Rotavirus is a leading cause of viral gastroenteritis among infants and young children aged between 6 months and 2 years. It is also an important cause of severe dehydrating diarrhea and electrolyte disturbances. The global mortality rate for rotavirus is high, estimated at 450,000-600,000 deaths per year. Epidemiologic data show that rotavirus remains the most common cause of severe diarrhea in developed countries. Therefore, vaccination serves as a primary prevention strategy to reduce rotavirus burden in order to diminish severe disease, death and use of public health resources.

Microbiology
Rotavirus is a double-stranded RNA virus in the family Reoviridae. It is an icosahedral virus composed of three layers: outer capsid, inner capsid, and internal core. The outer capsid contains two proteins: VP4 and VP7, which bear type-specific antigenic determinants and induce a serotype-specific protective immune response. The inner capsid contains VP6 protein, which bears group-specific antigenic determinants and represents viral structure protein. The internal core contains three structural proteins: VP1, VP2, and VP3. Rotavirus can be classified into serogroups by VP2 and VP6 (serogroups A to G). Serogroups A to C cause disease in humans, and serogroups D to G cause disease in animals. Serogroup A causes endemic rotavirus gastroenteritis in children worldwide, whereas serogroups B and C often cause epidemic diseases in all ages. Rotavirus is also classified into G serotype by the VP7 protein, and P serotype by the VP4 protein. VP4 and VP7 proteins induce neutralizing antibody production and are therefore very important for
vaccine production. Currently, there are at least 15 G serotypes and 14 P serotypes\textsuperscript{5}.

**Pathogenesis**

The pathogenesis of rotavirus infection in human remains incompletely understood. After ingestion, rotavirus replication progresses from the proximal to the distal small intestine. Rotavirus replication is restricted to mature small intestine villous epithelial cells, which leads to blunted or shortened intestinal villi\textsuperscript{6}. Dysfunction of villi resulted by rotavirus infection causes net fluid and electrolyte secretion from the intestine. Moreover, decreased disaccharidase enzyme activity, especially lactase deficiency from villi abnormality, causes osmotic diarrhea\textsuperscript{5}.

**Immune responses to rotavirus**

The immune response to rotavirus in human is still not completely understood as most studies have been conducted on rotavirus infection in animals. Natural infection or immunization with one rotavirus serotype can induce protection against a different serotype. This process is called heterotypic protection and may be mediated by antibodies (Abs) against cross-reactive epitopes of VP4 and VP7. Abs to VP7 are normally serotype-specific, but Abs to VP4 are cross-reactive. Children are more likely to be protected against rotavirus after exposure to re-infection with a G type\textsuperscript{7}. In response to infection, CD4\textsuperscript{+} helper T-cells produce cytokines to block rotavirus replication, and induce proper B-cell responses to produce Abs, especially IgA\textsuperscript{8}. CD8\textsuperscript{+} T cells could also play a role in the development of protective immunity\textsuperscript{9}. The presence of intestinal mucosal surface-derived rotavirus-specific IgA in feces, and rotavirus-specific IgA in serum, is a predictive factor of protection against the disease in natural infection, but not in vaccine trials\textsuperscript{10}.

**Clinical Manifestations of rotavirus infection**

Rotavirus infection is characterized by severe vomiting and severe dehydration in infants and children, while it causes asymptomatic infection or mild gastroenteritis in older children and adults. The incubation period of rotavirus infection is 2-3 days.
The clinical manifestations begin with low grade fever and vomiting for 2-3 days followed by watery diarrhea for 1-4 days.

**Diagnosis of rotavirus infection**

Even though the identification of rotavirus diarrhea is not required in all cases given the lack of specific treatment, the definite diagnosis of rotavirus infection can reduce unnecessary usage of antibiotics. The available diagnostic tests are commercially available antigenic assays by ELISA and latex agglutination test which can detect only serogroup A. Other diagnostic tests include RT-PCR which is the most useful test in epidemic studies, electron microscopy, polyacrylamide gel electrophoresis (PAGE) and viral culture.

**Treatment**

No specific treatment is available for rotavirus gastroenteritis. The main treatment is rehydration with oral rehydration solutions (ORS) or intravenous fluid in severe cases. Infected infants are recommended to continue breastfeeding and to resume their regular diet to the extent that they can tolerate it during dehydration.

**Natural protection**

It has been found that individuals who were previously infected with rotavirus are better protected against subsequent severe infection. The incidence of rotavirus infection decreased from 11.3 infections per 100 child-months among children without previous infection, to 4.2 infections per 100 child-months with three previous infections. A study revealed that 75% of children were protected against rotavirus diarrhea, and 88% were protected against severe rotavirus diarrhea after natural infection. The adjusted efficacy in protection against rotavirus diarrhea was 77%, 83%, and 92%, after the first, second, and third infection, respectively.

**Rotavirus vaccines**

The mechanism of rotavirus vaccines is similar to the effects of protection against disease that follows natural infection. Oral, attenuated rotavirus vaccines are
available. The vaccines are based on either animal or human rotavirus. The first licensed rotavirus vaccine, named Rotashield™, was an oral tetravalent-rhesus-human reassortant rotavirus vaccine introduced in the United States in August 1998. However, it was withdrawn 14 months after introduction because of strong association with intussusception. Currently, there are two licensed vaccines used worldwide; Rotarix™ and Rotateq™.

**Monovalent animal-origin rotavirus vaccines**

Studies of rotavirus vaccines began in 1970, and eventually three animal rotavirus vaccines were developed: two bovine rotavirus strains (RIT 4237 and WC3) and one rhesus strain (RRV). However, the protective capacity of these vaccines has been shown to be inconsistent.

In 2000-2001, a lamb strain rotavirus vaccine (LLR) was produced in China. It is a 3 mL liquid formula vaccine given as a single dose to children at 2-24 months of age. Efficacy studies of this vaccine have been limited and it is approved for use only in China.

**Human-rhesus reassortant rotavirus vaccines (Rotashield™)**

Rotashield™ was the first reassortant rotavirus vaccine that contained three rhesus-human reassortant strains (the VP7 gene of human serotypes G1, G2, G4 strains substituted for the VP7 gene of the parent rhesus rotavirus [RRV]), and one strain of serotype G3 of RRV.

**Association with intussusception:** Rotashield™ was used in the United States in August 1998, but was withdrawn from the market 14 months after introduction because of an epidemiologic link to intussusception. A cluster of 15 cases of intussusception was observed in children within 2 weeks after receiving the 1st dose of vaccine. The risk was estimated to increase by 22 times within 5-7 days of vaccination. In 1999, the CDC reported that the relative risk 3-7 days after the first and second vaccination was 37.2 and 3.8, respectively (Table 1). The consensus rate of 1 per 10,000 vaccinated infants was estimated to be the overall incidence of this adverse event. Three possible etiologies have been proposed for...
intussusception; the first hypothesis was that the RRV-human reassortant vaccine may be pathogenic in a manner different from natural infection. The second hypothesis was that the vaccine was probably given in a dose larger than normal infection, and the third hypothesis suggested that the heterologous host virus from RRV-human reassortant vaccine may be the pathogenic cause. The most likely cause of intussusception was the unique biological feature of the rhesus strain, whereby it invades gut-associated lymphoid tissue to a greater extent than RRV-human or bovine-human reassortant rotavirus, and causes lymphoid hyperplasia of Peyer’s patches\textsuperscript{21}.

### Table 1. Risk of intussusception after RotaShield\textsuperscript{TM} administration

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>Risk Period (days)</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>3-7</td>
<td>14.4 (7.0-29.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>8-14</td>
<td>5.3 (2.1-13.9)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>15-21</td>
<td>1.1 (0.3-3.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>First dose</td>
<td>3-7</td>
<td>37.2 (12.6-110.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>8-14</td>
<td>8.2 (2.4-27.6)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>15-21</td>
<td>1.1 (0.2-5.4)</td>
<td>0.87</td>
</tr>
<tr>
<td>Second dose</td>
<td>3-7</td>
<td>3.8 (1.0-14.0)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>8-14</td>
<td>1.8 (0.4-9.5)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>15-21</td>
<td>0.9 (0.1-8.6)</td>
<td>0.94</td>
</tr>
</tbody>
</table>


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Human-bovine reassortant rotavirus vaccines (RotaTeq™)

This vaccine is a pentavalent human-bovine reassortant vaccine containing five rotavirus strains; the first four reassortant rotaviruses express VP7 proteins (G1, G2, G3, G4) from the human rotavirus strain, attached to VP4 protein from the bovine rotavirus WC3, and the fifth reassortant virus expresses the attachment protein (P[8]) from the human rotavirus strain and outer capsid protein G6 from the bovine rotavirus strain.

**Efficacy:** RotaTeq™ was tested in a large phase III trial with more than 70,000 children enrolled from 11 countries, with most participants from the US and Finland. A total of three doses of vaccine were given; the first dose was given to children 6-12 weeks of age, with each subsequent dose given 4-10 weeks apart. The efficacy of RotaTeq™ against severe rotavirus gastroenteritis was 98%. The vaccine reduced hospitalization for G1-G4 rotavirus gastroenteritis by 96%, and reduced emergency room visits related to G1-G4 rotavirus gastroenteritis by 94%. A study conducted 3.1 years following the last dose of RotaTeq™ revealed that participants showed 94% efficacy against hospitalization and emergency room visits related to any serotype of rotavirus gastroenteritis.

In subgroup analysis of Rotavirus efficacy and safety trial (REST), pentavalent rotavirus vaccine also showed protective efficacy in premature infants and no impact of breastfeeding on vaccine efficacy.

**Safety:** Intussusception risk was evaluated 42 days after each vaccine dose, and the results showed that no increased risk of intussusception in the vaccine groups compared with the placebo groups. Diarrhea and vomiting were the most common adverse effects: 10.4% versus 9.1% for diarrhea, and 6.7% versus 5.4% for vomiting, in the vaccine and placebo groups, respectively.

A study conducted in the United States revealed that rotavirus immunization of infants reduced diarrhea hospitalizations of older children and adults. This suggested indirect protection of unvaccinated people or herd immunity.

**Administration:** RotaTeq™ is given orally in 2 mL doses. This vaccine was licensed by the US FDA in February, 2006. The recommended schedule is a three-dose regimen given at 2, 4, and 6 months of age. The first dose should be given between
6-12 weeks of age because there are insufficient data on the safety of the first dose of RotaTeq™ in older infants. Subsequent doses should be administered at 4-10 week intervals, and the complete three doses should be given by 32 weeks of age. RotaTeq™ can be given in conjunction with DTaP, Hib vaccine, IPD, hepatitis B vaccine, and pneumococcal conjugated vaccine.

Live-attenuated human rotavirus vaccine (Rotarix™)

Rotarix™ is a wild-type monovalent human rotavirus vaccine containing the G1P[8] strain, which represents the most common human rotavirus VP7 and VP4 antigens. Immunization with Rotarix™ provides at least partial cross-protection against most other serotypes.

**Efficacy:** A double-blind, placebo-controlled trial of Rotarix™, conducted in over 63,000 infants in Finland and South America, found that after administering two doses of the vaccine at 2 and 4 months of age, protective efficacy was 85% against severe rotavirus gastroenteritis with hospitalization, and 100% against the most severe dehydrating rotavirus gastroenteritis. It was better than the placebo in preventing rotavirus gastroenteritis from G1, G3, G4, and G9 serotypes, with 88-92% efficacy, but efficacy against G2 serotypes was not significant, at 41%.

The monovalent human rotavirus vaccine also showed evidence of cross protection to the emerging G9 strain: 77% (95%CI 18-96%) protective efficacy against severe rotavirus gastroenteritis in a Latin American Clinical study and the G2P[4] strain, with 77% (95%CI 42-91%) protective efficacy demonstrated in a case-control study in Brazil. Post-marketing studies showed that this rotavirus vaccine was also efficacious in less-developed countries with a larger number of rotavirus infected patients.

**Safety:** Another study revealed that there was no increase in intussusception among the vaccinated infant group (6 cases) compared with the placebo infant group (7 cases), within 31 days of any rotavirus vaccine dose. During the entire safety surveillance period, there were 9 intussusception cases in the vaccine group and 16 in the placebo group. There were no significantly different adverse events and
intussusceptions between vaccine group and placebo group from pooled analysis of clinical studies\textsuperscript{34}.

**Administration:** Rotarix\textsuperscript{TM} is given orally in 1 mL doses. This vaccine was first licensed in Europe in February 2006. The recommended administration is two doses to be given to children aged > 6 weeks, with a 4-week interval after the first dose. The 2 doses should be administered completely before 24 weeks of age.

**Comparison of RotaTeq\textsuperscript{TM} and Rotarix\textsuperscript{TM}**
Differences between RotaTeq\textsuperscript{TM} and Rotarix\textsuperscript{TM} include: composition of the parent strain of virus vaccine, dose regimen, percentage protection against severe rotavirus infection, and percentage reduction in hospitalization. Further details are shown in Table 2.

**Table 2. Comparison of RotaTeq\textsuperscript{TM} and Rotarix\textsuperscript{TM}**

<table>
<thead>
<tr>
<th>Trade name</th>
<th>RotaTeq\textsuperscript{TM}</th>
<th>Rotarix\textsuperscript{TM}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent strain</td>
<td>Bovine rotavirus strain</td>
<td>Human rotavirus strain</td>
</tr>
<tr>
<td>Dose regimen</td>
<td>3 doses at age 2, 4, and 6 months</td>
<td>2 doses at age 2 and 4 months</td>
</tr>
<tr>
<td>% protection against severe rotavirus infection</td>
<td>98</td>
<td>85</td>
</tr>
<tr>
<td>% reduction in hospitalization</td>
<td>63</td>
<td>42</td>
</tr>
</tbody>
</table>

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**Indication of rotavirus vaccination**

WHO and ACIP (the Advisory Committee on Immunization Practices) recommend rotavirus vaccination with either the monovalent human rotavirus vaccine or the pentavalent human-bovine reassortant rotavirus vaccine and that either should be included in all national immunization programs\textsuperscript{35, 36}.

**Contraindications for rotavirus vaccination**

Rotavirus vaccine should not be administered to infants with a history of severe allergic reaction to a previous dose of vaccine, and infants who are allergic to any ingredient of the vaccine. Infants with severe allergic reaction to latex rubber should not be given Rotarix\textsuperscript{TM} because the applicator is composed of latex rubber\textsuperscript{37}. Rotavirus vaccines should be avoided in infants with a history of intussusception\textsuperscript{38} and severe combined immunodeficiency\textsuperscript{39}.

**Precautions for rotavirus vaccination**

The potential risks and benefits should be considered before the administration of rotavirus vaccines to some infant groups. For example, the safety and efficacy of rotavirus vaccine has not been established in children with chronic gastrointestinal disease, such as Hirschsprung’s disease, and congenital malabsorption syndrome. Rotavirus vaccine’s benefits may outweigh risks in infants undergoing immunosuppressive drugs. For infants with moderate to severe gastroenteritis or other illnesses, the vaccine should be avoided until the illness is resolved\textsuperscript{37}.

**Special situations for rotavirus vaccination**

Rotavirus vaccines can be used in infants who are living in the same households with immunodeficient persons, because the protection of immunocompromised members afforded by infant immunization likely outweighs the risk of transmitting vaccine virus or vaccine-virus-associated diseases. Infants living with pregnant women may be vaccinated because the risk of infection from exposure to vaccine virus strains is very low due to pre-existing immunity. The re-administration of vaccine to infants after regurgitation or vomiting is not recommended. If a vaccinee is
hospitalized after a recent vaccination, additional precautions are not required other
than the universal precautions for preventing the spread of a vaccine virus\textsuperscript{40}.

**Porcine circovirus contamination of rotavirus vaccine**

In March 2010, Rotarix\textsuperscript{TM} was found to be contaminated with porcine circovirus 1
(PCV1) components. In May 2010, RotaTeq\textsuperscript{TM} was also found to be contaminated
with PCV1 and porcine circovirus 2 (PCV2). PCV1 and PCV2 are pig viruses which
are unlikely to cause illness in humans, and have been present since the early
stages of vaccine development. Because the benefits of rotavirus vaccines were felt
to outweigh the risk of PCV1 and PCV2 contamination the FDA recommended
continued use of both vaccines\textsuperscript{41}.

**Rotavirus vaccines under development**

- A bovine-human (UK) rotavirus reassortant tetravalent vaccine (BRV-TV): A study
  showed good efficacy against severe rotavirus gastroenteritis in parallel placebo-
  controlled trials of BRV-TV vaccine versus rhesus-rhesus-human rotavirus
  reassortant tetravalent vaccines (RRV-TV)\textsuperscript{42}.

- A human-bovine reassortant vaccine (116E, ROTAVAC): The 116E rotavirus strain
  is a naturally occurring reassortant strain G9P[11], containing one bovine rotavirus
  efficacy of 54 percent against severe rotavirus gastroenteritis have been completed
  but the vaccine is not yet licensed\textsuperscript{43}. 
REFERENCES


