

ATAGI Clinical advice to support the introduction of Rotarix® to replace RotaTeq® in specified Australian states (Western Australia, South Australia, Victoria and Queensland) from 1 July 2017

Key Points

- The oral rotavirus vaccine Rotarix® (given in a 2-dose schedule) will replace RotaTeq® (given in a 3-dose schedule) in Western Australia, South Australia, Victoria and Queensland from 1 July 2017. After 1 July 2017, Rotarix® will be the only rotavirus vaccine used under the NIP in Australia for children commencing their childhood schedule.
- Both products have equivalent vaccine effectiveness and have led to a marked reduction in severe gastroenteritis cases in all Australian jurisdictions.
- Rotarix® is administered at approximately 2 months (from 6 weeks) and 4 months of age. The main difference between Rotarix® age restrictions (compared to RotaTeq®) is that the 1st dose must be administered prior to 15 weeks of age and the 2nd dose prior to 25 weeks of age.
- During the brand switch period, some infants may potentially receive fewer doses than routinely scheduled when using the RotaTeq® brand. The specific recommendations will vary depending on the age of the child and rotavirus vaccination history.
- This document provides clinical advice to assist in the switch from RotaTeq® to Rotarix®.

Background

From 1 July 2017, the oral rotavirus vaccines funded and used under the National Immunisation Program (NIP) will change. This means that Rotarix®, currently used in four jurisdictions and given in a 2-dose schedule, will replace RotaTeq® (given in a 3-dose schedule) in specified Australian states (Western Australia, South Australia, Victoria and Queensland). After 1 July 2017, all states and territories will be using Rotarix® under the NIP. This will provide consistency across the NIP, including for children moving from one jurisdiction to another during the course of immunisation. It is important to note that the rotavirus vaccine schedule is not included in the definition of fully vaccinated in relation to eligibility for Commonwealth family assistance payments.

This document provides clinical advice to support the change from RotaTeq® to Rotarix® in relevant states/territories during this interim transition period as stock changes over.

The principles for use of both oral rotavirus vaccines are articulated in the current *Australian Immunisation Handbook* 10th edition (the *Handbook*),¹ Chapter 4.17 Rotavirus. Catch-up rotavirus vaccination of older infants or children is not recommended and infants are recommended to commence the course of rotavirus vaccination within specified age limits in Australia (shown in *Appendix 1*). This is to avoid a potential increased risk of vaccine-associated intussusception (a rare form of bowel blockage). The highest age-related incidence of intussusception (irrespective of vaccination) is in older infants and toddlers. If practicable, completion of a course of rotavirus vaccination using the same brand is preferred. However, during the brand switch period, it is recognised that some infants will need to complete schedules consisting of doses of both rotavirus vaccine brands or may potentially receive fewer doses than scheduled if using only one brand. Table 2 outlines potential scenarios and recommended responses during the RotaTeq® to Rotarix® switch period.

During the brand switch period, this clinical advice varies slightly from the advice in the current *Handbook* with regard to the number of RotaTeq® vaccine doses required to complete a rotavirus vaccine course.

The following clinical questions have been addressed below and form the background to the advice provided in this document:

1. What is the evidence on rotavirus vaccine effectiveness in infants who may receive a mixed or reduced dose schedule and what are the implications for effectiveness?
2. What are the safety implications for infants who may receive mixed schedules or inadvertently receive additional or late doses of rotavirus vaccines during the switch period?

1. The evidence for vaccine effectiveness of mixed or reduced dose schedules

Several studies in North America have conducted head-to-head assessments of vaccine effectiveness of Rotarix® and RotaTeq® in preventing rotavirus gastroenteritis hospitalisations and emergency department (ED) visits.²⁻⁶ The most recent of these examined children whose median age was 24 or 35 months.⁵

With regard to the use of reduced dose schedules, and specifically the effectiveness of only 2 doses of RotaTeq®, two of these studies have shown that although vaccine effectiveness point estimates differed marginally between the two brands of vaccines, confidence intervals overlapped.^{4,5} This suggests no statistical difference in the effectiveness of 2 doses of RotaTeq® (78% [95% CI 66%–85%]) in comparison with 2 doses of Rotarix® (80% [95% CI 68%–88%]).⁵ Of note, in this study, 3 doses of RotaTeq® (80% [95% CI 74%–84%]) compared with 2 doses of Rotarix® (80% [95% CI 68%–88%]) also appeared to have similar effectiveness in the prevention of rotavirus gastroenteritis requiring hospitalisation or ED visit. The point estimate for RotaTeq® 1-dose vaccine effectiveness (68% [95% CI 45%–82%]) was lower than for 1 dose of Rotarix® (96% [95% CI 67%–99%]) though confidence intervals also overlapped.⁵ Significant vaccine effectiveness was observed to the 7th year of life for RotaTeq® and the 3rd year of life for Rotarix® (which was introduced to the US some years after RotaTeq®).⁵

2. The evidence for safety of mixed dose schedules or late dose administration

One study that examined children who had been given mixed brand dose schedules (1 dose Rotarix® plus 1 dose RotaTeq®, order of vaccine receipt not provided) found an overall high vaccine effectiveness (95% [95% CI, 79%–99%]) of a 2-dose mixed series, though this was based on relatively small numbers of mixed-brand vaccinated children and longer-term protection (>2 years) was not assessed.³

There were no safety concerns raised in this and other studies that report on children receiving different brands, although they would be underpowered to detect risk differences with regard to the rarity of intussusception (IS).²⁻⁶ However, *prima facie*, there is no evidence to suggest that the risk of IS, or other more common adverse events following immunisation (AEFI), would be increased if a child received a mixed dose as compared with a same brand vaccine schedule.

In 2013, the World Health Organization (WHO) recognised that the manufacturers' age restrictions for rotavirus administration had prevented commencement of rotavirus vaccination in some children, especially in low and middle income countries (LMIC). While the WHO still recommends early and timely vaccination, its 2013 review examined the balance of evidence on safety and efficacy and was more permissive of rotavirus vaccination at a potentially older age than currently stated by the manufacturers, particularly in countries of high disease burden.⁷ As shown in the *Handbook*, age restrictions continue to apply in Australia and most other developed countries. Of note, there is no evidence to suggest that administration of a dose of either Rotarix® or RotaTeq® in the second half of the first year of life is associated with a higher risk of IS as compared with administration by the recommended age cut-offs. However, this remains a theoretical concern based on the higher overall (background) incidence of IS in the 6–12 month age group. Studies of rotavirus vaccine schedules with additional doses have been performed in LMIC settings, in order to examine both the potential for better vaccine efficacy and examine vaccine safety.^{8,9} None of these studies have shown any new or major safety concerns in infants who received additional doses.

Table 3 discusses the recommended responses to any potential error scenarios during the RotaTeq® to Rotarix® switch period.

Recommendations for the use of rotavirus vaccines during the brand transition period

The transition outcome is to move from a 3-dose RotaTeq® schedule to a 2-dose Rotarix® schedule administered at 2 months (from 6 weeks) and 4 months of age.

These recommendations recognise that, in the short period after 1 July 2017, providers may have some, little or no stock of RotaTeq® available for use. Table 1 gives an overview of the transition schedule and Table 2 describes the scenario-based recommendations, incorporating upper age limits when there is limited or no availability of RotaTeq®. Table 3 shows the recommended response to any inadvertent mis-administration of vaccine, such as too many or late doses.

Table 1. Overview of ATAGI's suggested rotavirus vaccine transition schedule from 1 July 2017. Note that age cut-offs and minimum intervals between doses also apply as shown below in Table 2. The infant age and the date of last dose must be checked.*

| Previous doses of RotaTeq® given | RotaTeq® available and Rotarix® available ↓ | RotaTeq® NOT available and Rotarix® available (must see Table 2 for more details) ↓ |
|----------------------------------|--|--|
| 0 | Do not commence RotaTeq® → | Follow 2-dose Rotarix® schedule |
| 1 | Give 2nd dose of RotaTeq® | Give 1 Rotarix® – No further doses required |
| 2 | Give 3rd dose of RotaTeq® | No further doses required** |

* Also refer to Table 4.17.1 in *The Australian Immunisation Handbook*¹ (Appendix 1).

** In this scenario, administration of a 3rd dose of vaccine (as Rotarix®) is not routinely recommended but would be acceptable if given prior to turning 25 weeks of age.

Table 2. Potential scenarios and recommended response during RotaTeq® to Rotarix® switch period for states and territories, 2017 Note: this table assumes no availability of RotaTeq®

| Options/Scenarios | AND infant age | Recommended response | Comments |
|--|----------------|---|---|
| Infant has NOT had a dose of any rotavirus vaccine AND is → | a) ≥15 weeks | a) Not eligible to commence any rotavirus vaccination dose. No subsequent doses to be administered. | |
| | b) 6–14 weeks | b) Commence 2-dose course of Rotarix® | |
| Infant has been given 1 previous dose of RotaTeq® or Rotarix® AND is → | 10–24 weeks | Eligible to receive a dose of Rotarix® | Ensure minimum interval of 4 weeks between vaccine doses Total of only 2 doses are needed to complete the course |
| Infant has been given 2 previous doses of RotaTeq® AND is → | a) 14–24 weeks | a) No more vaccine doses recommended* | |
| | b) >24 weeks | b) Not eligible to receive a dose of Rotarix® | |

* In this scenario, administration of a 3rd dose of vaccine (as Rotarix®) is not routinely recommended but would be acceptable if given prior to turning 25 weeks of age. If a dose is provided, ensure a minimum interval of 4 weeks since the last dose.

Table 3. Potential error scenarios caused by the inadvertent administration of a rotavirus vaccine dose and recommended response*

| Options/Scenarios following inadvertent dose administration | Recommended response | Comments |
|---|---|---|
| Infant >14 weeks receives 1st dose of Rotarix® | Reassure and discuss minimally increased risk of intussusception. Provide information on symptoms/signs of intussusception and response** | If infant is <25 weeks (upper limit for dose 2 Rotarix®), and minimum interval of 4 weeks between vaccine doses can be achieved, give a second dose of Rotarix® |
| Infant >12 weeks receives 1st dose of RotaTeq® | Reassure and discuss minimally increased risk of intussusception. Provide information on symptoms/signs of intussusception and response** | If infant is <25 weeks (upper limit for dose 2 Rotarix®), and minimum interval of 4 weeks between vaccine doses can be achieved, give a second dose of Rotarix® |
| Infant receives 3 doses of Rotarix® | Observe, reassure and discuss risk | |

* Note: Some of these errors may occur independently of any 'switch' in vaccine brands.

** See *Rotavirus vaccine and intussusception information for Parents and Guardians* on the NIP website at <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/ITO136-cnt>

Note: If *most* of an oral rotavirus vaccine dose has been spat out or vomited within minutes of administration, a single repeat dose can be administered during the same visit. If an infant regurgitates or vomits only a *small part* of a vaccine dose, it is not necessary to repeat the dose; that dose can be considered valid.

References

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9. Kompithra RZ, Paul A, Manoharan D, et al. Immunogenicity of a three dose and five dose oral human rotavirus vaccine (RIX4414) schedule in south Indian infants. *Vaccine* 2014;32 Suppl 1:A129-33.

Appendix 1

Table 4.17.1: Upper age limits for dosing 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® (GlaxoSmithKline) | 2 oral doses (1.5 mL/dose) | 2 and 4 months | 6–14* weeks | 10–24* weeks | N/A | 4 weeks |
| RotaTeq® (CSL Limited/Merck & Co Inc.) | 3 oral doses (2 mL/dose) | 2, 4 and 6 months | 6–12† weeks | 10–32† weeks | 14–32† weeks | 4 weeks |

* The upper age limit for receipt of the 1st dose of Rotarix® 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® 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.

For more information also see the Rotavirus chapter in *The Australian Immunisation Handbook*.¹