.50 (($50.00 × 54,600) + ($50.00 × 53,508 + 50.00 x 51, 367.68))
6.3.1. What non-financial benefits are expected?

In addition to a reduction in the medical and productivity costs associated with rotavirus, the annual number of rotavirus cases is anticipated to decrease by 68% (from 60,000 to 19,050), and the number of cases requiring general practice and hospital care is expected to decrease by 78% (from 7,020 to 1,526) and 87% (from 900 to 114), respectively (Rosevear & Urlich, 2012a). Each year, a universal rotavirus vaccination programme would also prevent 28,865 days off work and result in the gain of 116 quality adjusted life years (QALYs).

6.3.2. What is the cost-effectiveness of adding the rotavirus vaccine to the existing childhood immunisation schedule as three separate shots for infants aged between 6 and 32 weeks (Option 1), relative to a counterfactual scenario where the rotavirus vaccine is not available at all (Option 2)?

The economic assessment commissioned by the immunisation team addressed this question from both a societal and health payer’s perspective via a cost-benefit and cost-utility analysis, respectively (Rosevear & Urlich, 2012a). Overall, universal vaccination for rotavirus was not cost-saving from either a societal or health payer’s perspective. From a societal perspective, the programme would return $0.97 for every dollar spent, and from a health payer’s perspective the programme would cost $62k per QALY gained. For the programme to be cost-saving to the health payer, the price of the vaccine would need to drop from $50 per dose, to approximately $15 per dose (Rosevear & Urlich, 2012a).

Unless an intervention is clearly cost saving, whether an intervention is cost effective or not is a subjective judgement often made via comparisons to previous or competing investments. While in the UK health economists inferred from previous recommendations that NICE had a threshold of £20,000-£30,000 per QALY for new investments, the use of thresholds to indicate whether an intervention is ‘cost effective’ is problematic (NICE, 2009), particularly in New Zealand. This is because thresholds inadequately account for opportunity cost and affordability, and are incompatible with budgets and maximising health gains (Metcalfe & Grocott, 2010).

In New Zealand, pharmaceutical investments can only be considered ‘cost-effective’ when prioritised against other proposals at the time, and threshold levels must inevitably vary with available funds and PHARMAC’s other 8 criteria, thus thresholds cannot be inferred and calculated for New Zealand (Metcalfe & Grocott, 2010). In spite of this, the author of the economic assessment report for rotavirus uses a table referred to by Metcalfe and Grocott (2010) as incorrect, to infer a threshold of $15,000(NZ) per QALY and comment that the cost-utility value of rotavirus, despite not being cost saving to the health system, is ‘relatively expensive’ when compared with historical PHARMAC purchasing. This conclusion is incorrect.

6.2.2.2. Critical appraisal of assessment

A critical appraisal of the evaluation by Rosevear and Urlich (2012a) was undertaken using Drummond’s checklist for appraising economic evaluations (Drummond et al., 2005). The results of this appraisal showed that the evaluation performed well against six of the ten criteria.
The assessment:

1. posed a well-defined question in answerable form and stated the perspective of the analysis

2. provided a comprehensive description of competing alternatives

3. measured costs and consequences accurately in appropriate physical units. However, rather than using the same analytical technique for both perspectives (ie, cost-benefit analysis OR cost-utility analysis), the author chose to use a cost-benefit analysis for the societal perspective and a cost-utility analysis for the health payer’s perspective.

4. adjusted all costs and consequences for differential timing using the standard 3.5% discount rate. However, while a lifetime horizon was suggested in the tender, the timeframe and analytic horizon was not clearly stated and the report did not comment on the time interval between vaccination and realisation of health effect.

5. performed an incremental analysis of costs and consequences of alternatives (acknowledging that current private purchase levels were so low they didn’t need to be included).

6. allowed for uncertainty in the estimates of costs and consequences through the use of sensitivity analysis. However, the author did not include the number of doses in the sensitivity analysis. This is important as the original ITF recommendation was for 2 rather than 3 doses of the vaccine which was included in the model. This may have decreased the apparent cost-effectiveness of the universal rotavirus vaccination programme.

However, the study did not perform well on:

7. establishing the effectiveness of the vaccine programme – effectiveness data was not summarized through a systematic overview of clinical studies as this was excluded from the tender, and the search strategy and rules the author used for inclusion and exclusion were not outlined.

8. identifying all important and relevant costs and consequences for each alternative – while the analysis included all costs relevant to a societal perspective, it did not include all costs relevant to a health payer’s perspective. In particular, initial set-up costs of the vaccination programme, including promotion and education, were not included, and neither were the initial or on-going costs of an associated surveillance programme. This is important given that the cost of the vaccine itself represents only a small percentage of the total cost of delivering it to the public. Thus, 5% of the vaccine cost for administration is probably a considerable underestimate. Furthermore, including only hospitalised cases of rotavirus where it was the primary cause of hospitalisation, excludes nosocomial infection of other infant inpatients, which is an important cause of morbidity, delayed hospital discharge for those nosocomial infected, and increased cost of the original admissions (Ringenbergs, Davidson, Spence, & Morris, 1989). Likewise, the potential impact of ‘herd’ immunity has not been included.

9. valuing costs and consequences credibly – for some of the hospitalisation parameters costs for a single District Health Board in 2003 were inflated to 2011 values instead of using the proper costing methodology appropriate for the National Minimum Dataset (NMDS) for hospital discharges. Similarly, when compared with recent coverage data for immunisations in infants (70% coverage of 6 month olds), the coverage rates

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19 Health Report number: 20100423.


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assumed in the model were optimistic – with 91% for the first dose, and 98% and 96% for the second and third, respectively\(^\text{21}\). While these were reported to be coverage rates achieved for polio, when the reference for this was followed up, the coverage rates for polio at age 2 were a lot lower: 92.1%, 90.4% and 88.5%, for doses 1, 2 and 3 respectively \(\text{(Ministry of Health, 2005 pgs 23 & 63)}\). When compared with the author’s analysis of varicella, it appears that while the price of the varicella vaccine included a ‘wholesale discount’, the price of the rotavirus vaccine does not.

10. the inclusion of all issues of concern to users in the presentation and discussion of the study results – while an overall index or ratio of costs to consequences was provided, they were interpreted in a mechanistic fashion. Total annual costs of the vaccination programme were not mentioned (instead they were left for the reader to calculate) and there were a number of misleading statements that suggested the type of analysis (cost-utility vs cost-benefit) determined whether vaccination was ‘cost effective’ (as opposed to the inclusion or exclusion of productivity costs). While results were compared with those of others who have investigated the same question, few allowances were made for potential differences in study methodology, and the use of an inappropriate threshold to suggest cost-effectiveness was used. The study did not discuss the generalisability of results to other settings and patient/client groups and did not discuss issues of implementation, however it is recognised that this was beyond the scope of the tender.

It has been suggested that the modelled impact of rotavirus vaccination in infants may be underestimated in static disease models that do not capture the indirect effect of the vaccine on non-vaccinated age-groups (ie, herd immunity) \(\text{(Standaert, Strens, Van Bellinghen, & Van Vlaenderen, 2010)}\). This is likely to apply to the model used in this evaluation, whereby the potential impact of herd immunity was not considered and the influence of vaccination on decreasing the number of cases of nosocomial infection was also excluded. These two factors, combined with decreasing the number of doses in the program from three to two may improve the cost-effectiveness of a universal rotavirus vaccination program. However, the model also excluded the costs associated with surveillance if such a program were implemented. It is unclear whether the inclusion of these additional parameters would significantly affect the cost-effectiveness of the program, from either a societal or health payer’s perspective.

6.2.2.3. How does the assessment compare to others previously conducted in New Zealand and internationally?

The findings from the evaluation discussed above are comparable to a previous New Zealand study, and are similar to the simulation studies published overseas. In all studies, universal vaccination for rotavirus is more cost-effective from a societal perspective than a health payer’s perspective, and all have noted that slight changes in key parameters significantly affect the cost-effectiveness of vaccination. Only one study found universal vaccination to be cost-saving, and even this was only from a societal perspective. In all studies that compared the cost-effectiveness of the two available vaccine brands, Rotarix was more cost-effective than RotaTeq.

**New Zealand**

In 2009 Milne & Grimwood published a cost-utility analysis investigating the budget impact and cost-effectiveness of including three doses of pentavalent rotavirus vaccine in the New Zealand childhood immunization schedule compared with no vaccination \(\text{(Milne R \\& ...)\text{21}}\  \text{http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data}\)
Grimwood K, 2009). In contrast to the study by Rosevear and Ulrich (2012a), Milne & Grimwood (2009) included non-medical costs incurred for travelling to hospital. However, unlike Rosevear and Ulrich (2012a), Milne & Grimwood excluded home care cases that did not come to medical attention because no information was available on costs or incidence rates. The exclusion of these costs likely explains why the societal costs of rotavirus infection were only $7 million compared with $11 million in the report by Rosevear and Ulrich. The study found that the impact of vaccinating five successive birth cohorts at $50 per dose and 85% coverage would cost $67k per QALY gained from a health payer’s perspective and $46k per QALY from a societal perspective. While the health payer estimate was comparable to Rosevear & Ulrich’s estimate of $62k, the societal costs appear to be higher (despite not being directly comparable due to use of a cost-utility rather than cost-benefit analysis).

Internationally

As in New Zealand, studies overseas also note that universal vaccination for rotavirus gastroenteritis is more cost-effective from a societal perspective than a health payer’s perspective. Of the studies retrieved, only one noted that universal rotavirus vaccination would be cost-saving, and this was only from a societal perspective (Coyle et al., 2011). An investigation of the cost-effectiveness of rotavirus vaccination in Belgium, England and Wales, Finland, France and the Netherlands determined that universal vaccination was only likely to be cost effective in Finland from a health payer’s perspective (Jit et al., 2010). Similarly, a study conducted in Holland also found that universal vaccination was not cost-effective (Mangen et al., 2010). Others have noted that it is not possible to definitively state whether a universal rotavirus vaccination programme is cost effective in developed countries (Plosker, 2011).

Impact of brand choice

In all cost-utility analyses retrieved comparing the cost effectiveness of Rotarix and RotaTeq, Rotarix was more cost-effective from both a societal and health payer’s perspective than RotaTeq (Bilcke, Van Damme, & Beutels, 2009; Chodick et al., 2009; Cornejo, Rubio, Imaz, & Sarria-Santamera, 2011; Coyle et al., 2011; Mangen et al., 2010; Perez-Rubio et al., 2011; Samdal K, Hagen G, Flem E, & Klemp M, 2009). This suggests that if the analysis in New Zealand was repeated with Rotarix (2 doses) instead of RotaTeq (3 doses), universal vaccination may be more cost-effective, and potentially cost-saving from a societal perspective, though still not cost-saving from the perspective of the health payer.

Outstanding uncertainties

Studies note a number of limitations of cost-utility analyses that assess universal rotavirus vaccination programs. These specifically relate to the inclusion or exclusion of particular parameters – such as the cost of nosocomial infections and one versus two parents time off work, as well as the use of QALYs to measure gains over short periods of time, and using parental utility values as a proxy for child’s.

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) noted that the impact of nosocomial rotavirus infections had not been included in the economic evaluation submitted to them in supporting documentation submitted for consideration of adding RotaTeq to the National Immunisation Programme22. They also discussed that non-health gains had not been accepted previously in decisions, the difficulty of using QALYs to measure health gains over a short timeframe (meaning small changes in QALY gained affect the incremental cost-effectiveness substantially – between 45-75k to 105-200k), and the use parental utility values as a proxy for a child’s. While initially a decision was made not to

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22 Public Summary Document of July 2006 PBAC Meeting
publicly fund universal rotavirus vaccination, the contents of a subsequent application (presumably including the impact of nosocomial infections) changed this decision and now both RotaTeq and Rotarix are publicly funded as part of the national immunisation program.

6.3.3. Would the vaccine be more cost-effective if it were targeted to different population groups? If so, which groups?

Only two studies were retrieved suggesting that rotavirus would be more cost-effective if it were targeted to specific population groups, both of which were situated in Canada. Because of concerns about cost-effectiveness, Canada does not currently have universal rotavirus immunisation program (Verhagen, Manges, & Quach, 2010). An assessment of the possible impact of a targeted immunisation strategy on reducing nosocomial rotavirus gastroenteritis in specific high risk patients found that this could generate an important reduction among high-risk patients while limiting costs compared to universal vaccination (Verhagen et al., 2010). To determine to what extent a similar targeted vaccination strategy would be cost-effective in New Zealand requires another economic evaluation and investigation of more rigorous infection control methods as a first step (eg, hand washing compliance in hospitals, appropriate isolation procedures etc).

Another approach may be to use rotavirus hyperimmune bovine colostrum as prophylaxis to prevent in-hospital nosocomial infection (Davidson, 1996) if this is still available.

6.3.4. Does reducing the number of doses affect the cost-effectiveness of the vaccine?

There is evidence that RotaTeq provides a high level of protection between doses against hospitalisations and ED visits for rotavirus gastroenteritis starting as early as 14 days after the first dose (Dennehy et al., 2011). A study in the United States has also estimated that partial immunisation confers substantial protection, with 1 and 2 doses of RotaTeq 69% and 81% effective against hospitalisation and emergency department visits, respectively (Boom, Tate, Sahni, Rench, Hull et al., 2010). However, no studies were retrieved that specifically assessed the cost-effectiveness of reducing the number of doses.

6.4. Feasibility of adoption in the health system

6.4.1. Policy congruence

6.4.1.1. How does the addition of this vaccine fit with other policy and practices in immunisation and the wider health sector?

The Immunisation Technical Forum (ITF) initially recommended that the rotavirus vaccine be added to the National Immunisation Schedule in 2006. However, in “March 2010 the Ministry of Health agreed with the Minister not to seek funding for the introduction of rotavirus and varicella vaccines until immunisation for two-year-olds was closer to the target of 95%” (Ministry of Health, 2011b).

Since 2009 the Immunisation Health Target required District Health Boards to ensure that: 85% of two-year-olds be fully immunised by July 2010, 90% by July 2011 and 95% by July 201223. During this time the actual coverage achieved in this age group was: 86% (Jul09-10) and 89% (Jul10-11)24. While coverage has improved, the target was not met, raising the question of whether increasing coverage for existing vaccines on the schedule should

continue to receive higher priority than rolling out a new vaccine – particularly given coverage for 6 month olds\(^{25}\) (the youngest age for which coverage data is published) remains lower than total coverage rates at 70% and coverage rates for Maori, and infants residing in areas of high deprivation (deciles -9 &10) are even lower (55% and 61%, respectively).

Preliminary analysis of data collected from December 2007 to May 2008 from 24 diverse New Zealand General Practices suggests that low coverage may be due to the Immunisation Benefit Subsidy funding being inadequate remuneration to support service delivery at the practice level (Immunisation Advisory Centre, 2012).

Depending on whether the subsidy has changed since 2007/08, this finding might also support prioritising funding to improve current vaccination coverage, rather than funding a new vaccine. In New Zealand, anecdotal evidence suggests that currently outreach immunisation services costs between $250 and $1000 per hard to reach child\(^{26}\).

6.4.2. Organisational issues

6.4.2.1. How would the addition of the vaccine fit with the existing Immunisation Schedule?

The recommended delivery of the rotavirus vaccine at 6 weeks, 3 months and 5 months of age would fit well with the existing immunisation schedule. However, the timing of this vaccine, both of the first dose and the last dose is incredibly important for safety and efficacy as catch up doses are not possible where they may be with existing vaccines. In developing countries at least, the stringent age restriction have been noted to have the potential to result in major reductions in vaccine coverage in developing countries, where delays in the timing of vaccination are common and age is not accurately recorded (Umesh D. Parashar & Glass, 2009). While in New Zealand the accurate recording of age is less likely to be an issue, it is unknown to what extent the issues around timing may also apply here.

6.4.2.2. How would universal vaccination affect the use of other health services (ie, GP visits, hospitalisations, pharmaceutical consumption etc)?

Vaccination for rotavirus is anticipated to reduce the use of health services to an extent. However, as rotavirus is a relatively short-lived disease, the overall impact on health services of vaccination may be negligible. The mild nature of this disease, which rarely requires hospitalisation, is the main reason vaccination is cost saving from a societal perspective, but not from a health payer’s perspective.

As vaccination is delivered at the same time as the existing schedule, additional pressure on primary care is unlikely.

6.4.2.3. What are the health workforce implications of introducing universal vaccination for rotavirus?

The only additional workforce implications from adding the vaccine to the schedule would stem from the introduction of a surveillance system and the lab testing and mandatory reporting requirements associated with this. At this stage, the overall impact on the workforce of introducing such a surveillance system has not been investigated. Further work will be required to determine an affordable and cost-effective surveillance strategy.

\(^{25}\) Coverage rates for 6 month olds were chosen as coverage rates at 6 weeks and 3 months were unavailable.

\(^{26}\) GMs Planning & Funding, Waikato & Auckland District Health Boards
6.4.2.4. What additional health system factors would need to be addressed to ensure successful implementation of the proposed vaccination programme in New Zealand?

Sufficient coverage

For the benefits of rotavirus vaccination to be realised in New Zealand, sufficient uptake of the vaccine is necessary. The analysis to determine whether vaccination would be cost-effective assumed a coverage rate of 91%, which is 23% higher than the current coverage estimates observed for the target group, which is around 70%.

As discussed in section 6.4.1, uptake depends on the perceptions of the public, which are largely influenced by information. The support of clinicians for the vaccine and active promotion of the safety and benefits to both the public and health sector will therefore be crucial, along with a particular focus on ‘hard to reach’ groups like Maori and areas of high socio-economic deprivation. Further progress in timely vaccination may also be achieved by improving health care providers' reminder/recall systems, implementing educational interventions that address barriers to vaccination (Smith et al 2009).

Surveillance

The shifting dominance of particular strains of rotavirus post vaccination underscore the need for careful monitoring of strains to assess possible vaccine pressure-induced changes and vaccine effectiveness against various rotavirus genotypes (Hull et al., 2011; Mladenova, Iturriza-Gomara, Esona, Gray, & Korsun, 2011). Continued monitoring of rotavirus diarrhoea is also needed to determine if immunity wanes as vaccinated children get older, to better quantify the indirect benefits of vaccination (Jacqueline E. Tate et al., 2011), to assess the role of animal rotaviruses in human diseases (Banyai et al., 2009) and monitor the risk of intussusception. A brief summary of surveillance strategies employed overseas and options for New Zealand are provided below.

In Europe, a surveillance network, EuroRotaNet, comprising 16 laboratories in 15 European countries has been established to provide valuable background information on rotavirus strain diversity in Europe before the introduction of rotavirus vaccines, and to provide a robust method for surveillance during vaccine implementation (Iturriza-Gomara et al., 2009).

Australia has set up a laboratory-based Rotavirus Surveillance Program that reports annually on the genotypes of rotavirus strains responsible for hospitalisation of children with acute gastroenteritis Australia-wide (Kirkwood et al., 2010).

Even though Germany has not commenced a routine vaccination program, an RV-surveillance system is in place that could potentially monitor the effect of an RV-vaccination program once implemented (Koch & Wiese-Posselt, 2011).

The regional variation in different strains in New Zealand highlights the importance of ensuring multi-center surveillance to help monitor program effectiveness when rotavirus vaccines are introduced into New Zealand’s national childhood immunization schedule (Chandrahasen et al., 2010). However, the addition of rotavirus to the list of notifiable diseases, and mandatory tests of all cases, may not be necessary to achieve this. It has been suggested that a sentinel surveillance program is operationalized in two District Health Boards (DHBs) – one in the North Island (eg, Waikato) and one in the South Island (eg, Christchurch)27. These two DHBs would be required to arrange laboratory testing of all stool samples of children admitted to hospital with acute gastroenteritis. Community labs would then be used to monitor changes in the dominance of particular strains and the Ministry of Health would monitor nationwide changes in hospital admissions for gastroenteritis via the National Minimum Dataset (NMDS).

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27 This suggestion was provided by Professor Keith Grimwood following his presentation at the Ministry of Health on 8 March 2012.
Another alternative may be to test antigenemia in sera/plasma during routine practice to augment rotavirus surveillance to assess the effect of vaccination, rather than relying on the collection of stool samples, which has been acknowledged to be a cumbersome task (Patel et al., 2009).

6.4.3. Legal issues

6.4.3.1. Are there any legal considerations around continuing not to vaccinate, or around the decision to vaccinate?

Continuing not to vaccinate for rotavirus will not have any legal implications. However, depending on how surveillance of the incidence of rotavirus were to be undertaken, and whether or not it was to become ‘mandatory’ to notify, an amendment to schedule 1 of the Health Act 1956 may be required.

6.4.4. Budget impact

6.4.4.1. What impact would the introduction of universal vaccination have on the available budget for vaccines and the total budget of Vote: Health?

There has been a sharp increase in spending on vaccines by the Ministry of Health over the last five years due to the addition of new vaccines such as Gardasil (for Cervical Cancer) and Prevenar (for pneumococcal disease)28. Annual spending has increased from around $20-$40 million (2006/07) to between $60-$80 million (since 2008). Furthermore, this budget is just for the purchase of the vaccines and represents only a small percentage of the total cost of delivering the vaccines to the public. This expenditure does not include development or implementation costs. For example, the total costs for MeNZB were over $220 million, but the cost of purchasing the vaccine itself was only $75.4 million over six years.

The total estimated annual costs of delivering the three doses of the rotavirus vaccine to an entire birth cohort of approximately 60,000 is $14.4 million (Table 4). However, this estimate assumes 100% uptake, when it is more likely that only 80% (48,000) take up the first dose and 77% (46,200) will take up the second and third29. Thus, the overall annual cost may be closer to $10.6 million30. Assuming a budget of $60 million, the cost of the rotavirus vaccine (excluding promotion and surveillance), would comprise approximately 18% of the total available budget for vaccines.

Table 4: Estimated annual costs of delivering a universal rotavirus vaccination programme with 100% uptake.

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost per dose</th>
<th>Cost per person</th>
<th>Cost per cohort</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus vaccine (wholesale – excl GST &amp; freight)</td>
<td>$50.00</td>
<td>$150.00</td>
<td>$9,000,000.00</td>
<td>Manufacturers (2012)</td>
</tr>
<tr>
<td>Administration/delivery costs (2007/08)</td>
<td>$25.67</td>
<td>$77.01</td>
<td>$4,620,000.00</td>
<td>(Immunisation Advisory Centre, 2012)</td>
</tr>
</tbody>
</table>

28 Health Report number: 20100423


30 = (48,000×$75.67) + (46,200×$75.67) + (46,200×$75.67)
In addition to the annual costs of delivering the vaccine, in the first year of the vaccination programme substantial costs may be incurred through media advertising, distribution of information to GPs, and health promotion activities. Annually, the Ministry of Health spends between $891,095 (2010/2011) and $1,811,056 (2009/2010) on promoting immunisation.

Other sources suggest that these initial costs may be higher, and that there will also be ongoing promotion costs of at least $100,000 per year (Health Report number 20110143).

The delivery and the promotion of the vaccine will not be the only costs associated with a universal rotavirus vaccination programme; on-going surveillance of rotavirus strains will also be necessary.

The overall budget impact of implementing a universal vaccination programme for rotavirus will therefore be approximately $13.6 million annually. However, further work to confirm this estimate and establish the impact of the programme on the budget annually over the timeframe of interest, based on assumptions around increasing coverage and expected savings has not occurred. Likewise, both the ‘new technology’ scenario (eg, universal vaccination) needs to be modelled alongside the ‘baseline scenario’ (eg, status quo).

6.4.4.2. Is the universal public funding of rotavirus vaccination affordable and sustainable?

Vaccination policy is driven by several factors, including vaccine safety and efficacy, avertable disease burden, acceptability, and societal value (Kim, 2011). One measure of value is an intervention's cost-effectiveness, defined as the additional cost required per additional unit of health benefit produced as compared with the next-most-effective alternative (as discussed in section 6.3). However, it is important to differentiate cost-effectiveness (value for money) from affordability (financial resources required); indeed, interventions with high value may not always be affordable (Kim, 2011).

At this stage, the cost-effectiveness of universal vaccination for rotavirus is only directly comparable with universal vaccination for varicella due to the need for consistent methods. When compared with universal vaccination of children aged 15 months and 4 years against varicella, universal vaccination of infants for rotavirus is less cost-effective; rotavirus vaccination would cost $62k/QALY(Rosevear & Urlich, 2012a), compared with the most expensive scenario for varicella vaccination, which is estimated to cost, at most (scenario 1), $16k/QALY(Rosevear & Urlich, 2012b).

However, even if universal rotavirus vaccination of infants was more cost-effective than universal varicella vaccination of children aged 15 months and 4 years, it would have to be shown to provide better value than other bundled preventive health services targeting the

---

31 This is based on an estimate for the rheumatic fever programme. More accurate data should be located.
32 This is based on an estimate for the rheumatic fever programme. More accurate data should be located.
33 Health Report number: 20111006
same age groups, in this case children under five. While an explicit process of Programme Budgeting & Marginal Analysis (PBMA) has not been undertaken, there are indications that the introduction of either varicella or rotavirus vaccines may not be the next best spend to improve children’s health outcomes in New Zealand.

For instance, previously the Immunisation Awareness Society noted their concern that the introduction of additional childhood vaccines should not be at the expense of other measures that might improve the health of this age group such as encouraging breastfeeding up to the age of two and ensuring that all children have a healthy and nutritious diet, free from high-sugar and high-fat junk and fast food (Immunisation Awareness Society, 2012).

Similar sentiments have been expressed by others who have noted that increasing coverage of existing vaccines among hard to reach groups should be a higher priority than introducing additional vaccines, and that there are other areas of pressing concern for children, such as the high rates of respiratory disease and lower respiratory tract infections (specifically Bronchiectasis), skin infections (eg, cellulitis), rheumatic fever, family violence and avoidable injuries (to name a few)\textsuperscript{34}.

6.4.4.3. \textit{Programme Budgeting & Marginal Analysis (PBMA): Is universal rotavirus vaccination a better option than any of the other initiatives in vaccines?}

One of the best ways to determine the impact that funding a new vaccine will have on the budget, and how affordable and sustainable it is in the future, is to not just look at alternative vaccines and interventions on the horizon, but also to look at those interventions that are currently funded, but may be of less value than the new one under consideration. This process is called programme budgeting & marginal analysis, and normally starts by looking within specific programme budgets before looking across them.

Within the budget for vaccines, Cochrane reviews have identified two low value vaccine schedules (Cochrane Collaboration, 2012). For example, they recommend that patients with chronic obstructive pulmonary disease (COPD) should not receive the influenza vaccine because the addition of intranasal live attenuated virus for influenza does not confer any added benefit (Cochrane Collaboration, 2012) and that vaccines for preventing influenza in healthy adults should be discouraged (Cochrane Collaboration, 2012).

While in New Zealand the universal vaccination of all adults for influenza is not publicly funded (targeted to those over 65 years and certain ‘at risk groups’), a substantial amount of money is spent annually on promoting the vaccine\textsuperscript{35}, and the Immunisation Handbook 2011 does not list the vaccine as contraindicated for patients with COPD. With this considered, it may be worth examining the current immunisation schedule to see if money can be saved through better use of existing vaccines (through better targeting), and whether the funding of rotavirus vaccination through these savings is a better use of public money.

6.4.4.4. \textit{How difficult would it be to disinvest in this vaccination programme in the future?}

Anecdotally, once a vaccine has been placed on the schedule, it cannot be removed, and thus disinvestment is difficult. However, why this is, and whether the difficulty of disinvestment varies by vaccine is unclear and requires further investigation – possibly with clinical advisors, such as the Royal College of Pathologists Australasia (RACP) or the Royal New Zealand College of General Practitioners (RNZCGP).

\textsuperscript{34} Teleconference with GM Planning &Funding, Auckland DHB and Clinical Directors in the area of Children’s Health.

\textsuperscript{35} Health Report number: 20111006
6.4.5. Funding

Rotavirus is usually a mild and transient disease treated in the community by children’s caregivers, resulting in only 1.5% of rotavirus cases being hospitalised, and less than 1 death annually (Rosevear & Urlich, 2012a). Given that caregivers lost productivity is the most significant impact (as opposed to morbidity experience by the child), and that vaccination is more cost-effective from a societal perspective than a health payer’s perspective, if the primary reason for vaccination was to reduce productivity loss from rotavirus, it will be important to confirm that such loss indeed occurs. Furthermore, given that savings are accrued to the wider society, whether that be employers or individuals (rather than the health sector), there is also a rationale for exploring whether Vote: Health is the appropriate funding source, or whether funding by individuals, employers of another government department, is more appropriate.

6.4.5.1. Should funding of the rotavirus vaccine come from Vote: Health or elsewhere?

While the Ministry of Health (Vote: Health) will bear the cost for the vaccination programme, it could be argued that the primary benefits of the programme (increased productivity) may be more closely aligned with the priorities of other government agencies (e.g., Ministry of Economic Development and Ministry of Social Development) than those of the Ministry of Health. A similar argument could be made with respect to individuals funding vaccination themselves (to insure against loss of income) or employers (to insure against the lost productivity).

From a clinical standpoint, rotavirus is predominantly a relatively benign disease in children that is short-lived and results in few deaths or hospitalisations. From an economic standpoint, universal vaccination can reduce the time taken off work by caregivers to care for sick children. As the main drivers of the ‘cost’ of rotavirus are these productivity costs, rather than medical costs, a universal vaccination programme will increase the costs to Vote: Health, while the benefits (increased productivity), may be more closely aligned with a different Vote. If it is determined that the societal costs of rotavirus warrant intervention, then it is worth considering whether the costs of the vaccination programme should be funded by the budget anticipated to accrue the savings.

If rotavirus is a burden on society, and results in a significant loss of income for individuals or productivity losses for employers, prior to making any decision based on the anticipated ‘productivity savings’ from publicly funded vaccination, further investigation into the reasons why individuals or their employers are not currently funding vaccination should be undertaken.

Scuffham et al (1999) argues that the rationale for a fully-subsidised routine programme must rest upon observations regarding the extent to which the market, left to its own devices, fails to achieve socially optimal outcomes. With regards to the public funding of the rotavirus vaccine, this means that the cost, as oppose to awareness of the availability of a safe & effective vaccine, and perceptions of the seriousness of the disease, is the main reason uptake is low. Currently it is unclear whether caregivers associate their children getting rotavirus with a significant loss of income or whether employers believe the productivity of their business is significantly affected by caregivers taking sick days to care for children with rotavirus. Further work to establish caregiver’s preferences around rotavirus vaccination, and the cause of current ‘market failure’ in New Zealand is required.

It is also possible that the cause of market failure may vary by population group. For instance, while cost and information may be the primary determinants of uptake among Maori and individuals residing in the most deprived areas, information and changing perceptions may be the primary determinants of uptake among Europeans and those residing in the least deprived areas. If this is the case, and it is shown that cost is the primary barrier to particular groups not having the rotavirus vaccine, there may be a stronger case for targeting the public funding of rotavirus vaccination to individuals on low incomes,
and those susceptible to infection (see section 6.2.2) rather than universally funding vaccination for all. However, limiting the volumes of ‘publicly funded vaccine’ may reduce the bargaining strength of the government, making it less able to secure the vaccine at a good price, for both those for whom it is subsidised, and those able to privately pay. This is an issue which requires further exploration if targeting is identified as the preferred option.

7. Conclusion

While there is evidence that rotavirus vaccination is clinically safe and effective in most circumstances, it is rarely deemed cost-effective. Furthermore, when the societal, ethical, and feasibility of adoption domains are considered, it becomes clear that universal vaccination of infants for rotavirus in New Zealand may not be the best use of public funding at present, and that there are higher priorities for funding in vaccination and child health more generally.

Internationally, it is evident that countries that have introduced universal rotavirus vaccination have seen declines in the number of cases and hospitalisations associated with the disease and that there may be indirect benefits for the unvaccinated population through herd immunity. While there were initial concerns around the clinical safety of early rotavirus vaccines related to the heightened risk of intussusception (Rotashield), large phase III pre-licensure clinical trials of Rotarix and RotaTeq vaccines have not detected an increased risk (though postmarketing surveillance indicates the possibility of an increased risk shortly after the first dose in some populations). The most common adverse effects from vaccination are fever and vomiting. While there is evidence supporting the co-administration of both Rotarix and RotaTeq vaccines alongside DTaP-IPV-HepB/Hib, only evidence supporting the co-administration of Rotarix alongside PCV10 was retrieved. Following the introduction of routine rotavirus vaccination, the United States, Australia and parts of Europe have all observed changes in the predominant strains of rotavirus circulating in the population, and in some instances, away from the strains targeted by the vaccine necessitating on-going laboratory surveillance.

However, despite good evidence on clinical safety & effectiveness, there is insufficient evidence to say whether health practitioners and individuals would support a universal vaccination programme in New Zealand. Recent evidence from overseas and the coverage rates for existing vaccines on the schedule in New Zealand suggest that rotavirus vaccination may not be seen as a high priority or acceptable use of public funding at a societal level – particularly in the context of disparities in coverage for existing publicly-funded immunisations.

Furthermore, a universal rotavirus vaccination programme for infants is unlikely to be cost-saving from a health payer’s or societal perspective. From a societal perspective, the programme would return $0.97 for every dollar spent, and from a health payer’s perspective the programme would cost $62k per QALY gained. For the programme to be cost saving to the health payer, the price of the vaccine would need to drop from $50 per dose, to approximately $15 per dose (Rosevear & Urlich, 2012a). While reducing the number of doses from three to two is likely to increase the cost-effectiveness of the program, it is unlikely to produce cost-savings to the health sector. In all cost-utility analyses retrieved comparing the cost effectiveness of Rotarix and RotaTeq, Rotarix was more cost-effective from both a societal and health payer’s perspective than RotaTeq. The cost-effectiveness of the program to the health sector may also be improved if the costs of nosocomial infection were included in the analysis. However, results are still unlikely to be cost-saving.

An additional consideration is whether a universal rotavirus vaccination programme would be the best use of public money when compared with other potential spending in the space of vaccines or child health more generally. Compared with universal vaccination of children against varicella, universal vaccination of infants against rotavirus is less cost-effective from both a health payer’s and societal perspective.
As it is delivered orally, it may be more feasible and acceptable to parents than the vaccination for varicella. However, rather than funding the addition of either vaccine to the schedule the money may be better spent on increasing coverage rates for existing vaccines on the schedule (including among ‘hard to reach’ population groups), saved to fund other, potentially more beneficial vaccines on the horizon (ie, against cancer and Alzheimer’s), or spent in other areas of child health which are likely to produce greater health gains.

Furthermore, prior to implementation a comprehensive surveillance system will need to be established to monitor waning immunity, changing dominance of specific rotavirus strains and the risk of intussusception. The costs to, and burden on, the health sector of setting up a new system, or making rotavirus a notifiable disease under the existing system have not been included in the current evaluation of cost-effectiveness. Once these costs are included, the cost-effectiveness of universal vaccination is likely to further decrease from the perspective of the health payer.

8. Options

The decision to publicly fund the universal vaccination of infants for rotavirus is complex and hinges on a number of uncertainties, which may, depending on the level of risk decision-makers are comfortable with, require further research and analysis. The different options, their associated strengths and weakness, and the potential next steps required are summarised in Table 5. Which option that is chosen will depend on what decision-makers hope to achieve through publicly funding rotavirus vaccination. For instance, what is the main problem they are hoping to solve, or the main outcome they wish to obtain?

If the main priority is to reduce the morbidity associated with all cases of the disease (mild & severe), and to reduce the time taken off work by parents to care for sick children (ie, to increase productivity gains) then options 1 or 2 may be best. If the main priority is to reduce severe cases of the disease in the most cost-effective way to the health payer, then option 3 might be best. If the main priority is to avoid additional costs to the health sector then option 4 might be best.

Table 5: Strengths and weakness of different options for publicly funding rotavirus vaccination in New Zealand

<table>
<thead>
<tr>
<th>Option</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Next Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Public funding of three-dose vaccination for all infants at 6 weeks, 3 months, and 5 months with RotaTeq</td>
<td>- reduces incidence of mild and severe rotavirus and associated hospitalisations - may save some of the societal costs associated with caregiver time off work - potential herd immunity with sufficient uptake</td>
<td>- not cost-saving to health payer or to society - significant investment in surveillance required.</td>
</tr>
<tr>
<td>2</td>
<td>Public funding of two-dose vaccination for all infants at 6 weeks and 3 months with Rotarix</td>
<td>- reduces incidence of mild and severe rotavirus and associated hospitalisations - more cost-effective to society &amp; health payer than option 1</td>
<td>- still not cost-saving to health payer or to society - significant investment in surveillance required</td>
</tr>
<tr>
<td></td>
<td>Targeted public funding of vaccination (high risk &amp; vulnerable patients)</td>
<td>- potential herd immunity with sufficient uptake</td>
<td>- cost-effectiveness to society may be reduced - price of vaccine may increase due to small numbers - risk to immune compromised population higher than in options 1 &amp; 2 – less likely to benefit from herd immunity.</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>No public funding of rotavirus vaccination, only private purchase (ie, status quo)</td>
<td>- cost-avoided for the health payer</td>
<td>- current incidence of rotavirus and related hospitalisations likely to continue - societal costs from lost productivity will continue - private costs of vaccine remain high due to lack of bulk purchasing by government - equity issues associated with ‘user pays’ – unequal impact on low income groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Glossary of Terms

Budget Impact Analysis (BIA) or Financial analysis

- a procedure for comparing only the financial costs and cost offsets of competing options, rather than comparing their clinical and economic costs and benefits (Ryan, 2010).

Cost-benefit analysis (CBA)

- an economic evaluation that compares the proposed technology with its main comparator(s) in which both costs and benefits are measured in monetary terms to compute a net monetary gain/loss or benefit gain/loss (Ryan, 2010).

Cost-effective (value for money)

- a proposed technology is considered cost-effective for a specified main indication if the incremental benefits of the proposed technology versus its main comparator(s) justify its incremental costs and harms (Ryan, 2010).

Cost-utility analysis (CUA)

- an economic evaluation that compares the proposed technology with its main comparator(s) in which costs are measured in monetary terms and outcomes are measured in terms of extension of life and the utility value of that extension, e.g. using quality-adjusted life years (QALYs) (Ryan, 2010).

Critical appraisal

- a strict process to assess the validity, results and relevance of evidence (Ryan, 2010).

Disability-adjusted life years (DALYs)

- a unit of healthcare status that adjusts age-specific life expectancy by the loss of health and years of life due to disability from disease or injury. DALYs are often used to measure the global burden of disease (Ryan, 2010).

Discount rate

- the interest rate used to discount or adjust future costs and benefits so as to arrive at their present values, e.g. 3.5%. This is also known as the opportunity cost of capital investment (Ryan, 2010).

Discounting

- the process used in economic analyses to convert future costs or benefits to present values using a discount rate. Discounting costs reflects societal preference for costs to be experienced in the future rather than the present. Discounting benefits reflects a preference for benefits to be realised in the present rather than at a later date (Ryan, 2010).

Economic evaluation

- application of analytical methods to identify, measure, value, and compare costs and consequences of alternatives being considered; addresses issue of efficiency to aid decision making for resource allocation. It is an umbrella term covering CBA, CEA, CMA and CUA (Ryan, 2010).

Effectiveness

- the extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) in routine clinical practice (contrast
with **Efficacy** (Ryan, 2010).

**Efficacy**
the extent to which a technology produces an overall health benefit (taking into account adverse and beneficial effects) when studied under controlled research conditions (contrast with **Effectiveness**) (Ryan, 2010).

**Epidemiology**
the study of the distribution and determinants of health-related conditions or events in defined populations (Ryan, 2010).

**Generalisability**
the problem of whether one can apply or extrapolate results obtained in one setting or population to another. Term may also be referred to as ‘transferability’, ‘transportability’, ‘external validity’, ‘relevance’, or ‘applicability’ (Ryan, 2010).

**Health outcome**
a change (or lack of change) in health status caused by a therapy or factor when compared with a previously documented health status using disease-specific measures, general quality of life measures or utility measures (Ryan, 2010).

**Health payer’s perspective**
economic analysis is taken from the perspective of the funder, and excludes costs and savings to other (non-healthcare) government departments. This does not prevent these costs from being considered in a qualitative manner elsewhere in the report (Grocott et al., 2007).

**Health technology assessment (HTA)**
this is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value (Ryan, 2010).

**Incidence**
the number of new cases of a disease or condition that develop within a specific timeframe in a defined population at risk. It is usually expressed as a ratio of the number of affected people to the total population (Ryan, 2010).

**Incremental costs**
the absolute difference between the costs of alternative management strategies of the same medical condition, disease or disorder (Ryan, 2010).

**Marginal benefit**
the additional benefit (e.g. in units of health outcome) produced by an additional resource use (e.g. another healthcare intervention) (Ryan, 2010).

**Marginal cost**
the additional cost required to produce one additional unit of benefit (e.g. unit of health outcome) (Ryan, 2010).

**Perspective**
this is the viewpoint from which an economic evaluation is conducted. Viewpoints that may be adopted include that of the patient, the public
healthcare payer or society.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>the number of people in a population with a specific disease or condition at a given time and is usually expressed as a ratio of the number of affected people to the total population (Ryan, 2010).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Productivity costs</td>
<td>the costs associated with lost or impaired ability to work because of morbidity or death (Ryan, 2010).</td>
</tr>
<tr>
<td>Quality-adjusted life year (QALY)</td>
<td>a unit of healthcare outcomes that adjusts gains (or losses) in years of life subsequent to a healthcare intervention by the quality of life during those years. QALYs can provide a common unit for comparing cost-utility across different technologies and health problems. Analogous units include Disability-Adjusted Life Years (DALYs) and Healthy-Years Equivalents (HYEs) (Ryan, 2010).</td>
</tr>
<tr>
<td>Societal perspective</td>
<td>economic evaluations taken from a ‘societal perspective’ include costs and consequences beyond those experienced by the health sector or potentially beyond the scope of the health sector's control. These costs would include not only those to other government departments, but also productivity costs.</td>
</tr>
</tbody>
</table>
9. References


Nosherwan, A., Murphy, A. M., Sasaki, E., Martin, C., Quinn, S., Harty, S., et al. (2010). Is rotavirus gastroenteritis a more severe illness in patients of non-Irish ancestry? Archives of Disease in Childhood, Conference: Royal College of Paediatrics and
Rotavirus Vaccine Assessment Report 2012

Child Health Annual Conference, RCPCH 2010 Coventry United Kingdom.


10. Appendix 1: Immunisation Programme

The government subsidises a number of free immunisations through the National Immunisation Schedule, which is a mix of universal programmes (everyone of a particular age is eligible) and targeted programmes (only people with certain conditions are eligible). The largest component is the annual influenza immunisation programme targeted at adults over 65 and people with conditions that put them at risk from influenza. The most familiar component is the series of childhood immunisations to protect babies from infectious diseases like diphtheria, whooping cough, measles, and polio. There are also immunisations delivered in schools to Year 7 and 8 students. One of the six health targets is for 95% of 2-year olds to be fully immunised by July 2012.

Generally, the Ministry of Health purchases vaccines, while the District Health Boards (DHBs) are responsible for funding and planning how they get delivered to their communities. Most immunisations are given at general practices that are paid a fixed fee by DHBs for each immunisation visit. But immunisations are also given by special outreach services, public health units, in hospitals, and in some workplaces. Many immunisations are now recorded on the National Immunisation Register, which allows very accurate monitoring of immunisation coverage and also helps providers identify children and families who may have missed out.

The Immunisation Team oversees the whole immunisation system and specifically carries out these functions:

1. recommending to the government which vaccines should be free and for whom
2. purchasing and ordering vaccines worth around $50 million per year
3. communicating with providers and the public about immunisation programmes
4. servicing three advisory groups: the Immunisation Technical Forum, the Immunisation DHB Forum, and the Immunisation Coverage Forum
5. business owner of the National Immunisation Register
6. using data from the National Immunisation Register to identify the demographic, geographic, or programme factors that influence immunisation rates
7. project managing specific programmes like the annual influenza programme and the new human papillomavirus vaccine programme to prevent cervical cancer
8. publishing the Immunisation Handbook
9. managing contracts to deliver some national immunisation services
10. liaising with District Health Boards to share good practice and monitor progress towards the health target

11. Appendix 2: HTA repositories searched
Search term: Rotavirus

Listed below are the various HTA agencies/repositories that were searched.

Agency for Healthcare Research and Quality

*No HTA found

Adelaide Health Technology Assessment

*No HTA found

Australia and New Zealand Horizon Scanning Network – Technologies Assessed

*No HTA found

MSAC

*No HTA found

Danish Centre for Evaluation and Health Technology Assessment

*No HTA found

Belgian Health Care Knowledge Centre

Cost-effectiveness analysis of rotavirus vaccination of Belgian infants

Institute of Health Economics

Economics of Childhood Immunizations in Canada: Data Book (Rotavirus is a core component)
Ontario Health Technology Advisory Committee

*No HTA found

National Coordinating Centre for Health Technology Assessment

*No HTA found

Quality Improvement Scotland

*No HTA found

National Horizon Scanning Centre

*No HTA found

VA Technology Assessment

*No HTA found

California Health Technology Assessment

*No HTA found

Washington Health Technology Assessment

*No HTA found

Ludwig Boltzmann Institut für Health Technology Assessment

*No HTA found

Haute Autorité de Santé

*No HTA found

Norwegian Knowledge Centre for the Health Services
Cost-effectiveness of childhood vaccination against rotavirus in Norway

http://www.nokc.no/Publikasjoner/Kostnadseffektivitet+av+rotavirus+i+det+norske+barnevaksinasjonsprogrammet.8170.cms?language=english

Swedish Council on Technology Assessment in Health Care

*No HTA found

Catalan Agency for Health Technology Assessment and Research

*No English HTA found

Blue Cross Technology Evaluation Centre

*No HTA found

AETMIS

*No HTA found

McGill Technology Assessment Unit

*No HTA found

MONASH Center for Clinical Effectiveness

*No HTA found

Centre for Reviews and Dissemination

*Nothing found that wasn't already noted above.
12. Appendix 3: Search strategies

Search strategy for EMBASE – English Only

Search Conducted on 11-November-2011
Database: Embase <1996 to 2011 Week 44>
Search Strategy:

1 rotavirus.mp. (7409)
2 exp Rotavirus/ (5262)
3 exp Rotavirus Infections/ (639)
4 1 or 2 or 3 (7409)
5 exp Rotavirus Vaccines/ (2227)
6 exp Vaccines/ (132049)
7 exp Vaccines/ (132049)
8 5 or 6 or 7 (132049)
9 4 and 8 (2639)
10 rotateq.mp. (538)
11 "Rix 4414".mp. (57)
12 "WC-3".mp. (14)
13 rotarix.mp. (549)
14 10 or 11 or 12 or 13 (704)
15 9 or 14 (2652)
16 limit 15 to (meta analysis or "systematic review") (33)
17 exp United States/ or exp Europe/ or exp Canada/ or exp Australia/ or exp New Zealand/ or New Zealand.cp. (1203150)
18 15 and 17 (618)
19 16 or 18 (645)
20 limit 19 to (english language and yr="2009 -Current") (237)

Search strategy for EMBASE – Non-English Only

Search of Embase conducted on 11-November-2011
Database: Embase <1996 to 2011 Week 44>
Search Strategy:

1 rotavirus.mp. (7409)
2 exp Rotavirus/ (5262)
3 exp Rotavirus Infections/ (639)
4 1 or 2 or 3 (7409)
Search strategy for Ovid MEDLINE® - English Only

Searches Completed on 28-October-2011
Database: Ovid MEDLINE(R) <1948 to October Week 3 2011>
Search Strategy:

--------------------------------------------------------------------------------
1     rotavirus.mp. (9930)
2     exp rotavirus/ (6416)
3     exp rotavirus infections/ (5163)
4     1 or 2 or 3 (9930)
5     exp rotavirus vaccines/ (946)
6     exp vaccines/ (154421)
7     vaccin*.mp. (228309)
8     5 or 6 or 7 (232634)
9     4 and 8 (2506)
10    rotarix.mp. (110)
11    rotateq.mp. (162)
12    ("rix4414" or rix4414).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (109)
13    "wc-3".mp. (11)

5     exp Rotavirus Vaccines/ (2227)
6     exp Vaccines/ (132049)
7     exp Vaccines/ (132049)
8     5 or 6 or 7 (132049)
9     4 and 8 (2639)
10    rotateq.mp. (538)
11    "Rix 4414".mp. (57)
12    "WC-3".mp. (14)
13    rotarix.mp. (549)
14    10 or 11 or 12 or 13 (704)
15    9 or 14 (2652)
16    limit 15 to (meta analysis or "systematic review") (33)
17    exp United States/ or exp Europe/ or exp Canada/ or exp Australia/ or exp New Zealand/ or New Zealand.cp. (1203150)
18    15 and 17 (618)
19    16 or 18 (645)
20    limit 19 to yr="2009 -Current" (261)
21    limit 19 to english language (559)
22    20 not 21 (24)
14 10 or 11 or 12 or 13 (260)
15 9 or 14 (2515)
16 limit 15 to meta analysis (9)
17 15 and systematic review*.mp. (9)
18 exp United States/ or exp Europe/ or exp Canada/ or exp Australia/ or exp New Zealand/ or New Zealand.cp. (2187652)
19 15 and (16 or 17 or 18) (589)
20 limit 19 to (english language and yr="2009 -Current") (184)

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**Cochrane Library**

#1 (rotavirus).ti,ab,kw 427
#2 MeSH descriptor Rotavirus explode all trees 184
#3 MeSH descriptor Rotavirus Infections explode all trees 247
#4 (#1 OR #2 OR #3) 427 edit delete
#5 MeSH descriptor Rotavirus Vaccines explode all trees 166
#6 MeSH descriptor Vaccines explode all trees 6435
#7 (vaccin*).ti,ab,kw 9563
#8 (#5 OR #6 OR #7) 9598
#9 (#4 AND #8) 265
#10 (rotarix).ti,ab,kw or (rotateq).ti,ab,kw or "rix 4414":ti,ab,kw or "wc-3":ti,ab,kw
#11 (#9 OR #10) 265
#12 (#11), from 2009 to 2011 60

*studies that fell outside the geographic parameters noted in the Medline search strategy were manually culled.

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**Search strategy for Ovid MEDLINE ® - Non-English Only**

Search Run 28 October 2011

Database: Ovid MEDLINE(R) <1948 to October Week 3 2011>

Search Strategy:

1 rotavirus.mp. (9930)
2 exp rotavirus/ (6416)
3 exp rotavirus infections/ (5163)
4 1 or 2 or 3 (9930)
5 exp rotavirus vaccines/ (946)
6 exp vaccines/ (154421)
7 vaccin*.mp. (228309)
8 5 or 6 or 7 (232634)
9 4 and 8 (2506)
10 rotarix.mp. (110)
11 rotateq.mp. (162)
12 ("rix4414" or rix4414).mp. (109)
13 "wc-3".mp. (11)
14 10 or 11 or 12 or 13 (260)
15 9 or 14 (2515)
16 limit 15 to meta analysis (9)
17 15 and systematic review*.mp. (9)
18 exp United States/ or exp Europe/ or exp Canada/ or exp Australia/ or exp New Zealand/ or New Zealand.cp. (2187652)
19 15 and (16 or 17 or 18) (589)
20 limit 19 to yr="2009 -Current" (196)
21 limit 19 to english language (530)
22 20 not 21 (12)

***************
12.1. National Health Committee (NHC) and Executive
The National Health Committee (NHC) is an independent statutory body which provides advice to the New Zealand Minister of Health. It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and health sector with greater value for the money invested in health. The NHC Executive is the secretariat that supports the Committee. The NHC Executive’s primary objective is to provide the Committee with sufficient information for them to make recommendations regarding prioritisation and reprioritisation of interventions. They do this through a range of evidence-based reports tailored to the nature of the decision required and time-frame within which decisions need to be made.


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