

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 12 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.⁽¹⁾

Intussusception is most common in infants between the ages of 4–10 months. Few cases occur in the first two months of life.^(2,3) 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.^(1,4,5)

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.⁽³⁾ 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.^(2,3) 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.⁽³⁾

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 suboptimal access to health care, such as in Africa, however, case fatality rates for intussusception are generally about 9%.⁽³⁾ 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.

Intussusception & rotavirus vaccination

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.⁽⁶⁾ 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.^(7,8) Clinical trials of ROTAVAC[®] and ROTASIIL[®] were not designed to evaluate whether there was any increase in the risk of intussusception following vaccination.^(9,10)

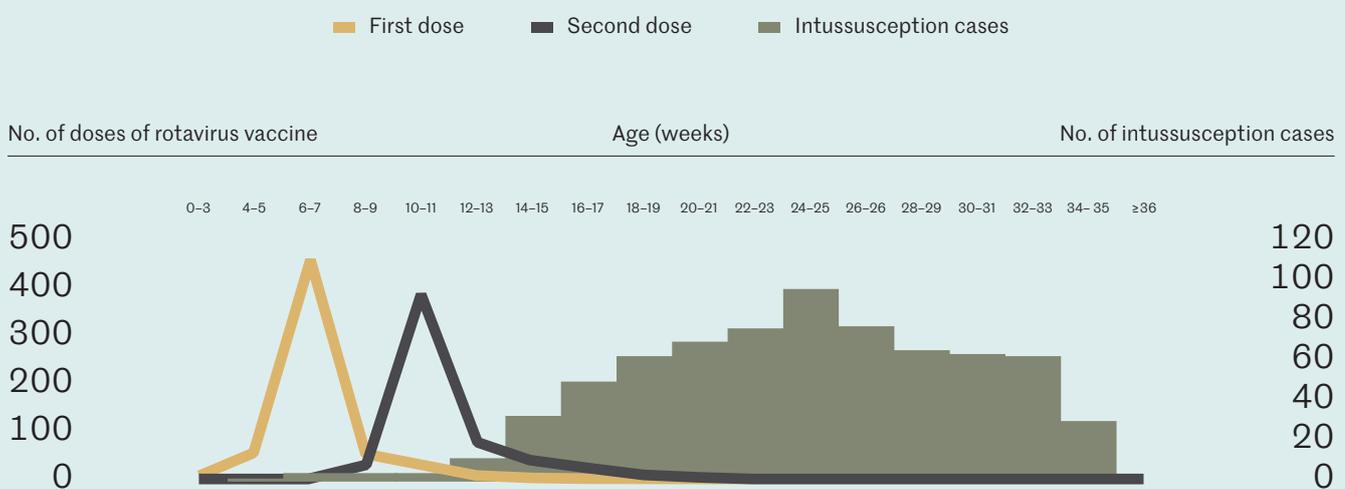
However, large post-licensure studies in several high- and middle-income countries have found a small increased risk of intussusception following vaccination with either ROTARIX or RotaTeq—but at a substantially lower level than

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.⁽¹¹⁻¹⁹⁾ 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.^(12,20)

NO INCREASED RISK OF INTUSSUSCEPTION 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.⁽²⁰⁾ 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).⁽²⁾

Risk-benefit ratio

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 several 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.⁽²¹⁾ 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 causing 47 hospitalizations

annually and about 1 death every 20 years.⁽²²⁾ This results in a benefit-to-risk ratio of 221 rotavirus hospitalizations avoided for every 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.⁽⁶⁾

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.⁽¹⁴⁾ For more about WHO's recommendations, see Rotavirus vaccines: WHO position paper—January 2013 (this and other resources are available at rotacouncil.org).⁽⁶⁾

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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.

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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 rotacouncil.org.