

# Rotavirus vaccines (Rotarix and RotaTeq) for prevention of rotavirus gastroenteritis

## Summary

- Two oral rotavirus vaccines (Rotarix and RotaTeq) are listed on the National Immunisation Program to prevent rotavirus gastroenteritis in infants and children.
- State immunisation co-ordinators will decide which of the two vaccines to supply on the basis of tender arrangement with different manufacturers.
- Oral rotavirus vaccination protects most young children against severe dehydrating rotavirus gastroenteritis that most commonly occurs between 3 and 35 months of age. It does not provide lifetime protection.
- Rotarix is a live, monovalent, human attenuated vaccine given in 2 doses (one course) at 2 and 4 months of age. RotaTeq is a live, pentavalent, human–bovine reassortant vaccine given in 3 doses (one course) at 2, 4 and 6 months of age.
- Oral rotavirus vaccines can be given at the same time as other routine childhood vaccines.
- Both vaccines demonstrate similarly high levels of protection against severe rotavirus gastroenteritis. In clinical trials vaccination reduced the rate of severe rotavirus gastroenteritis by 85% to 98%, and the rate of hospitalisation for gastroenteritis of any cause by 42% to 59%.<sup>1,2</sup>
- Safety and efficacy of either vaccine has not been established in infants under 6 weeks of age.
- Rotarix and RotaTeq are not interchangeable. Infants who receive a first dose of either vaccine should complete the entire course of vaccination using the same oral rotavirus vaccine.
- There is no evidence that one oral rotavirus vaccine is more effective than the other.

## NIP listing

Rotarix and RotaTeq are available on the National Immunisation Program (NIP) for vaccination of all infants to prevent rotavirus gastroenteritis.

## Reason for NIP listing

RotaTeq was listed on the basis of acceptable cost-effectiveness compared with standard medical management without rotavirus vaccination.<sup>3</sup> The Pharmaceutical Benefits Advisory Committee accepted that RotaTeq and Rotarix were similar in terms of efficacy and safety, and recommended listing Rotarix on the basis that Rotarix was no less effective than RotaTeq, and at a similar cost (cost minimisation).<sup>4</sup>

The PBAC has recently become responsible for making recommendations for funding of vaccines under the NIP. Previously, the Australian Technical Advisory Group on Immunisation (ATAGI) fulfilled this role. ATAGI will continue to provide technical advice about vaccines to the PBAC and the Minister for Health and Ageing.

However, the process for listing vaccines on the NIP now mirrors the process for medicines, with a company seeking listing making a submission to the PBAC, who consider the cost-effectiveness of the new vaccine and make a recommendation to the Minister.

ATAGI also produces the *Australian Immunisation Handbook*. The 9th edition is expected to be published in 2007.

## Place in therapy

Clinical trials have shown that both Rotarix and RotaTeq are highly effective in preventing severe rotavirus gastroenteritis and reducing hospitalisations due to rotavirus gastroenteritis in children.<sup>1,2</sup>

### Rotavirus causes severe dehydrating gastroenteritis

Rotavirus is the most common cause of severe gastroenteritis in infants and children under the age of 5 years.<sup>5,6</sup> A highly contagious non-enveloped RNA virus, rotavirus is mainly transmitted from person to person, and through fomites via the faecal–oral route.<sup>7</sup> Viral shedding in the stools of infected patients often begins before symptoms develop<sup>8</sup> and may continue for more than 25 days in infants with severe disease.<sup>9</sup> Severe dehydrating gastroenteritis occurs more commonly in first infection, particularly in infants 3–35 months of age.<sup>10</sup>

### Rotavirus is a common cause of child hospital admissions

Rotavirus-related disease accounts for 50% of all hospital admissions for diarrhoea in children under 5 years<sup>11</sup>, with an estimated 10,000 children in this age group admitted with rotavirus gastroenteritis annually.<sup>11</sup> Most cases requiring hospitalisation (43.7%) occur in the first year of life.<sup>13</sup> Rotavirus is also responsible for an estimated 22,000 emergency department visits and 115,000 general practitioner visits in children under 5 years.<sup>11</sup> The financial cost of childhood rotavirus-related illness to the Australian health care system is estimated at \$30 million each year.<sup>11</sup>

Rotavirus hospitalisation rates vary across Australia. The highest rates are in the Northern Territory (149 per 100,000), where the percentage of cases for infants aged 2–11 months is twice the national average.<sup>14</sup> Vaccination may be particularly beneficial for Indigenous children, who are infected at a younger age<sup>15</sup> and whose average annual rate of hospitalisation for rotavirus gastroenteritis is more than 4 times that of non-Indigenous children under 12 months of age.<sup>14</sup>

### Preventing hospital-acquired infection

A secondary goal of vaccination is the prevention of nosocomial rotavirus infection. Rotavirus is recognised as a major aetiological factor in paediatric nosocomial diarrhoea<sup>16</sup>, with an estimated 25% of all rotavirus hospitalisations attributed to infections acquired while children are in hospital.<sup>17</sup> A prospective study of paediatric nosocomial infection in an Adelaide hospital found that 14% of children (31 of 220) under 3 years admitted without gastroenteritis acquired rotavirus while in hospital and that hospitalisation was prolonged in this population (11 days versus 8 days,  $p < 0.05$ ).<sup>18</sup>

### Rotavirus vaccination reduces the severity of infections

While previous naturally acquired rotavirus infection does not confer immunity, it does reduce the severity of subsequent infections.<sup>19–21</sup> Based on this observation it was anticipated that rotavirus vaccines would require at least 2 doses to induce sufficient cumulative immunity to prevent moderate to severe infection most commonly associated with first infection.<sup>21</sup> ‘Catch-up’ immunisation and immunisation of older infants is not recommended for safety reasons (see Safety issues) and because natural immunity gained over time negates the benefits of vaccination in this population.

### Rotavirus vaccines are effective in preventing rotavirus gastroenteritis

The efficacy of Rotarix and RotaTeq in preventing rotavirus gastroenteritis has been established in two large-scale clinical trials. The two key trials of Rotarix<sup>2</sup> and RotaTeq<sup>1</sup> (see Table 1) were conducted in different geographical settings and employed different clinical criteria to assess rotavirus gastroenteritis and severity. The observed differences in point estimates of efficacy may be due to non-comparable study populations and classifications of disease severity used, preventing any conclusions regarding the comparative efficacy of these products.

### Rotarix and RotaTeq are effective against common circulating rotavirus strains

RotaTeq is a live, reassortant, pentavalent human–bovine rotavirus vaccine containing 5 rotavirus reassortants: G1, G2, G3, G4 and P[8] derived from human and

bovine viral species.<sup>22</sup> Rotarix is a live, monovalent, human attenuated rotavirus vaccine derived from the most common human rotavirus strain G1P[8].<sup>23</sup>

RotaTeq significantly reduced the number of hospitalisations and emergency department visits for rotavirus gastroenteritis caused by individual serotypes G1, G3, G4 and G9 in the REST study.<sup>1,22</sup> Efficacy of Rotarix was demonstrated against severe rotavirus gastroenteritis caused by serotypes G1, G3, G4 and G9.<sup>2</sup>

There are some data for the efficacy of both vaccines against G2 rotavirus; however, protection may be less than with other strains.\* On re-analysis of the REST study, efficacy of RotaTeq was demonstrated against hospitalisation and emergency department visits for G2 rotavirus (92% [95% CI 35% to 99%]).<sup>24</sup> For Rotarix, pooled analysis of four studies demonstrated efficacy of Rotarix against severe rotavirus gastroenteritis caused by G2 (71% [95% CI 20% to 91%]).<sup>23</sup>

Substantial geographical variation exists from year to year in the prevalence of rotavirus strains across Australia.<sup>13,25–29</sup> The changing pattern of prevailing rotavirus serotypes may affect the efficacy of rotavirus vaccines over time. The efficacy of current rotavirus vaccines has not been sufficiently established against emerging rotavirus strains such as G12.<sup>13</sup>

### Protection for more than 2 rotavirus seasons has not been established

Protective efficacy of RotaTeq and Rotarix has been demonstrated through two full rotavirus seasons.<sup>1,2,30</sup> During the first and second rotavirus seasons Rotarix provided 90% efficacy (95% CI 10% to 100%) and 83% efficacy (95% CI 7% to 98%), respectively, against severe rotavirus gastroenteritis.<sup>30</sup> RotaTeq demonstrated an efficacy of 98% (95% CI 88% to 100%) against severe rotavirus gastroenteritis during the first season and 88% (95% CI 49% to 99%) efficacy through a second rotavirus season.<sup>1</sup>

### Rotavirus vaccines can be given with routine childhood vaccines

Rotarix and RotaTeq can be given with any of the following routine childhood vaccines:<sup>22,23</sup>

- diphtheria–tetanus–acellular pertussis vaccine (DTPa)
- *Haemophilus influenzae* type b vaccine (Hib)
- inactivated polio vaccine (IPV)
- hepatitis B vaccine
- pneumococcal vaccine.

\* The uncertainty is because in these trials very few infections were caused by serotypes other than G1 and this is reflected in the wide confidence intervals.

**Table 1: Summary of key findings of large-scale rotavirus vaccine trials**

Rotavirus vaccine	Study population	Protection against severe rotavirus gastroenteritis	Protection against any rotavirus gastroenteritis	Reduction in rate of rotavirus-associated hospitalisation	Reduction in rate of hospitalisation for severe gastroenteritis of any cause
<b>Rotarix</b> Rota-023 <sup>2</sup>	63,225 healthy infants from Latin America and Finland	85% (95% CI 72% to 92%)* from 2 weeks after dose 2 until 1 year of age	Not included	85% (95% CI 70% to 94%)* from 2 weeks after dose 2 until 1 year of age	42% (95% CI 29% to 53%) from 2 weeks after dose 2 until 1 year of age
<b>Rotarix</b> Rota-036 <sup>23</sup>	3994 healthy infants from Europe	96% (95% CI 90% to 99%) from 2 weeks after dose 2 until 1 year of age	87% (95% CI 80% to 92%) from 2 weeks after dose 2 until 1 year of age	100% (95% CI 82% to 100%) from 2 weeks after dose 2 until 1 year of age	Not included
<b>RotaTeq</b> Rotavirus Safety and Efficacy Trial (REST) <sup>1</sup>	68,038 healthy infants from 11 countries, including the USA and Finland	98% (95% CI 88% to 100%) <sup>†</sup> from 2 weeks after dose 3 through first full rotavirus season	74% (95% CI 67% to 80%) <sup>†</sup> from 2 weeks after dose 3 through first full rotavirus season	96% (95% CI 91% to 98%) <sup>‡</sup> from 2 weeks after dose 3 for up to 2 years	59% (95% CI 52% to 65%) <sup>‡</sup> after dose 1 for up to 2 years

\*Efficacy cohort (n = 17,867); <sup>†</sup>Clinical efficacy substudy (n = 4512); <sup>‡</sup>Effectiveness cohort (n = 57,134)

Rotarix can also be given with meningococcal serogroup C vaccine.<sup>23</sup> Co-administration of RotaTeq with meningococcal serogroup C vaccine is not currently included in the RotaTeq product information.<sup>22</sup> Studies have shown that immune responses and safety profiles of co-administered vaccines were unaffected. Administration of rotavirus vaccine, or placebo, with routine childhood vaccines was associated with a comparable adverse-reaction profile.<sup>22,23</sup>

### Safety and efficacy in premature infants

Rotarix was well tolerated in premature infants (29–36 weeks' gestation) but data regarding its efficacy in this population are currently unavailable.<sup>23</sup> RotaTeq can be given to premature infants (25–36 weeks' gestation) according to chronological age.<sup>22</sup> Vaccination of older infants and children is not recommended.

### Safety issues

Both Rotarix and RotaTeq were generally well tolerated in clinical trials. No serious adverse events occurred compared with placebo in two, large phase III clinical trials involving about 130,000 infants.

### Vaccine side effects

Very common adverse effects of RotaTeq ( $\geq 10\%$ ) reported by parents within the first week after the first dose included diarrhoea (18% of vaccine recipients versus 15% of placebo recipients), vomiting (10% versus 8%) and pyrexia (21% versus 19%).<sup>22</sup>

Adverse reactions reported with a higher incidence in Rotarix recipients than placebo recipients included irritability (46% versus 42%), loss of appetite (16% versus 12%), diarrhoea (5% versus 3%), flatulence (2% versus 0.8%) and fever (9% versus 7%).<sup>23</sup>

### Risk of intussusception

A previous live rotavirus vaccine, Rotashield, was voluntarily withdrawn in the US in 1999 less than 12 months after licensing because of an association with intussusception (a rare\* but potentially fatal condition) among otherwise healthy infants.<sup>31–34</sup> There is evidence that the risk of vaccine-related intussusception was age

related, with most cases (80%) in half the infants receiving their first dose of vaccine after 3 months of age.<sup>33,35</sup>

The incidence of naturally occurring intussusception increases with age and peaks around 6 months of age.<sup>36</sup> The first dose of Rotarix should be given between 6 and 14 weeks of age, and the first dose of RotaTeq between 6 and 12 weeks of age, when the background incidence of naturally occurring intussusception is low.<sup>22,23,33,36</sup> The final dose of Rotarix and RotaTeq should be given by 24 weeks and 32 weeks of age, respectively, to minimise the overlap with naturally occurring intussusception.<sup>22,23,36</sup>

The possibility of an excess risk of intussusception with either vaccine cannot be completely ruled out until the vaccines are used in larger numbers of infants.<sup>35</sup> Recent postmarketing surveillance data from the US do not suggest to date an association between RotaTeq and intussusception.<sup>37</sup>

### Immunocompromised infants

The safety and efficacy of Rotarix and RotaTeq have not been established in immunocompromised infants, including infants with HIV.

### Contraindications to rotavirus vaccination

- Known or suspected hypersensitivity to any components of the vaccine.<sup>22,23,38</sup>
- History of chronic gastrointestinal disease that increases susceptibility to developing intussusception.<sup>23</sup>
- As with other vaccines, rotavirus vaccination should be postponed in acute febrile illness.<sup>22,23</sup>

### Use with caution

Consider potential risks and benefits in administering rotavirus vaccines in the following contexts.<sup>22,23,38</sup>

- History of gastrointestinal disease: the efficacy and safety of rotavirus vaccine has not been established in infants with pre-existing and/or active gastrointestinal illnesses. Pre-existing chronic gastrointestinal disease, which does not increase susceptibility to intussusception, is not a contraindication to vaccination. Postpone vaccination in children with moderate to severe diarrhoea or vomiting.

\* Average annual incidence 10.1 per 100,000 infants in Australia under 1 year, 1994–2000.<sup>36</sup>

- Infants with known or suspected primary or secondary immunodeficiency states, including those with HIV.
- Immunocompromised contacts: viral shedding in stools, particularly after the first vaccine, could pose a risk of transmission of virus to close contacts. Advise contacts to observe good hygiene practices (washing hands regularly, especially after changing nappies).
- The interval between receipt of blood products and vaccination should be as long as possible, but rotavirus vaccines should not be delayed beyond the upper age limits for dosing.

Report suspected adverse events after immunisation to the relevant health authority in Australian Capital Territory, New South Wales, the Northern Territory, Queensland, South Australia and Western Australia. In Victoria and Tasmania suspected adverse reactions should be reported to the Adverse Drug Reactions Advisory Committee (ADRAC) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

For more information on reporting of adverse events following immunisation, see the Immunise Australia Program website ([www.immunise.health.gov.au](http://www.immunise.health.gov.au)).

## Dosing issues

Rotarix and RotaTeq are for oral use only. **Never inject either vaccine.** For practical aspects of administration see Table 2.

## Administration

Administer the liquid to the inside of the cheek. Replacement of partially lost doses due to spitting or regurgitation is not advised because the safety of administering higher than the recommended dose of rotavirus vaccines has not been established. The efficacy of a partially administered dose is unknown.<sup>38</sup> Feeding restrictions after administration are not necessary. For infants who inadvertently received the first dose of either vaccine later than the recommended cut-off age, complete vaccination as per the schedule, as long as minimum dose intervals can be maintained and the full vaccination course can be completed within the recommended upper age limit.<sup>10,38</sup>

## Information for patients

Advise parents and/or carers of the following.<sup>22,23,38</sup>

- Children who receive rotavirus vaccination are less likely to develop severe rotavirus-associated gastroenteritis and are less likely to be hospitalised or require medical attention for gastroenteritis.<sup>22,23</sup>

**Table 2: Practical aspects of rotavirus vaccination<sup>22,23,38</sup>**

Rotavirus vaccine	Vaccine presentation	Course	First dose administered	Age for routine doses	Minimum dose intervals
<b>Rotarix</b> (oral administration only)	White powder in glass vial requiring reconstitution with diluent in glass pre-filled syringe (for oral use only)	2 doses. Complete vaccine course by 24 weeks of age	6–14 weeks	2 and 4 months	4 weeks
<b>RotaTeq</b> (oral administration only)	Ready-to-use liquid oral doses, available as single pre-filled 2 mL unit doses in plastic dosing tube with twist-off cap	3 doses. Complete vaccine course by 32 weeks of age	6–12 weeks	2, 4 and 6 months	4 weeks

- Vaccination against rotavirus provides most infants with protection against severe dehydrating gastroenteritis during the time at which they are most at risk. It does not provide lifetime protection.<sup>22,23</sup>
- Like most vaccines, rotavirus vaccines do not provide complete protection. Gastroenteritis due to rotavirus and other infections may still occur. Gastroenteritis may result from rotavirus infection or other infectious or non-infectious causes.<sup>22,23</sup> Advise parents to seek medical treatment for their child if they develop gastroenteritis and/or any signs of mild to moderate dehydration, including:<sup>39</sup>
  - restlessness or irritability (sleepiness/listlessness, in severe dehydration)
  - sunken eyes
  - thirst and drinking eagerly (drinking poorly or not at all, in severe dehydration).
- Maintain good hygiene practices — handwashing regularly and after nappy changes, especially in households where there is an immunocompromised contact.
- Report any adverse effects of vaccination. Contact their doctor immediately if the infant shows any signs or symptoms of atypical gastrointestinal upset.
- Rotavirus vaccines are not interchangeable. Infants who receive a first dose of either vaccine should complete the entire course of vaccination using the same rotavirus vaccine. Therefore, if a family moves to a State with a different vaccine they may need to pay for the remaining dose(s) of the original vaccine. Advise parents of different number of doses per course for different vaccines.

Suggest or provide the Rotarix or RotaTeq consumer medicine information (CMI) leaflet (available at [www.nps.org.au/consumers](http://www.nps.org.au/consumers)).

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.