Rotavirus Disease and Vaccines:
Frequently Asked Questions
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<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency (previously EMEA)</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
A. Rotavirus disease overview

1. What is rotavirus?
Rotavirus is a contagious virus that can cause diarrheal illness, also known as gastroenteritis, which may be severe particularly in infants and young children. It is often accompanied by vomiting and fever, and if left untreated it can lead to severe dehydration and death. While not the only cause of diarrhea, rotavirus is the leading cause of severe diarrhea in young children worldwide.

2. How many young children die from or are hospitalized for rotavirus each year?
Globally, rotavirus is responsible for more than 450,000 deaths each year in children younger than five years of age and is responsible for millions of hospitalizations and clinic visits each year.1,2 It affects children around the world in high- and low-income countries alike. While rotavirus deaths and hospitalizations vary by region and country, the vast majority (95 percent) of rotavirus deaths in young children are found in low-income countries in Africa and Asia.1 Five percent of all deaths in children younger than five years of age are due to rotavirus.1

3. What percentage of diarrhea-related deaths and hospitalizations is due to rotavirus?
Rotavirus is estimated to cause 37 percent of the approximately 800,000 diarrheal deaths and 40 percent of the 9 million diarrhea-related hospitalizations in children under five years of age worldwide.1-3

4. What percentage of all child deaths is due to rotavirus?
Rotavirus diarrhea accounts for an estimated 5 percent of all deaths in children under five.1 Diarrhea from all causes is responsible for approximately 9 percent of all under-five deaths worldwide.4

5. What is the leading cause of moderate-to-severe diarrhea in low-income countries? What did the Global Enteric Multicenter Study (GEMS) find?
The public health burden of rotavirus was confirmed by the Global Enteric Multicenter Study (GEMS), the first comprehensive global study of childhood diarrheal disease, which was conducted in seven study sites in sub-Saharan Africa and South Asia. GEMS found that rotavirus is the overall leading cause of moderate-to-severe diarrhea among infants and toddlers under two years of age and a major cause among children under five years of age in these settings.5
6. Who is at risk for rotavirus infection?

Nearly every child is at risk of infection, regardless of location, hygiene practices, or access to safe drinking water or sanitation. Children six months to two years of age are most vulnerable to infection, along with premature infants, the elderly, and those with weakened immune systems. While older children and adults can get rotavirus infections, these are usually asymptomatic or mild.

7. Can a child become infected with rotavirus multiple times?

Vaccinated and unvaccinated children may develop rotavirus disease more than once because neither the vaccine nor natural infection provides full immunity (protection) from future infections. Usually a person’s first infection with rotavirus causes the most severe symptoms.

8. What are the symptoms of rotavirus?

Once a person has been exposed to rotavirus, it takes about two days for symptoms to appear. Symptoms include diarrhea, vomiting, fever, and abdominal pain. Vomiting and watery diarrhea may last from three to eight days in a child infected with rotavirus. Additional symptoms include loss of appetite and dehydration, which can be especially harmful for young children and lead to death.

9. How is rotavirus spread?

Rotavirus is shed (passed from a person’s body into the environment) in the feces (stool) of infected persons. The virus spreads by the fecal–oral route; this means that the virus must be shed by an infected person in his/her feces and then enter a susceptible person’s mouth to cause infection.

Rotavirus is highly contagious and resilient. It spreads easily from person to person through contaminated hands and objects, such as toys and surfaces. Rotavirus can live on contaminated hands for hours and surfaces for days. Children can spread the virus both before and after they become sick with diarrhea. They also can pass rotavirus to family members and other people with whom they have close contact.

10. What is the treatment for rotavirus?

Rotavirus cannot be treated with antibiotics or other drugs. Mild rotavirus infections can be treated effectively in the same manner as other forms of diarrhea, by providing fluids and salts (oral rehydration therapy) until the disease runs its course. However, children with severe rotavirus diarrhea urgently need intravenous fluids, or they risk dying from dehydration. In low-income countries, this type of urgent health care is often inaccessible or unavailable, making rotavirus prevention through vaccination critical to saving children’s lives.
11. **How can we prevent rotavirus?**

Vaccination is the best way to protect children from rotavirus and the dehydrating diarrhea that it can cause. Improvements in water quality, hygiene, and sanitation stop bacteria and parasites that cause other forms of diarrhea but do not adequately prevent the spread of rotavirus. Lifesaving rotavirus vaccines should be introduced as part of a comprehensive approach to control diarrheal disease, along with other interventions including oral rehydration therapy, exclusive breastfeeding, zinc treatment, and improvements in water and sanitation.

12. **How big of a threat is rotavirus to children’s health and well-being?**

Rotavirus is the most common cause of severe diarrhea in children. Rotavirus is estimated to cause approximately 37 percent of diarrheal deaths in children under age five worldwide, killing more than 450,000 children each year. It also causes about 40 percent of all hospitalizations for diarrheal disease in children under age five worldwide. While every child is at risk of rotavirus infection, more than 95 percent of rotavirus deaths occur in low-income countries, where access to treatment for severe rotavirus-related diarrhea may be limited or unavailable. Rotavirus vaccines provide the best protection against rotavirus and are saving children’s lives and improving health where they are in use.

13. **Where can I find more information on rotavirus disease?**

More information on rotavirus disease is available from the US Centers for Disease Control and Prevention (CDC): Rotavirus page.
B. Rotavirus vaccines overview

1. Why are rotavirus vaccines needed/necessary?

Vaccines are the best way to protect children from rotavirus and the dehydrating diarrhea that it can cause. Improvements in hygiene, water quality, and sanitation that stop many bacteria and parasites that cause other types of diarrhea do not adequately prevent the spread of rotavirus. Rotavirus vaccines are a critical part of a comprehensive strategy to prevent and manage diarrheal disease. Introducing rotavirus vaccines with other diarrhea prevention and treatment methods, such as oral rehydration therapy, zinc supplementation, exclusive breastfeeding, improved hygiene, water quality, sanitation, and nutrition, can significantly reduce child illnesses and deaths.

2. Are rotavirus vaccines approved and recommended by the World Health Organization (WHO)?

Rotavirus vaccines Rotarix® and RotaTeq® are both approved and recommended by WHO. The vaccines were initially approved for use in Europe and America on the basis of efficacy data from these regions in 2006. Subsequently, after proof of efficacy in Asia and Africa, WHO recommended that rotavirus vaccines be introduced into every country’s national immunization program, particularly in countries where diarrheal disease is a major health problem.

3. What rotavirus vaccines are available?

There are two orally administered rotavirus vaccines available on the global market today:

- Rotarix®, manufactured by GlaxoSmithKline (GSK).
- RotaTeq®, manufactured by Merck & Co., Inc.

There are three orally administered rotavirus vaccines licensed for national markets only:

- ROTAVAC®, manufactured by Bharat Biotech International Limited and licensed for use in India in 2014.
- Rotavin-M1®, manufactured by the Center for Research and Production of Vaccines and licensed for use in Vietnam in 2007.

Other new vaccines are being developed by manufacturers in India, China, and Brazil, and may be available soon.
4. **How are rotavirus vaccines administered?**

Both Rotarix® and RotaTeq® are given orally, with each dose having a volume of ~2 cubic centimeters given through a nozzle that has to pass through the lips and be deposited on the inside of the cheek.

5. **When do children receive rotavirus vaccines?**

Each country has its own immunization schedule. Both rotavirus vaccines are given orally but differ in the number of doses given. In general, in low-income countries, RotaTeq® is given in three doses at 6 weeks, 10 weeks, and 14 weeks of age, and Rotarix® is given in two doses at 6 weeks and 10 weeks of age. In middle- and upper-income countries, RotaTeq® is given in three doses at 2 months, 4 months, and 6 months of age, and Rotarix® is given in two doses at 2 months and 4 months of age. Differences in rotavirus immunization schedules are generally due to existing routine immunization program schedules and the logistics of delivering multiple vaccines at the same time.

In many low-income countries, due to challenges related to health service access, children may not receive their vaccines on schedule. WHO recommends in its rotavirus position paper that countries consider providing rotavirus vaccination to these children even if later than the immunization schedule because the benefits of rotavirus vaccination, including preventing hospitalizations and deaths from diarrhea, far exceed any possible low-level risks associated with the vaccine.

6. **When did the currently globally available rotavirus vaccines, Rotarix® and RotaTeq®, become licensed and prequalified?**


7. **Was there another/earlier rotavirus vaccine? What about RotaShield®?**

RotaShield® was the first rotavirus vaccine available in the US in 1998. In 1999, RotaShield® was voluntarily withdrawn from the market by the manufacturer because intussusception was found to be a rare but potential side effect (1 case of intussusception for every 10,000 infants vaccinated). While a small risk of intussusception has also been associated with current vaccines, the risk (between 1 to 6 excess cases per 100,000 vaccinated infants) is much smaller than that of RotaShield®. WHO and immunization advisory committees in countries

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*a In South Africa, for example, Rotarix® is given at 6 and 14 weeks of age.*
with published intussusception studies have unanimously upheld their recommendation for universal rotavirus vaccination because the substantial benefits of vaccination far outweigh the potential low-level risk of intussusception.12,14,16

To learn more about intussusception, please see section D, “Rotavirus vaccines safety and potential side effects,” below.

8. How many countries are now using rotavirus vaccines?

As of January 1, 2016, 80 countries have introduced rotavirus vaccines in their national immunization programs (i.e., public sector).17 Other countries, such as Canada, the Philippines, and Thailand, have introduced rotavirus vaccines in pilot or regional introductions. Rotavirus vaccines are also available in more than 100 countries through the private market.

To learn more about worldwide rotavirus vaccine introductions, please visit PATH’s Rotavirus Vaccine Access and Delivery website: Country introductions of rotavirus vaccines.17

9. Which Gavi-eligible countries have introduced rotavirus vaccines?

Gavi, the Vaccine Alliance, began offering support for rotavirus vaccines in 2006. As of January 1, 2016, rotavirus vaccines have been introduced in 37 Gavi-eligible countries:17

- 2006: Nicaragua
- 2008: Bolivia
- 2009: Honduras
- 2010: Guyana
- 2011: Sudan
- 2012: Ghana, Rwanda, Moldova, Yemen, Armenia, Malawi, Tanzania
- 2013: Georgia, Haiti, The Gambia, Burkina Faso, Ethiopia, Zambia, and Burundi
- 2014: Mali, Cameroon, Sierra Leone, Republic of the Congo, Angola, Zimbabwe, Madagascar, Uzbekistan, Togo, Djibouti, Kenya, Niger, Eritrea, Senegal, Mauritania
- 2015: Tajikistan, Mozambique, Guinea-Bissau

For more information on Gavi and Gavi eligibility criteria, please visit www.gavi.org. To learn more about Gavi-supported rotavirus vaccine introductions, please visit PATH’s Rotavirus Vaccine Access and Delivery website: Country introductions of rotavirus vaccines.17

10. Will Gavi support the introduction of rotavirus vaccines in more countries?

As of January 1, 2016, Gavi has approved three additional countries for rotavirus vaccine support: Central African Republic, Côte d’Ivoire, and Liberia.18
C. Rotavirus vaccine efficacy, effectiveness, and impact

1. **What is the “real-world” impact of rotavirus vaccines? Have countries experienced reductions in death and hospitalizations after introducing rotavirus vaccines?**

Rotavirus vaccines are dramatically improving the health and well-being of children around the world by substantially reducing severe diarrhea. Swift and significant declines in hospitalizations and deaths due to rotavirus and all-cause diarrhea have been observed in many of the countries that have introduced rotavirus vaccines into their national immunization programs, including Austria, Australia, Belgium, Bolivia, Brazil, El Salvador, Finland, Honduras, Mexico, Nicaragua, Panama, the United States, and Venezuela.\(^\text{19}\)

A recent review of available clinical trial data from countries routinely using rotavirus vaccines in their national immunization programs (excluding those that have introduced recently due to data not yet being available), found that rotavirus vaccines have reduced rotavirus hospitalizations by 49-92 percent and all-cause diarrhea hospitalizations by 17-55 percent.\(^\text{20}\) In addition, the review found that all-cause diarrhea deaths were reduced by 22-50 percent in some settings.\(^\text{20}\)

To learn more about the impact of rotavirus vaccines, please visit PATH’s Rotavirus Vaccine Access and Delivery website: [Tables | Rotavirus vaccine impact].\(^\text{19}\)

2. **Do rotavirus vaccines also protect children and adults who have not been vaccinated? Do they enable herd immunity?**

In some countries where rotavirus vaccines have been introduced, researchers are finding significant reductions in rotavirus diarrhea hospitalizations in unvaccinated adults and children, suggesting the benefits of rotavirus vaccines extend beyond infants and provide indirect protection to unvaccinated children and adults by reducing spread of the virus (an effect called herd immunity).\(^\text{19;21}\)

3. **How many lives can be saved with these vaccines?**

In Gavi-eligible countries, where 95 percent of deaths due to rotavirus occur, more than 2.4 million child deaths can be prevented by 2030 by accelerating access to lifesaving rotavirus vaccines.\(^\text{22}\) If used in all Gavi-eligible countries, rotavirus vaccines could prevent an estimated 180,000 deaths and avert 6 million clinic and hospital visits each year, thereby saving US$68 million annually in treatment costs.\(^\text{22}\)

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\(^b\) Effectiveness refers to how well a vaccine works against a disease outcome in a setting of routine vaccine use (“real-world” use). Vaccine impact is the overall reduction in disease burden due to the vaccine. How well a vaccine works in controlled settings such as a clinical trial is referred to as efficacy.
4. **Does the vaccine provide 100 percent protection against rotavirus? Can you still get rotavirus even with the vaccine?**

While no medical intervention or product is 100 percent effective, rotavirus vaccines do provide the best protection available today against rotavirus, the most common cause of severe diarrhea. Research suggests that rotavirus vaccines are most effective at preventing the most severe and life-threatening cases of rotavirus. A small proportion of vaccinated infants may develop rotavirus disease more than once because neither the vaccine nor natural infection provides full protection from future infections. Usually, a person’s first infection with rotavirus causes the most severe symptoms.

5. **How long do rotavirus vaccines provide protection against rotavirus? Does protection decline over time?**

In high-income countries, rotavirus vaccines have been shown to protect infants through the third year of life. In low-income countries, the rotavirus threat is greatest during the first year of life. In clinical studies in Africa and Asia, rotavirus vaccines have been shown to provide the greatest protection during this first year. Efficacy in the second year of life may be lower in low-income countries, but further evaluation is required to understand in which populations and under what circumstances vaccine efficacy declines.

6. **Do rotavirus vaccines work equally well in both high- and low-income countries?**

Clinical studies have shown that rotavirus vaccine efficacy against severe rotavirus during the first year of life has ranged from 85 to 98 percent in middle- to high-income countries, including in Latin America, and 51 to 64 percent in low-income countries in Africa and Asia.

7. **Why is rotavirus vaccine efficacy different between high- and low-income countries?**

Data from clinical studies in middle- and high-income countries demonstrate higher vaccine efficacy than data from low-income countries. While we do not know why this difference in efficacy exists, lower efficacy of oral vaccines is typical in impoverished, high-mortality settings. This is seen with other orally administered vaccines like polio, cholera, and typhoid. Several factors may contribute to lower efficacy, such as the age of the child when the vaccine is administered, co-administration with oral polio vaccine, possible interference by maternal antibodies, micronutrient deficiencies, persistent exposure to pathogens, higher prevalence of co-infections, or wide varieties of virus strains. The Vaccine Implementation Technical Assistance Consortium (VITAC), PATH, and others are studying these factors so that national health ministries will ultimately be able to optimize rotavirus vaccination strategies and provide children the best possible protection.
8. **Will rotavirus vaccines be useful in low-income countries even if the efficacy is lower?**

Although lower vaccine efficacy was observed in some clinical trials in certain low-income countries compared with data from high-income countries, rotavirus vaccines are expected to have a *major* public health impact in areas where the rotavirus burden is greatest—such as in low-resource settings in Africa and Asia.\(^{23,35}\) Efficacy is only one factor in assessing the potential impact of a vaccine; the other critical factor is the incidence of severe disease. The vaccine likely will have a greater impact than we have seen elsewhere, even at a lower efficacy rate, because rotavirus vaccines will still substantially reduce severe cases of rotavirus diarrhea—those that are most life threatening.\(^{23,35}\)

9. **Are rotavirus vaccines cost-effective?**

Rotavirus vaccines are cost-effective and not only improve child health, but they also save lives. Vaccination lessens the tremendous economic and health burden of rotavirus disease, thereby contributing to poverty reduction and economic growth. Published studies have consistently concluded that the introduction of rotavirus vaccines into low-income countries would be cost-effective using internationally established criteria.\(^{36}\)

10. **Are there different strains of rotavirus? What rotavirus strains are contained in the currently globally licensed rotavirus vaccines, Rotarix® and RotaTeq®?**

Globally, five rotavirus strains comprise approximately 90 percent of all typed strains.\(^{37}\) Rotarix® is derived from a single strain that was isolated from an infant with rotavirus diarrhea.\(^{32}\) RotaTeq® is derived from a collection of five different strains made from mixtures (reassortants) of human and bovine rotaviruses.\(^{10}\) Rotavirus strains vary by region and by country. In general, rotavirus strain diversity is greatest in low-resource regions.\(^{37}\)

11. **Do rotavirus vaccines protect against strains not found in the vaccine?**

Yes. Current rotavirus vaccines protect against a wide variety of strain types, even those not contained in the vaccines.\(^{25,38-41}\) Rotavirus strain diversity is a complex issue as new strains emerge or evolve and appear in the human population through instances such as natural, molecular evolution.\(^{42,43}\) Although the diversity and distribution of rotavirus strains differ from year to year and region to region, clinical trials and post-licensure evaluations of the two rotavirus vaccines currently on the market, including studies in low-income countries in Africa and Asia, found that these vaccines provide protection against a broad range of rotavirus strains.\(^{25,38-41,44}\)
12. Does strain variation have any effect on vaccine efficacy?

In settings with a diversity of circulating rotavirus strains, studies show that rotavirus vaccines provide protection against a broad range of rotavirus strains, even strains not included in the vaccines.24;26;38;39;41

13. Where can I find more information on the real-world impact (effectiveness) of rotavirus vaccines?

More information on the real-world impact of rotavirus vaccines is available on PATH’s Rotavirus Vaccine Access and Delivery website: Tables | Rotavirus vaccine impact.19

D. Rotavirus vaccine safety and potential side effects

1. Are rotavirus vaccines safe?

Both vaccines on the global market today, Rotarix®, manufactured by GlaxoSmithKline, and RotaTeq®, manufactured by Merck & Co., Inc., have strong safety records, including clinical trials involving tens of thousands of infants as well as clinical experience with millions of recipients in the more than 65 countries around the world that have introduced the vaccines into national immunization programs, and the benefits of these vaccines are substantial and far exceed any possible low-level risks.11;45-49 However, no medical products, such as drugs or vaccines, are 100 percent safe.

The ROTAVAC® safety profile has been evaluated by the WHO Global Advisory Committee on Vaccine Safety (GACVS) based only on data from pre-licensure clinical trials, as ROTAVAC® has been recommended for inclusion but not yet rolled out into India’s Universal Immunization Programme. GACVS concluded that it supports further use of the vaccine.50

2. What are potential side effects of rotavirus vaccination?

Most children who get vaccinated will not experience any side effects. However, there is a slight chance of a few minor symptoms, which include diarrhea, vomiting, and irritability. In rare cases, a condition called intussusception has been associated with rotavirus vaccination. WHO and immunization advisory committees in countries with published vaccine safety data have unanimously upheld their recommendations for universal rotavirus vaccination because the substantial benefits of vaccination to prevent hospitalizations and death far outweigh the potential low-level risk of intussusception.12;14-16
3. **What is intussusception?**

Intussusception is when one portion of the bowel slides into the next, much like the pieces of a telescope. When this occurs, it creates a blockage in the bowel. If it is not detected and treated early, it can cause internal bleeding, a hole in the intestines, and infection in the abdomen, because the intestinal tissue has died from the decreased blood flow. In some cases surgery might be required. If untreated, intussusception can be fatal.

4. **What causes intussusception and who is susceptible to intussusception?**

Intussusception is a rare event but occurs worldwide. It occurs naturally in about 74 per 100,000 children globally and 50 per 100,000 children in the United States and other high-income countries. In most cases the cause is unknown. Some cases may be caused by a polyp or tumor in the bowel—both of these are groups of cells growing in the bowel that are not normal. Although people of any age can get intussusception, it is most common among infants in the first year of life, generally between the ages of four and seven months.

Studies have shown a small increase in cases of intussusception shortly after the first or second dose of rotavirus vaccine (within three weeks of the first dose in the US and Australia). These studies have not determined whether rotavirus vaccines affect the overall incidence of intussusception among all infants in a population.

5. **Why do a small number of infants develop intussusception after rotavirus vaccination, while most infants who get vaccinated do not?**

The reasons why some infants develop intussusception after rotavirus vaccination are not known. The reasons why unvaccinated infants develop intussusception are also not known in most cases.

6. **How is intussusception diagnosed and treated?**

Intussusception can be detected by examining the abdomen or performing an ultrasound. The best procedure to diagnose intussusception is a special type of enema, where liquid and/or air is put into the back passage using a catheter. This procedure is usually done in a hospital. The procedure is often successful in unblocking the bowel and the baby can usually go home after a short period of observation. If this procedure is unavailable, an operation is needed to unblock the bowel. After surgery, babies will need to stay in hospital for a few days and be given intravenous fluids until able to feed normally.

Some countries lack surveillance systems and clinical staff to monitor and diagnose intussusception. It is therefore imperative when giving a rotavirus vaccine for the vaccinator to remind caregivers about how to recognize danger signs of intussusception and when to seek health care.
7. **Is there a link between currently globally licensed rotavirus vaccines Rotarix® and RotaTeq® and intussusception?**

Yes. Studies have been conducted in Australia, Brazil, Mexico, and the United States to assess safety following the introduction of Rotarix® and RotaTeq® rotavirus vaccines. Results from these studies show a potential low-level risk of intussusception shortly after the first or second dose of rotavirus vaccine:

**Table 1.** Estimated risk of intussusception and benefits of rotavirus vaccination in Australia, Brazil, Mexico, and the United States

<table>
<thead>
<tr>
<th>Country</th>
<th>Diarrhea hospitalizations (deaths) prevented by vaccination</th>
<th>Intussusception hospitalizations (deaths) potentially caused by vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Australia</em></td>
<td>7,000 (0)</td>
<td>6 (0)</td>
</tr>
<tr>
<td><em>Brazil</em></td>
<td>69,600 (640)</td>
<td>55 (3)</td>
</tr>
<tr>
<td><em>Mexico</em></td>
<td>11,600 (663)</td>
<td>41 (2)</td>
</tr>
<tr>
<td><em>United States</em></td>
<td>53,444 (14)</td>
<td>35-166 (0.1-0.5)</td>
</tr>
</tbody>
</table>

Note: Table is derived from Table 6 in Yen et al, 2014. Estimates are for one fully vaccinated birth cohort followed to age 5 years.\(^{13}\)

However, the World Health Organization (WHO)’s Global Advisory Committee on Vaccine Safety, the US Centers for Disease Control and Prevention (CDC), the US Food and Drug Administration, the European Medicines Agency, and immunization advisory committees in countries with published intussusception studies have reviewed the data and determined that the benefits of rotavirus vaccination to prevent severe rotavirus diarrhea outweigh the low-level risk of intussusception.\(^{12;14-16;46;53}\) WHO, CDC, and immunization advisory committees in countries with published intussusception studies have upheld their recommendations to administer rotavirus vaccines to infants to prevent severe rotavirus diarrhea.\(^{12;14-16}\)

8. **What are the positions of the World Health Organization (WHO) and of immunization advisory committees in countries with published intussusception studies on the safety and continued use of Rotarix® and RotaTeq®?**

Based on the established benefits of rotavirus vaccination to prevent hospitalizations and death and the rare occurrence of intussusception, WHO, CDC, and immunization advisory committees in countries with published intussusception studies recommend the continued use of rotavirus vaccines for infants to prevent severe rotavirus diarrhea.\(^{12;14-16}\)

The benefits of rotavirus vaccination are substantial and include prevention of hospitalization for severe rotavirus diarrhea and death. The benefits of the vaccines outweigh the small increased risk of intussusception. Many countries that have introduced rotavirus vaccines have
experienced significant reductions in severe diarrhea, underscoring the incredible potential for rotavirus vaccines to improve child health and save lives.

9. Were large-scale clinical trials conducted to assess the safety of Rotarix® and RotaTeq® rotavirus vaccines before introduction?

Yes. The risk of intussusception for Rotarix® and RotaTeq® was assessed in large clinical trials prior to licensure in the United States, Finland, and Latin America. Each trial involved more than 60,000 participants and no increased risk for intussusception was observed. Researchers found that the risk of intussusception was similar among children who received the vaccine and those who received a placebo, indicating that the currently available vaccines are safe for use.

However, the clinical trials were not large enough to detect the low-level risk of intussusception identified in the post-licensure studies. In addition, while clinical trials are useful for assessing safety, they are conducted in specific populations under restricted conditions, which may differ from routine use of the vaccine. Thus, post-licensure surveillance is essential to detect any unexpected or rare side effects that require careful follow-up on hundreds of thousands of infants.

10. How do the rates of intussusception in RotaShield® (withdrawn from market in 1999) compare to the rates of intussusception found with the newer vaccines, Rotarix® and RotaTeq®?

The low-level risks of intussusception observed with the currently globally licensed vaccines Rotarix® and RotaTeq® are lower than the risk identified with the first rotavirus vaccine, RotaShield®, which was withdrawn from the market in 1999. RotaShield® posed an excess risk of intussusception in approximately 1 per 10,000 vaccinated infants in the US. The risk of intussusception with Rotarix® or RotaTeq® ranges from 1 to 6 excess cases per 100,000 vaccinated infants.

11. Has the new Indian-developed rotavirus vaccine ROTAVAC® been evaluated for a risk of intussusception?

Yes, during pre-licensure clinical trials, as ROTAVAC® has been recommended for inclusion but not yet rolled out into India’s Universal Immunization Programme. During the Phase 3 clinical trials of the vaccine, infants receiving ROTAVAC® did not experience a significantly higher level of adverse events compared to infants receiving placebo. At its meeting in June 2014, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety profile of ROTAVAC® using this clinical trial data. Because no cases of intussusception occurred in proximity to the time of vaccination, GACVS noted that the available evidence
“argues strongly against” a causative relationship between ROTAVAC® and intussusception and concluded that it supports further use of the vaccine.50

Because clinical trials are not large enough to assess low levels of risk such as the risk of intussusception, GACVS also recommends continued post-licensure safety surveillance—including intussusception surveillance—in India as well as in all countries that have introduced rotavirus vaccines.

12. Why are WHO, regulatory agencies, immunization advisory committees, and rotavirus vaccine manufacturers evaluating rotavirus vaccines so carefully for intussusception?

Currently globally licensed rotavirus vaccines Rotarix® and RotaTeq® are closely evaluated for a risk of intussusception because the first generation rotavirus vaccine, RotaShield®, which was withdrawn from the market in 1999, was associated with a small risk of intussusception after its routine introduction into the United States market.

Although neither Rotarix® or RotaTeq® were associated with intussusception during the clinical trials, post-marketing surveillance of rotavirus vaccines in Australia, Brazil, Mexico, and the United States has indicated there is a small increased risk of intussusception associated with rotavirus vaccines.13;15;45;52;56-60

While clinical trials are useful for assessing safety, they are not large enough to assess low levels of risk and they are conducted in specific populations under restricted conditions, which may differ from routine use of the vaccine. Thus, post-licensure monitoring and surveillance studies (such as case-series studies) are essential to detect any unexpected or rare side effects.

13. Where can I find more information on intussusception?

More information on intussusception is available from:

- US Centers for Disease Control and Prevention:
  - Vaccine Safety: Rotavirus
  - Rotavirus Vaccine Information Statement
  - Rotavirus Vaccine and Intussusception Update: CDC Expert Commentary [video].
- US Food and Drug Administration:
  - RotaTeq (Rotavirus Vaccine) Questions and Answers
  - Information on Rotarix- Labeling Revision Pertaining to Intussusception
- World Health Organization:
  - Update on intussusception following rotavirus vaccine administration (GACVS report Dec 2013)
position paper replaces the August 2007 position paper and December 2009 update])
- Rotavirus Vaccines and Intussusception (GACVS report Dec 2011)
- Rotavirus Vaccines and Intussusception (Global Advisory Committee on Vaccine Safety [GACVS] report Dec 2010)
- Australian Government Department of Health
  - Rotavirus vaccination and the risk of intussusception (Therapeutic Goods Administration)
  - Rotavirus vaccine and intussusception information for Parents and Guardians (Immunise Australia)

14. Do rotavirus vaccines contain a pig virus (porcine circovirus)?

In March 2010, DNA fragments of porcine circovirus were found in both globally licensed rotavirus vaccines. Porcine circovirus is a small, circular virus composed of a single strand of DNA. Porcine circovirus is not pig or animal material but a virus commonly found in pigs that is not known to cause illness in humans. While porcine circovirus has sometimes been referred to as the “pig virus” by the media, this is only because the virus is commonly found in pigs. DNA from porcine circovirus can be found in an enzyme obtained from pig pancreas. The DNA was found in rotavirus vaccines because this enzyme is used during some manufacturing steps in the production of rotavirus vaccines.

15. Is there a safety risk associated with the porcine circovirus that has been found in rotavirus vaccines?

The US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data from clinical trials and the spontaneous reports of porcine circovirus and concluded that there was no evidence of a public health risk. Additionally, the regulatory agencies and WHO found that all data supported the continued safety of the vaccines and that the proven benefits of vaccination far outweighed any known risk associated with use of rotavirus vaccines.

16. Where can I find more information on porcine circovirus?

More information on porcine circovirus is available from:

- US Food and Drug Administration: Information for Parents and Caregivers.
- World Health Organization: Porcine circoviruses and rotavirus vaccines.
References


15. Cortese M. Summary of intussusception risk and benefits of rotavirus vaccination in the United States. Atlanta, GA.


