

## Rotavirus

### ROTAVIRUS VACCINES FOR AUSTRALIAN CHILDREN: INFORMATION FOR IMMUNISATION PROVIDERS

#### Disease and epidemiology

- Rotavirus is the most common cause of acute severe gastroenteritis in children <5 years of age.
- Before the introduction of rotavirus vaccination, there were approximately 500,000 deaths due to rotavirus each year, predominantly in developing countries.
- Before the introduction of rotavirus vaccine to the National Immunisation Program, there were approximately 10,000 hospitalisations and 22,000 Emergency Department visits due to rotavirus in children <5 years of age in Australia each year. This represented approximately half of all the hospitalised cases of acute gastroenteritis in children this age group.
- Since the introduction of rotavirus vaccines in Australia, there has been a 60–70% decline in rotavirus hospitalisations in children <5 years of age. This represents approximately 7,000 children who have avoided hospitalisation for gastroenteritis each year.

#### Who should be vaccinated

- Rotavirus vaccines are recommended and funded under the National Immunisation Program (NIP) for routine immunisation of Australian infants in the first year of life, in either a 2- or 3-dose course starting from around 2 months of age.
- Immunisation of older infants, children and adults is not recommended.

#### Vaccines

- Two oral live attenuated rotavirus vaccines are available in Australia. They are Rotarix<sup>®</sup>, a human monovalent vaccine (given in a 2-dose schedule at 2 and 4 months of age), and RotaTeq<sup>®</sup>, a pentavalent human bovine reassortant vaccine (given in a 3-dose schedule at 2, 4 and 6 months of age).
- Rotavirus vaccines first became available in early 2006, and were added to the NIP across Australia from 1 July 2007.
- Upper limits on the recommended age of administration of rotavirus vaccines are in place; be sure to check the infant's age prior to immunisation.

#### The disease

Rotavirus is an RNA virus that has a characteristic wheel-like appearance when viewed by electron microscopy (the name rotavirus is derived from the Latin *rota*, meaning 'wheel'). An Australian researcher, Professor Ruth

Bishop, and colleagues originally described rotaviruses as the cause of infant gastroenteritis in 1973.<sup>1</sup> There are a number of different strains of rotavirus, classified by the 'G' and 'P' outer proteins on the virus. Five strains (G1,

G2, G3, G4 and G9) have accounted for around 90% of the serotypes seen worldwide and in Australia.<sup>2</sup>

Rotaviruses are transmitted by the faecal–oral route. Large numbers of viral particles are shed in faecal matter and the virus is quite stable in the environment, so contamination of hands and objects (fomites) is relatively easy. These routes of transmission are common in day-care centres, family homes and aged care facilities. In addition, virus excretion can occur in individuals without symptoms.<sup>2</sup>

Children can be infected with rotavirus several times during their lives. The spectrum of illness ranges from mild, watery diarrhoea of limited duration to severe dehydrating diarrhoea with vomiting and fever, which can result in death. The clinical features of rotavirus gastroenteritis are non-specific, so diagnosis can only be confirmed by laboratory testing of faecal specimens. Infections occurring in the first few months of life are generally asymptomatic.<sup>3</sup>

## Epidemiology

Rotavirus is the leading cause of severe acute gastroenteritis in infants and young children. Rotavirus is found in all countries, and almost every child in the world will suffer at least one infection by the time they are 3 years of age. Prior to the introduction of rotavirus vaccines worldwide, an estimated 450,000 children worldwide died each year from rotavirus gastroenteritis, most of whom lived in developing countries.<sup>4</sup> Worldwide, rotavirus causes nearly 2 million hospitalisations each year.<sup>5</sup>

The peak incidence of severe rotavirus disease in Australia is between 6 and 24 months of age,<sup>2</sup> but disease peaks at an earlier age in Aboriginal and Torres Strait Islander children, particularly those in the Northern Territory.

In Australia, it was estimated that prior to vaccine introduction, there were approximately 10,000 hospitalisations due to rotavirus in children <5 years of age each year, with rotavirus accounting for around half the hospitalisations for any acute gastroenteritis in this age group.<sup>6,7</sup> This translated to about 4% of children (1 in 27) being hospitalised with rotavirus gastroenteritis by the age of 5 years. In addition, an estimated 115,000 children <5 years of age visited a GP, and 22,000 children required an Emergency Department visit for rotavirus.<sup>6,8</sup> On average, there was one death recorded as being due to rotavirus each year in Australia.<sup>8</sup> Overall, Indigenous Australian infants and children were hospitalised with

rotavirus gastroenteritis about 3–5 times more commonly than their non-Indigenous peers.<sup>9-11</sup>

Rotavirus infections follow a seasonal pattern in temperate Australia with peak incidence in mid to late winter. However, in the northern tropical and arid regions of Australia, there is no consistent seasonal pattern and disease peaks are unpredictable.<sup>10</sup>

Following the introduction of rotavirus vaccination to the National Immunisation Program (NIP) in 2007, there has been a marked decline in hospitalisations for rotavirus and laboratory confirmed rotavirus gastroenteritis (see '[Vaccine efficacy/effectiveness](#)' below).<sup>12-15</sup>

## Who should be vaccinated

### National Immunisation Program (NIP)

Two rotavirus vaccines became available in Australia on the private market in May 2006. Rotavirus vaccination commenced for all infants in the Northern Territory in October 2006, and in the remaining states and territories from 1 July 2007 under the NIP.

Rotavirus vaccines are only recommended for use in young infants. The vaccines are given at either 2 and 4 months of age (Rotarix<sup>®</sup>, 2-dose schedule) or at 2, 4 and 6 months of age (RotaTeq<sup>®</sup>, 3-dose schedule); see more detail in '[Vaccines, Administration](#)' below. Immunisation providers should consult their state or territory health department for details of the program in their locality, as the vaccine in use varies. At the time of writing, Rotarix<sup>®</sup> was used in the Northern Territory, New South Wales, Tasmania and the Australian Capital Territory. RotaTeq<sup>®</sup> was used in Victoria, South Australia, Queensland and Western Australia.

### Others

Use of rotavirus vaccine in older children and adults is not recommended (see '[Other considerations](#)' below). Unlike other routine childhood vaccines, there are upper age limits on the administration of rotavirus vaccines (see '[Vaccines, Administration](#)' below). In addition, most older children and adults will have partial immunity to rotavirus disease because of previous infection (or immunisation) at a younger age (see '[Other considerations](#)' below).

## Vaccines

The two oral rotavirus vaccines available are Rotarix<sup>®</sup> (GlaxoSmithKline) and RotaTeq<sup>®</sup> (bioCSL/Merck & Co Inc). There are differences in the composition and number of doses required of each vaccine. Rotarix<sup>®</sup> vaccine contains a single, attenuated human rotavirus of serotype

G1P1A[8]. RotaTeq<sup>®</sup> is a human–bovine reassortant vaccine containing five vaccine viruses (types G1, G2, G3, G4 and P1A[8]).

### Administration

Rotavirus vaccines are administered orally at the same time as the other vaccines on the childhood immunisation schedule. The interval separating the doses should be no less than 4 weeks.<sup>16,17</sup> The ages of administration for

which the rotavirus vaccines are registered for use in Australia are shown in the [table](#) below.<sup>18</sup> It is important for immunisation providers and parents to note that, unlike other NIP vaccines, there are *upper* limits for the administration of both the 1st and final doses of rotavirus vaccines. If the 1st dose of rotavirus vaccine is not provided by the specified age, the vaccine course should not be started.

### Recommended upper age limits for administration of oral rotavirus vaccines\*

	Doses	Age of routine oral administration	Recommended age limits for dosing			Minimum interval between doses
			1st dose	2nd dose	3rd dose	
Rotarix <sup>®</sup> (GlaxoSmithKline)	2 oral doses (1.5 mL/dose)	2 and 4 months	6–14* weeks	10–24* weeks	None	4 weeks
RotaTeq <sup>®</sup> (bioCSL /Merck & Co Inc)	3 oral doses (2 mL/dose)	2, 4 and 6 months	6–12 <sup>†</sup> weeks	10–32 <sup>†</sup> weeks	14–32 <sup>†</sup> weeks	4 weeks

\* The upper age limit for receipt of the 1st dose of Rotarix<sup>®</sup> is immediately prior to turning 15 weeks old, and the upper age limit for receipt of the 2nd dose is immediately prior to turning 25 weeks old.

† The upper age limit for receipt of the 1st dose of RotaTeq<sup>®</sup> is immediately prior to turning 13 weeks old. The 2nd dose of vaccine should preferably be given by 28 weeks of age to allow for a minimum interval of 4 weeks before receipt of the 3rd dose. The upper age limit for the 3rd dose is immediately prior to turning 33 weeks old. For infants presenting for their 2nd dose after reaching 29 weeks of age, a 2nd and final dose can be given, provided the upper age limit of 32 weeks (immediately prior to turning 33 weeks old) has not been reached.

### Vaccine efficacy/effectiveness

Both rotavirus vaccines have been shown to have similar efficacy against rotavirus gastroenteritis (of any severity) of around 70%. The efficacy against severe rotavirus gastroenteritis is higher and ranged from 85% to 100% in clinical trials in many different countries.<sup>19-21</sup> Overall, the vaccines prevented around half (42–58%) of all hospital admissions for acute gastroenteritis of any cause in young children,<sup>19-21</sup> suggesting that rotavirus is responsible for a greater proportion of severe gastroenteritis than previously recognised.

Following the introduction of rotavirus vaccines in Australia, there has been a 64% decline in rotavirus-coded hospitalisations in children <3 years of age. There has also been a 39% decline in non-rotavirus-coded gastroenteritis hospitalisations for children in the same age group.<sup>13</sup> Overall, in children <5 years of age, an estimated 7,000 hospitalisations from rotavirus gastroenteritis have been prevented each year, compared to what would have been expected without vaccination.<sup>13</sup> A Queensland study reported a vaccine effectiveness for

RotaTeq<sup>®</sup> of 89.3% against rotavirus-coded hospitalisations in the first year of the program.<sup>22</sup>

### Vaccine safety

The rotavirus vaccines currently registered in Australia were evaluated in some of the largest and most stringent testing in clinical trials ever undertaken for any vaccine. This was, in part, because a previous rotavirus vaccine called RotaShield<sup>®</sup>, which was licensed in the United States in 1998, was withdrawn from the US market within 9 months because it was shown to be associated with an increased risk of intussusception (a rare form of bowel blockage that is most common in infants aged 4–10 months). For this reason, the clinical trials of Rotarix<sup>®</sup> and RotaTeq<sup>®</sup> limited the administration of the 1st and final doses of vaccine to infants.<sup>19,20</sup> However, as these trials did not test the vaccines in older infants, the current vaccines are not recommended for use in infants older than the age limits stated in the [table](#) above.

The current rotavirus vaccines (Rotarix<sup>®</sup> and RotaTeq<sup>®</sup>) differ in composition to RotaShield<sup>®</sup>. Clinical trials of these vaccines had enough participants to exclude an

increased risk of intussusception in vaccine recipients comparable in magnitude to that seen with RotaShield®.

Post-marketing monitoring of the safety of the two currently used rotavirus vaccines has been conducted in Australia, the United States and other countries. The first study from Australia suggested a small increased risk of intussusception in infants in the first week after the first vaccine dose (similar for both vaccine brands).<sup>23</sup> Subsequently, a larger nationwide study has shown a small increase in the risk of intussusception in the first week after the first dose and, to a lesser extent, the second dose of both rotavirus vaccines.<sup>24</sup> The increased risk of intussusception after rotavirus vaccination is estimated as approximately 6 additional cases of intussusception among every 100,000 infants vaccinated, or 14 additional cases per year in Australia.<sup>24</sup>

Intussusception is a rare condition (approximately 200 cases occurring annually in infants each year in Australia) and the cause is usually unknown. Prompt medical attention is needed if intussusception is suspected. It is important that immunisation providers and parents/carers are aware of the signs and symptoms of this condition. More information is available on both the Therapeutic Goods Administration (TGA) ([www.tga.gov.au/safety/alerts-medicine-rotavirus-130828.htm](http://www.tga.gov.au/safety/alerts-medicine-rotavirus-130828.htm)) and Immunise Australia ([www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-rotavirus](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-rotavirus)) websites.<sup>25,26</sup>

The overall benefits of preventing gastroenteritis from rotavirus are much greater than the small risk of intussusception. Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation (ATAGI) have recommended the continued use of rotavirus vaccine for infants under the NIP.

Vomiting and diarrhoea have not been noted as important adverse events in post-marketing surveillance of rotavirus vaccines. Vaccine recipients may have a 1–3% higher risk of developing diarrhoea or vomiting in the week after vaccine administration. The incidence of fever, irritability and other adverse events was similar in both vaccine and placebo recipients in clinical trials.<sup>18-20,27,28</sup>

## **Contraindications/precautions**

### **Contraindications**

Rotavirus vaccine should not be given to any infant who has hypersensitivity to any component of the vaccine or who has had an anaphylactic reaction to a previous dose of either rotavirus vaccine.

Rotavirus vaccine should not be given to any infant with a previous history of intussusception or a congenital abnormality that may predispose them to intussusception.<sup>18</sup>

Rotavirus vaccine should not be given to infants with severe combined immunodeficiency (SCID). Case reports indicate prolonged vaccine virus-associated gastrointestinal disease after rotavirus vaccination in infants with SCID.<sup>29,30</sup> As these infants are unlikely to generate a protective immune response to the vaccine, and because of the potential harm, rotavirus vaccines are contraindicated for infants with SCID.

As recommended for all vaccines, rotavirus vaccine should not be given during any moderate to severe febrile illness (see 'Precautions' below).<sup>16,17</sup>

### **Precautions**

Infants with an acute moderate to severe illness, including acute gastroenteritis, should not be vaccinated until their condition has improved. However, infants with mild gastroenteritis can be vaccinated.<sup>27,28</sup>

Infants with pre-existing chronic gastrointestinal conditions (such as congenital malabsorption syndrome, Hirschsprung's disease, short-gut syndrome) are at risk of more severe disease from rotavirus and so stand to benefit more from vaccination. However, neither safety nor efficacy of vaccination has been established for infants with such conditions. Providers should consider the potential risks and benefits of administering rotavirus vaccine to such infants.<sup>18,27,28</sup>

While rotavirus vaccination is not recommended for infants who are severely immunocompromised, the risk for infants with less severe immunocompromising conditions may be less than the risk of infection. This should be considered in the context of the infant's specific condition and with appropriate specialist advice.

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated.<sup>27,28</sup> Vaccine rotaviruses can be shed in the stool of vaccine recipients, particularly after the 1st dose. However, the protection of the immunocompromised household member afforded by vaccination of young children in the household outweighs the small risk for transmitting vaccine virus to the immunocompromised person and any subsequent theoretical risk for vaccine virus-associated disease.<sup>18,27,28</sup>

Hospitalised infants, including premature infants, who are otherwise clinically stable and at the appropriate chronological age, can be given rotavirus vaccines in the

hospital setting, particularly if delaying the dose would preclude completing the immunisation schedule on time.<sup>18,27,28</sup> Administration of oral rotavirus vaccines to hospitalised infants has not been studied in clinical trials. Limited data on the use of rotavirus vaccine in premature infants with ileostomies suggested that vaccination was well tolerated.<sup>31</sup> Both rotavirus vaccines are shed in the stool, particularly following the 1st dose. However, studies looking at horizontal transmission (i.e. person-to-person spread) have not been performed.

### Concomitant administration

Rotavirus vaccines can be co-administered with other vaccines on the NIP. Evidence from clinical trials suggests that co-administration of oral rotavirus vaccines is safe and does not interfere with the immune response to the other vaccine antigens. Although co-administration of rotavirus vaccines with BCG vaccine has not been assessed in clinical trials, there is unlikely to be any interference between the two vaccines and they can be co-administered at any time in relation to one another.

### Interchangeability

There are no studies that address the interchangeability of the two available rotavirus vaccines. Completion of a vaccination course should be with rotavirus vaccine from the same manufacturer whenever possible. In the situation where an infant moves to a state or territory where the different vaccine is funded, and has not completed the course of vaccination recommended in the state or territory they are leaving, the following approach is suggested. Because RotaTeq<sup>®</sup> is given in a 3-dose schedule, if either dose 1 or 2 of vaccine was given as RotaTeq<sup>®</sup>, a 3rd dose of either rotavirus vaccine should be given, provided that the upper age limit for that dose and the inter-vaccine interval (4 weeks between any doses) are met. Parents/providers can be counselled that, in the event that fewer doses than the recommended number have been administered, it is still likely that partial protection against rotavirus disease has been provided.

## Other considerations

### Why is catch-up immunisation or primary immunisation of older infants and children not suggested?

The three main reasons why catch-up immunisation or immunisation of older children is not considered appropriate are: (1) the concerns regarding intussusception (discussed in '[Vaccine safety](#)' above); (2) lack of data about the efficacy and safety of the vaccines in older infants or children; and (3) the main burden of rotavirus disease is in children <3 years of age. Older

children are usually protected from developing severe disease due to rotavirus because they have acquired partial immunity from being infected earlier in life.<sup>2,32</sup> Unlike other childhood diseases, such as measles and chickenpox, natural rotavirus infection doesn't offer lifetime protection, but provides protection from severe disease when subsequently exposed to the virus. Similarly, vaccination of adults is not recommended because it is likely that they may have partial pre-existing immunity and are unlikely to experience severe rotavirus disease.

### Advice to parents

Rotavirus causes about half of all episodes of hospitalised gastroenteritis in infants and young children. Rotavirus vaccine is the best way to protect children against rotavirus disease. Rotavirus vaccination provides similar protection to natural infection, but without causing disease along the way.<sup>2</sup> The vaccine will not prevent diarrhoea and vomiting caused by other infectious agents but is very good at preventing severe diarrhoea and vomiting caused by rotavirus. Both vaccines are about 70% protective against any rotavirus gastroenteritis, and between 85% and 100% effective in preventing severe rotavirus gastroenteritis. Children who receive the rotavirus vaccine are less likely to be hospitalised, visit the Emergency Department or see a doctor for gastroenteritis.<sup>19,20,27,28</sup>

The overall benefits of preventing gastroenteritis from rotavirus are much greater than the small risk of intussusception. Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation (ATAGI) have recommended the continued use of rotavirus vaccine for infants.<sup>25</sup>

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