

# ROTAVIRUS VACCINE SAFETY

Rotavirus vaccines currently available on the international market have been shown to be safe. The main safety concern has been a very small increased risk of a rare obstructed bowel syndrome called intussusception. Intussusception occurs naturally in infants under 24 months of age regardless of rotavirus vaccination status, but a very small increased risk has been found in some countries following the introduction of rotavirus vaccines, especially within the first week after the first dose is given.

While the risk of an infant developing intussusception following rotavirus vaccination is very low, it has received a lot of attention. Because of this, it is important to understand that any recorded increases in intussusception have been greatly outweighed by the swift and significant reduction in rotavirus hospitalizations—for details on the estimated risk-benefit ratios, see page 3.

## What is intussusception?

Intussusception is a rare but serious condition in infants in which a segment of the intestine folds (or “telescopes”) onto itself, creating an obstruction. Symptoms include severe abdominal pain, vomiting, and rectal bleeding. If not treated, it can lead to perforation of the gut and even death.<sup>(1)</sup>

Intussusception is most common in infants between the ages of 4–10 months. Few cases occur the first two months of life.<sup>(2,3)</sup> The causes of this condition are largely unknown, although there is some evidence of a link with exposure to viruses and bacteria, as well as changes in diet and the maturing of the gut of infants.<sup>(1,4,5)</sup>

## Intussusception symptoms

- Stool mixed with blood and mucus
- Vomiting
- A lump in the abdomen
- Weakness or lack of energy
- Diarrhea<sup>(6)</sup>

## Intussusception in infants

Intussusception is the most common naturally-occurring cause of bowel obstruction in infants, though it is still relatively rare, with incidence rates in infants of less than 100 per 100,000.<sup>(3)</sup> In the U.S., for instance, there are an estimated 1,200–1,500 cases per year in a birth cohort of 4.5 million, or around 33–34 per 100,000 infants.<sup>(2,3)</sup> However, there are large differences in incidence rates of intussusception by region and country—with annual rates as low as nine per 100,000 in Bangladesh and as high as 300 or more per 100,000 in Vietnam and South Korea.<sup>(3)</sup>

According to numerous hospital-based studies, intussusception rarely results in death—with case fatality rates of less than 1% in many regions and countries. In countries with limited access to a pediatric surgeon, such as in Africa, however, case fatality rates for intussusception are generally about 9%.<sup>(3)</sup> This underscores the need to obtain better estimates of the incidence of this condition in infants and to monitor any impact that rotavirus vaccination may have.

Rotavirus vaccines were first linked to intussusception when an increase in cases was observed in the U.S. following the introduction of the first live oral rotavirus vaccine—RotaShield® (Wyeth Laboratories, Inc.)—in 1998. The vaccine, used only in the U.S., caused an estimated one or two additional cases of intussusception per 10,000 infants vaccinated.<sup>(7)</sup> As a result, the vaccine was withdrawn from the market within 14 months of its licensure.

The U.S. Food and Drug Administration consequently required as a condition of licensure that clinical trials of other rotavirus vaccines be large enough to rule out an increased risk of intussusception of the level seen with RotaShield, and that large post-licensure evaluations be conducted. Efficacy trials of RotaTeq® and ROTARIX® each included 60,000 to 70,000 infants; neither found any increased risk of intussusception.<sup>(8,9)</sup> Clinical trials of ROTAVAC® and ROTASIIL® were not designed to evaluate whether there was any increase in the risk of intussusception following vaccination with the aim that post-licensure surveillance would identify this rare event, if it occurred.<sup>(10,11)</sup>

However, large post-licensure studies in several high- and middle-income countries have found a small increased risk of intussusception following vaccination with either ROTARIX or RotaTeq—but at a substantially lower level than RotaShield. These studies have found that both vaccines cause one to seven additional intussusception cases per 100,000 infants vaccinated, with the majority of studies showing an excess risk of two or fewer cases per 100,000.<sup>(12–20)</sup> Post-licensure studies of RotaTeq in Africa and Rotavac in India have not found any increased risk of intussusception. Post-licensure studies for ROTAVAC and ROTASIIL are underway.

Most rotavirus vaccine-associated cases in these studies occurred within the first week following vaccination—usually after the first dose—though several studies also show a smaller increased risk shortly after the second dose. As the vaccine virus is replicating rapidly for several days after vaccination, it causes a local inflammatory response, which has been linked to the development of intussusception.<sup>(13,21)</sup>

It's important to compare the significant public health benefits of rotavirus vaccination demonstrated around the world to the small increased risk of intussusception following rotavirus vaccination found in some countries.

Post-licensure surveillance studies of intussusception estimated that for every intussusception hospitalization caused by rotavirus vaccination, hundreds to more than 1,000 rotavirus hospitalizations are prevented. An analysis of 14 Latin American countries encompassing 9.5 million infants found that vaccination would prevent around 145,000 hospitalizations and 4,100 deaths each year due to rotavirus gastroenteritis, while causing an additional 172 hospitalizations and 10 deaths from intussusception.<sup>(22)</sup> This yields a benefit-to-risk ratio of 841:1 for hospitalizations and 345:1 for deaths. The ratios are likely to be greater in reality, since the analysis did not take into account the indirect protection of unvaccinated children.

A similar study conducted in France estimated that, assuming a coverage rate of 92% for two doses of ROTARIX, the vaccination would prevent more than 10,000 rotavirus hospitalizations and 14 deaths per year, while being associated with 47 intussusception-related hospitalizations annually and about 1 intussusception death every 20 years.<sup>(23)</sup> This results in a benefit-to-risk ratio of 221 rotavirus hospitalizations avoided for every one hospitalization caused by intussusception and 284 rotavirus-related deaths prevented for every death due to intussusception.

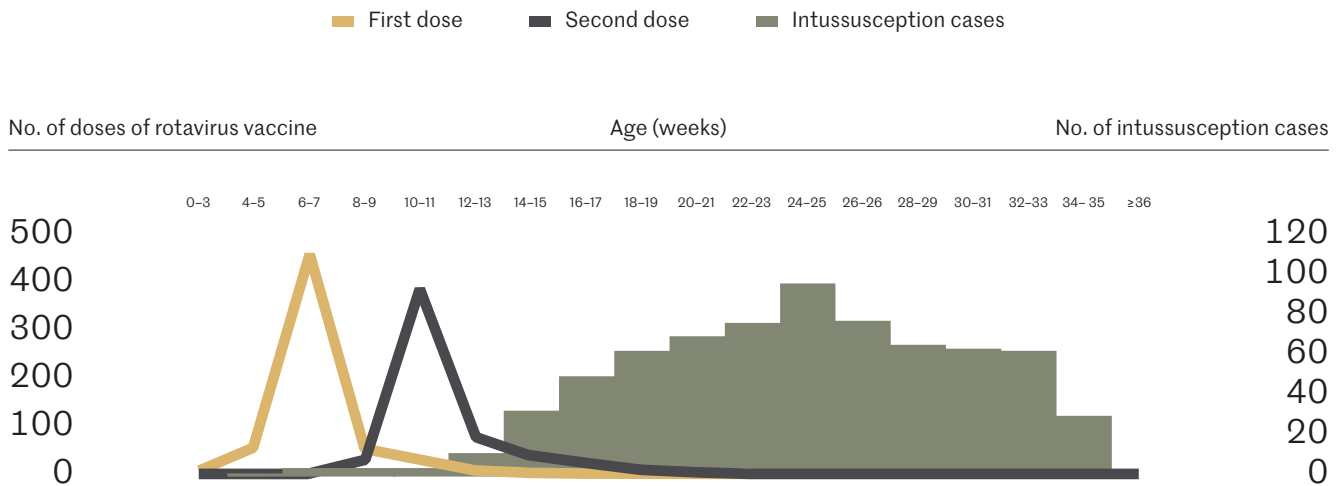
## WHO recommendations

WHO recommends that the first dose of rotavirus vaccine be administered as soon as possible after 6 weeks of age, along with DPT vaccination.<sup>(7)</sup>

Countries should include information about intussusception and its danger signs when training health workers. Health workers should also communicate with the public about the signs of both intussusception and dehydration. This is critical since studies have shown a lack of awareness among doctors and parents about the small possibility of intussusception following rotavirus vaccination.<sup>(15)</sup> For more about WHO's recommendations, see Rotavirus vaccines: WHO position paper—July 2021 (this and other resources are available at [preventrotavirus.org](http://preventrotavirus.org)).<sup>(7)</sup>

# No increased risk of intussusception has been found in Africa.

## AGES AT IMMUNIZATION AND THE ONSET OF INTUSSUSCEPTION AT SENTINEL SITES IN 7 AFRICAN COUNTRIES, 2012–2016



The African Intussusception Surveillance Network conducted a study from 2012 to 2016 in seven African countries that have introduced ROTARIX—Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia and Zimbabwe—to determine if the vaccine increases the risk of intussusception.<sup>(21)</sup> The study

identified 717 intussusception cases in infants through active surveillance in 29 major pediatric hospitals in large urban areas in the seven countries. The study found that few cases occurred shortly after vaccination with either dose, and most occurred well after the 21-day post-vaccination

period considered to be high risk. The incidence of intussusception was, in fact, no higher during these 21 days following vaccination than the usual incidence rates in these countries. Read more about the benefit-risk ratio in other regions in “Rotavirus vaccination and intussusception—Science,

surveillance, and safety: A review of evidence and recommendations for future research priorities in low and middle income countries,” from Human Vaccines & Immunotherapeutics (October 2016).<sup>(22)</sup>

## REFERENCES

- Bines, J., *Post-marketing surveillance of rotavirus vaccine safety*. 2009, World Health Organization: Geneva, Switzerland. p. 43.
- Yen, C., et al., *Rotavirus vaccination and intussusception - Science, surveillance, and safety: A review of evidence and recommendations for future research priorities in low and middle income countries*. *Hum Vaccin Immunother*, 2016. 12(10): p. 2580–2589.
- Jiang, J., et al., *Childhood intussusception: a literature review*. *PLoS One*, 2013. 8(7): p. e68482–e68482.
- Tate, J.E., et al., *Trends in National Rotavirus Activity Before and After Introduction of Rotavirus Vaccine into the National Immunization Program in the United States, 2000 to 2012*. *The Pediatric Infectious Disease Journal*, 2013. 32(7): p. 741–744.
- Reddy, S., et al., *Safety monitoring of ROTAVAC vaccine and etiological investigation of intussusception in India: study protocol*. *BMC Public Health*, 2018. 18(898): p. 898.
- Mayo Clinic, *Intussusception*. *Mayoclinic.org*
- World Health Organization, *Rotavirus vaccines WHO position paper—July 2021*. *Wkly Epidemiol Rec*, 2021. 28(96): p. 301–320.
- Ruiz-Palacios, G.M., et al., *Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis*. *New England Journal of Medicine*, 2006. 354(1): p. 2725–2732.
- Vesikari, T., et al., *Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine*. *N Engl J Med*, 2006. 354(1): p. 23–33.
- Bhandari, N., et al., *Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial*. *Lancet*, 2014. 383(9935): p. 2136–2143.
- Kulkarni, P.S., et al., *A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants*. *Vaccine*, 2017. 35(45): p. 6228–6237.
- Weintraub, E.S., et al., *Risk of intussusception after monovalent rotavirus vaccination*. *N Engl J Med*, 2014. 370(6): p. 513–9.
- Patel, M.M., et al., *Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil*. *N Engl J Med*, 2011. 364(24): p. 2283–2292.
- Velazquez, F.R., et al., *Postmarketing Surveillance of Intussusception Following Mass Introduction of the Attenuated Human Rotavirus Vaccine in Mexico*. *Pediatr Infect Dis J*, 2012. 31(7): p. 736–744.
- Stowe, J., et al., *The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation*. *Vaccine*, 2016. 34(32): p. 3684–9.
- Haber, P., et al., *Intussusception after monovalent rotavirus vaccine—United States, Vaccine Adverse Event Reporting System (VAERS), 2008–2014*. *Vaccine*, 2015. 33(38): p. 4873–7.
- Yung, C.F., et al., *Intussusception and Monovalent Rotavirus Vaccination in Singapore: Self-Controlled Case Series and Risk-Benefit Study*. *J Pediatr*, 2015. 167(1): p. 163–9.
- Yih, W.K., et al., *Intussusception risk after rotavirus vaccination in U.S. infants*. *N Engl J Med*, 2014. 370(6): p. 503–12.
- Haber, P., et al., *Intussusception after rotavirus vaccines reported to US VAERS, 2006–2012*. *Pediatrics*, 2013. 131(6): p. 1042–9.
- Carlin, J.B., et al., *Intussusception risk and disease prevention associated with rotavirus vaccines in Australia’s National Immunization Program*. *Clin Infect Dis*, 2013. 57(10): p. 1427–1434.
- Tate, J.E., et al., *Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa*. *N Engl J Med*, 2018. 378(16): p. 1521–1528.
- Desai, R., et al., *Potential intussusception risk versus health benefits from rotavirus vaccination in Latin America*. *Clinical Infectious Diseases*, 2012. 54(10): p. 1397–1405.
- Lamrani, A., et al., *A benefit-risk analysis of rotavirus vaccination, France, 2015*. *Euro Surveill*, 2017. 22(50): p. 28–37.

More Reading: Rotavirus vaccination and intussusception—Science, surveillance, and safety: A review of evidence and recommendations for future research priorities in low and middle income countries. *Hum Vaccin Immunother*. 2016 Oct; 12(10): 2580–2589.

ROTA Council thanks the following organizations for their support: Bharat Biotech, Bill & Melinda Gates Foundation, CDC, GSK, PATH, and Sabin Vaccine Institute. Suggested Citation: ROTA Council at International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. (2022). Rotavirus Disease and Immunization: Rotavirus Vaccine Safety.

# ROTAVIRUS VACCINE SAFETY

## KEY FACTS

### Rare

Some post-marketing studies of ROTARIX® and RotaTeq® have shown a small increased risk of intussusception—a naturally-occurring bowel obstruction in infants—following rotavirus vaccination in several high- and middle-income countries. Studies for ROTAVAC® and ROTASIIL® are underway.

### Evaluation

No increased risk of intussusception following rotavirus vaccination was shown in a seven-country post-marketing evaluation in Africa.

### Benefits

Studies show that the benefits of the vaccine, in preventing many rotavirus hospitalizations and deaths, greatly outweigh the very small increased risk of intussusception following vaccination.



For more information please visit [preventrotavirus.org](http://preventrotavirus.org).