



Australian Government
Department of Health and Ageing

Information for Immunisation Providers
February 2011

Rotavirus vaccine and intussusception



IMMUNISATION

Summary information

Key Points

1. Inform parents and carers of young infants receiving rotavirus vaccine of the rare risk of intussusception following the vaccine and how to be alert to the signs and symptoms of the condition.
2. Do not give rotavirus vaccine outside the recommended age limits.
3. Do not give rotavirus vaccine to a baby with a history of intussusception.
4. Report any cases of intussusception following rotavirus vaccination through the usual reporting arrangements for adverse events following immunisation in your State and Territory.

Risk of intussusception

- There is new evidence from Australian and overseas studies suggesting a small increased risk of intussusception in infants following rotavirus vaccination.
- The increased risk appears to occur mainly in the first 1- 7 days following the first dose of rotavirus vaccine.
- Intussusception is rare, with an annual incidence under 12 months of age in Australia of 80 per 100,000, or about 200 cases per year. The increased risk would result in 2 additional cases of intussusception among every 100,000 infants vaccinated, or 6 additional cases per year in infants in Australia.
- It is also possible there may be a similar increased risk of intussusception after the second dose of rotavirus vaccine and that a smaller increased risk may continue for up to 21 days after vaccination.

- Some studies have suggested that there may be a compensatory reduction in intussusception among older infants and children vaccinated against rotavirus as babies.
- Studies to further evaluate these uncertainties are continuing and results will be made available as soon as possible.
- There is some indication that giving rotavirus vaccine later than the recommended upper age limits for each dose may increase the risk of intussusception.
- As there may be an increased risk of recurrence, rotavirus vaccine should not be given to a baby who has had intussusception.

Benefits and recommendations

- The very low risk of intussusception must be balanced against the benefits of rotavirus vaccination. Prior to the introduction of rotavirus vaccine, there were an estimated 10,000 hospitalisations annually in children under 5 years of age due to rotavirus gastroenteritis in Australia and on average one childhood death from rotavirus each year. Since the introduction of Rotarix® and RotaTeq® to the National Immunisation Program in 2007, this has been reduced by over 70%.
- Both rotavirus vaccines (Rotarix® and RotaTeq®) continue to be registered by the Therapeutic Goods Administration (TGA) for the prevention of rotavirus gastroenteritis.
- Based on the well-established benefits of rotavirus vaccination and the rare occurrence of intussusception, the Australian Technical Advisory Group on Immunisation (ATAGI) recommends the continued use of rotavirus vaccine for infants under the National Immunisation Program.

Role of providers

- Immunisation providers should inform parents and carers of young infants being vaccinated against rotavirus of the rare risk of intussusception and how to be alert for the signs and symptoms of the condition. The risks from rotavirus infection and benefits of vaccination should also be discussed. A Fact Sheet for parents can be downloaded from the Immunise Australia Website www.immunise.health.gov.au
- Health professionals should report any cases of intussusception following rotavirus vaccination through the usual reporting arrangements for adverse events following immunisation in their State or Territory. These reports will then be forwarded to the TGA.
- The TGA has published a report on its investigation of the association between rotavirus vaccine and intussusception on its Website at www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm

Detailed information

What is intussusception?

Intussusception is a telescoping of one segment of the bowel into itself, causing obstruction. It is a rare condition, with an annual incidence under 12 months of age in Australia of 80 per 100,000, which represents approximately 200 cases per year. The peak incidence is between 5 and 10 months of age, with 80% of cases before 24 months of age. It is more common in males than females (5:3 in Australian studies). Most cases in infants are idiopathic, with no recognised triggering event or underlying structural abnormality. There may be some familial predisposition. Recurrence is seen in 5-10% of non-surgically-treated cases, usually within 6 months.

What are the common presenting symptoms of intussusception?

Intussusception initially causes pain, manifested as crying but often associated with pallor. The crying may be intermittent initially. Vomiting is the single most common symptom and signs of intestinal obstruction (distension and absent or reduced bowel sounds) are usually present. If there is vascular compromise due to the obstruction, there may be intestinal bleeding (the classic red currant jelly stool) but this is often late and/or absent.

What is the case severity of intussusception?

With currently available diagnostic modalities and skilled reduction using air or contrast material, intussusception rapidly resolves in the majority of infants. About 30% of infants with intussusception require surgical reduction and 10% result in intestinal resection. A recent review of state-wide cases conducted by the National Centre for Immunisation Research and Surveillance (NCIRS) for NSW Health found that, of 132 confirmed cases, 11% resolved spontaneously and 28% required surgery, with one infant admitted postoperatively to intensive care. There was no difference in case severity in recently vaccinated infants compared to other cases. No deaths from intussusception have been recorded in Australia for the past 15 years.

Intussusception and rotavirus vaccines

Intussusception was found to be a rare but significant side effect of the first generation rotavirus vaccine (RotaShield®) that was available in the United States in 1998-1999. RotaShield was estimated to cause intussusception in 10-20 of every 100,000 doses to infants, resulting in voluntary withdrawal from the US market in October 1999.^{1,2} RotaShield was never used in Australia or other countries outside the US.

Subsequently, two new, “next generation” rotavirus vaccines, Rotarix® (GSK) and RotaTeq® (Merck, marketed by CSL), were developed. Both vaccines were tested in large studies designed to exclude a risk of intussusception similar to RotaShield. In each of these pre-registration studies, approximately 35,000 infants were given rotavirus vaccine, with no increased risk of intussusception observed.^{3,4} As even large pre-registration safety studies cannot detect rare events, post-marketing studies have been undertaken in a number of countries.

What new information do we have about intussusception and rotavirus vaccines?

Australian data

In Australia, two post-marketing studies have been conducted to investigate whether the new rotavirus vaccines are associated with intussusception. The first study was conducted using two surveillance systems, the Paediatric Enhanced Disease Surveillance (PAEDS) hospital-based network and the Australian Paediatric Surveillance Unit (APSU). The study, which covered the first 18 months after rotavirus vaccination commenced, found an apparent four-fold increased risk in intussusception in babies within one week of being given the first dose of either vaccine, but no overall increase in rates of intussusception up to the age of 9 months, compared with historical data.⁵

Subsequently, a larger study using data on all hospitalised cases coded as having intussusception from NSW, Victoria and Western Australia was commissioned by the Therapeutic Goods Administration (TGA).⁶ This study, which included many of the cases of intussusception analysed in the other study but used a different methodology, also found an approximately four-fold increase in the occurrence of intussusception in the 1-7 days following the first dose of both Rotarix and RotaTeq. There is also a suggestion that an increased risk of intussusception may occur following the second dose of vaccine and that a lower level

risk could extend into the second or third week beyond either dose. A separate analysis of the NSW cases undertaken by NCIRS for NSW Health made similar findings. Further analyses are required to clarify the second dose risk and time period.

Based on the age-specific incidence of intussusception, the increased risk in the 1–7 days after the first dose translates to approximately 2 additional cases of intussusception occurring in every 100,000 infants vaccinated or approximately 6 additional cases each year in children less than 12 months of age in Australia. This risk estimate is significantly lower than the risk observed in association with RotaShield (approximately 10/100,000 infants). It is also possible that there is a reduction in intussusception in older infants and children vaccinated against rotavirus as babies, but this is speculative at this time and longer term studies are needed.

The TGA has published a report on its investigation of the association between rotavirus vaccine and intussusception on its Website www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm

Overseas data

A similar four to five fold increased risk of intussusception was found in the week following the first dose of Rotarix in a cohort of Mexican infants.^{7,8} These findings have not been replicated in Brazil or in other studies.^{7,8,9} For RotaTeq, two post-marketing studies in the United States have not shown any increased risk of intussusception to date.^{7,8,10,11} However, insufficient data are yet available to allow detection of a level of risk as low as that observed in the Mexican and Australian studies.

The Australian Technical Advisory Group on Immunisation (ATAGI) considers that, although there are some differences in findings across the studies to date, both vaccines present a similar low risk

of intussusception. As the benefits and risks apply equally to both vaccines, there is no preference for which vaccine is used.

Further collection and analysis of surveillance data are ongoing, both in Australia and internationally. New data will be reviewed as they become available.

What is the benefit of giving rotavirus vaccine?

Prior to the availability of rotavirus vaccine, almost every child was infected by rotavirus by the age of 5 years. Approximately 10,000 children under 5 years of age were hospitalised each year in Australia and there was on average one childhood death from rotavirus each year.^{12,13} The introduction of the rotavirus vaccine into the National Immunisation Program in 2007 has led to a more than 70% decline in annual rotavirus hospitalisations in the under 5 year age group.¹⁴ Positive laboratory tests for rotavirus, notifications of rotavirus gastroenteritis and emergency department visits for acute gastroenteritis in young children have also declined.¹⁵

Should I continue to give rotavirus vaccine?

Yes. Both vaccines, Rotarix® and RotaTeq®, continue to be registered by the Therapeutic Goods Administration (TGA) for the prevention of rotavirus gastroenteritis. Based on the proven benefits of rotavirus vaccination and the rare occurrence of intussusception, the Australian Technical Advisory Group on Immunisation (ATAGI) recommends the continued use of both rotavirus vaccines for infants under the National Immunisation Program.

The World Health Organization (WHO) issued a statement on 22 September 2010 advising that post-marketing surveillance indicates the possibility of an increased risk of intussusception shortly after the first dose of rotavirus vaccination in some populations.⁷ The WHO also advises that the documented benefits of rotavirus vaccination greatly outweigh the risks found in studies to date.

The US Advisory Committee on Immunization Practices has also issued a statement recommending the continued use of rotavirus vaccines.¹¹

What should I advise parents?

Immunisation providers should advise the parents and carers of infants who receive rotavirus vaccination of this new information and how to be alert for the symptoms and signs of intussusception. The possible small increase in risk should be balanced against the demonstrated benefits of rotavirus vaccination. Information for parents is available in a Fact Sheet in Question and Answer format on the Immunise Australia website (see link below).

Parents and carers should also be advised of the need to have the rotavirus vaccine on time as there is some evidence that the risk of intussusception may be increased if a vaccine dose is given later than recommended.

Should I give rotavirus vaccine to a baby with a history of intussusception?

No. As there may be an increased risk of recurrence, rotavirus vaccine should not be given to a baby who has had intussusception.

Reporting of suspected intussusception following vaccination

Health professionals should report any cases of intussusception following rotavirus vaccination through the usual reporting arrangements for adverse events following immunisation in their State or Territory. These reports will then be forwarded to the TGA.

Contact information for further details

More information regarding rotavirus and intussusception is on the Immunise Australia Website www.immunise.health.gov.au, through the Immunise Australia Information Line on 1800 671 811 (between 8:30am and 5pm Eastern Australian Time) and on the TGA website www.tga.gov.au

References

1. Withdrawal of Rotavirus Vaccine Recommendation. *MMWR* 1999;48(3):1107.
2. Murphy T, Gargiullo P, Massoudi M, Nelson D et al. Intussusception among infants given an oral rotavirus vaccine. *New England Journal of Medicine* 2001; 344(8):564-72.
3. Ruiz-Palacios G, Pérez-Schael I, Velázquez F, H HA, Breuer T et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *New England Journal of Medicine* 2006;354(1):11-22.
4. Vesikari T, Matson D, Dennehy P, Damme PV et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *New England Journal of Medicine* 2006;354(1):23-33.
5. Buttery JP, Danchin MH, Lee KJ, Carlin JB, et al. Intussusception following rotavirus vaccine administration: post marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011 In Press. doi:10.1016/j.vaccine.2011.01.088.
6. Therapeutic Goods Administration. Rotavirus vaccination and risk of intussusception: A report of TGA's investigation of a possible safety signal. February 2011. www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm
7. World Health Organisation, Global Advisory Committee on Vaccine Safety. Statement on Rotarix and RotaTeq vaccines and intussusception. 22 September, 2010. http://www.who.int/vaccine_safety/topics/rotavirus/rotarix_and_rotateq/intussusception_sep2010/en/index.html
8. Department of Health and Human Services Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP). Summary Report October 27-28, 2010. Pages 152 – 171. <http://www.cdc.gov/vaccines/recs/acip/downloads/min-oct10.pdf>

9. Velázquez FR, Colindres R, Grajales C, Hernández MT et al. Postmarketing surveillance of intussusception following mass introduction of the human rotavirus vaccine in Mexico: an interim analysis. *Excellence in Paediatrics*, London, December 2–4, 2010.
10. Haber P, Patel M, Izurieta H, Baggs J et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. *Pediatrics* 2008;121(6):1206-12.
11. Centers for Disease Control and Prevention (CDC). Statement Regarding Rotarix® and RotaTeq® Rotavirus Vaccines and Intussusception. <http://www.cdc.gov/vaccines/vpd-vac/rotavirus/intussusception-studies-acip.htm>
12. Galati JC, Harsley S, Richmond P, Carlin JB. The burden of rotavirus-related illness among young children on the Australian health care system. *ANZ Journal of Public Health* 2006;30: 416–421.
13. Newall AT, MacIntyre R, Wang H, Hull B, Macartney K. Burden of severe rotavirus disease in Australia. *J Paediatr Child Health* 2006; 42(1 9): 521–527.
14. Macartney KK, Porwal M, Dalton D, Cripps T et al Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme. *J Paediatr Child Health* 2011; published online: 18 Jan 2011 DOI: 10.1111/j.1440-1754.2010.01953.x
15. Lambert SB, Faux CE, Hall L, Birrell FA et al. Early evidence for direct and indirect effects of the infant rotavirus vaccine program in Queensland. *Med J Aust* 2009; 191: 157-160.

www.immunise.health.gov.au

All information in this publication is correct as of February 2011

