Diarrheal disease has been recognized in humans since antiquity. Until the early 1970s, a bacterial, viral, or parasitic etiology of diarrheal disease in children could be detected in fewer than 30% of cases. In 1973, Bishop and colleagues observed a virus particle in the intestinal tissue of children with diarrhea by using electron micrography. This virus was subsequently called “rotavirus” because of its similarity in appearance to a wheel (rota is Latin for wheel). By 1980, rotavirus was recognized as the most common cause of severe gastroenteritis in infants and young children in the United States. It is now known that infection with rotavirus is nearly universal, with almost all children infected by 5 years of age. Rotavirus is responsible for 20–60 deaths per year in the United States and up to 500,000 deaths from diarrhea worldwide. A vaccine to prevent rotavirus gastroenteritis was first licensed in August 1998 but was withdrawn in 1999 because of its association with intussusception. Second-generation vaccines were licensed in 2006 and 2008.

Rotavirus
Rotavirus is a double-stranded RNA virus of the family Reoviridae. The virus is composed of three concentric shells that enclose 11 gene segments. The outermost shell contains two important proteins—VP7, or G-protein, and VP4, or P-protein. VP7 and VP4 define the serotype of the virus and induce neutralizing antibody that is probably involved in immune protection. From 1996 through 2005, five strains of rotavirus (G1–4, G9) accounted for 90% of isolates from children younger than 5 years in the United States. Of these, the G1 strain accounted for more than 75% of isolates.

Rotavirus is very stable and may remain viable in the environment for weeks or months if not disinfected.

Rotaviruses cause infection in many species of mammals, including cows and monkeys. These animal strains are antigenically distinct from those causing human infection, and they rarely cause infection in humans.

Pathogenesis
The virus enters the body through the mouth. Viral replication occurs in the villous epithelium of the small intestine. Replication outside the small intestine and systemic spread of the virus (viremia) are believed to be uncommon in immunocompetent persons. Infection may result in decreased intestinal absorption of sodium, glucose, and water, and decreased levels of intestinal lactase, alkaline phosphatase, and sucrase activity, and may lead to isotonic diarrhea.

The immune correlates of protection from rotavirus are poorly understood. Serum and mucosal antibodies against
VP7 and VP4 are probably important for protection from disease. Cell-mediated immunity probably plays a role in recovery from infection and in protection.

Recovery from a first rotavirus infection usually does not lead to permanent immunity. After a single natural infection, 38% of children are protected against any subsequent rotavirus infection, 77% are protected against rotavirus diarrhea, and 87% are protected against severe diarrhea. Reinfection can occur at any age. Subsequent infections confer progressively greater protection and are generally less severe than the first. Recurrent rotavirus infections affect persons of all ages. Recurrent infections are usually asymptomatic or result in mild diarrhea that may be preceded or accompanied by vomiting and low-grade fever.

**Clinical Features**

The incubation period for rotavirus diarrhea is short, usually less than 48 hours. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. The first infection after 3 months of age is generally the most severe. Infection may be asymptomatic, may cause self-limited watery diarrhea, or may result in severe dehydrating diarrhea with fever and vomiting. Up to one-third of infected children may have a temperature greater than 102°F (39°C). The gastrointestinal symptoms generally resolve in 3 to 7 days.

The clinical features and stool characteristics of rotavirus diarrhea are nonspecific, and similar illness may be caused by other pathogens. As a result, confirmation of a diarrheal illness as rotavirus requires laboratory testing.

**Complications**

Rotavirus infection in infants and young children can lead to severe diarrhea, dehydration, electrolyte imbalance, and metabolic acidosis. Children who are immunocompromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation may experience severe or prolonged rotavirus gastroenteritis and may have evidence of abnormalities in multiple organ systems, particularly the kidney and liver.

**Laboratory Diagnosis**

The most widely available method for confirmation of rotavirus infection is detection of rotavirus antigen in stool by enzyme immunoassay (EIA). Several commercial test kits are available that detect an antigen common to human rotaviruses. These kits are simple to use, inexpensive, and very sensitive. Other techniques (such as electron microscopy, reverse transcription polymerase chain reaction, nucleic acid hybridization, sequence analysis, and culture)
are used primarily in research settings. Rotavirus antigen has also been identified in the serum of patients 3–7 days after disease onset, but at present, routine diagnostic testing is based primarily on testing of fecal specimens.

Epidemiology

Occurrence
Rotavirus occurs throughout the world. The prevalence of rotavirus strains varies by geographic area, and strains not included in the vaccine are present in some parts of the world.

Reservoir
The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be rare and probably does not lead to clinical illness. Although immunodeficient persons may shed rotavirus for a prolonged period, a true carrier state has not been described.

Transmission
Rotaviruses are shed in high concentration in the stool of infected persons. Transmission is by fecal-oral spread, both through close person-to-person contact and by fomites (such as toys and other environmental surfaces contaminated by stool). Rotaviruses are also probably transmitted by other modes such as fecally contaminated food and water and respiratory droplets.

Temporal Pattern
In temperate climates, disease is more prevalent during fall and winter. In the United States, annual epidemic peaks usually progress from the Southwest during November and December and spread to the Northeast by April and May. The reason for this seasonal pattern is unknown. In tropical climates, the disease is less seasonal than in temperate areas.

Communicability
Rotavirus is highly communicable, as evidenced by the nearly universal infection of children by age 5 years. Infected persons shed large quantities of virus in their stool beginning 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms. Rotavirus may be detected in the stool of immunodeficient persons for more than 30 days after infection. Spread within families, institutions, hospitals, and child care settings is common.
**Rotavirus**

**Rotavirus Disease in the United States**
- Estimated 3 million cases per year*
- 95% of children infected by 5 years of age
- Highest incidence among children 3 to 35 months of age
- Responsible for 5% to 10% of all gastroenteritis episodes among children younger than 5 years of age

*Prevaccine era

**Rotavirus Disease in the United States**
- Annually* responsible for:
  - more than 400,000 physician visits
  - more than 200,000 emergency department visits
  - 55,000-70,000 hospitalizations
  - 20-60 deaths
- Annual direct and indirect costs estimated at approximately $1 billion

*Prevaccine era

**Risk Groups for Rotavirus Infection**
- Groups with increased exposure to virus
  - children in child care centers
  - children in hospital wards (nosocomial rotavirus)
  - caretakers, parents of these children
  - children, adults with immunodeficiency-related diseases (e.g., severe combined immunodeficiency, HIV, bone marrow transplant)

**Secular Trends in the United States**
Rotavirus infection is not nationally notifiable in the United States. Estimates of incidence and disease burden are based on special surveys, cohort studies, and hospital discharge data.

In the prevaccine era an estimated 3 million rotavirus infections occurred every year in the United States and 95% of children experienced at least one rotavirus infection by age 5 years. The incidence of rotavirus is similar in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent the infection.

Infants younger than 3 months of age have relatively low rates of rotavirus infection, probably because of passive maternal antibody, and possibly breastfeeding. The incidence of clinical illness is highest among children 3 to 35 months of age. Rotavirus infection of adults is usually asymptomatic but may cause diarrheal illness.

In the United States, rotaviruses are responsible for 5% to 10% of all gastroenteritis episodes among children younger than 5 years of age. However, they are the most common cause of severe diarrheal disease and account for a higher proportion of severe episodes leading to clinic or hospital visits. Rotavirus accounts for 30% to 50% of all hospitalizations for gastroenteritis among U.S. children younger than 5 years of age, and more than 70% of hospitalizations for gastroenteritis during the seasonal peaks.

In the prevaccine era rotavirus infection was responsible for more than 400,000 physician visits, more than 200,000 emergency department (ED) visits, 55,000 to 70,000 hospitalizations each year, and 20 to 60 deaths. Annual direct and indirect costs were estimated at approximately $1 billion, primarily due to the cost of time lost from work to care for an ill child.

Rotavirus activity in the United States decreased significantly after introduction of rotavirus vaccine in 2006.

Groups at increased risk for rotavirus infection are those with increased exposure to virus. These include children who attend child care centers, children in hospital wards (nosocomial rotavirus), caretakers and parents of children in child care or hospitals, and children and adults with immunodeficiency-related diseases (e.g., severe combined immunodeficiency disease (SCID), HIV, bone marrow transplant).

**Rotavirus Vaccines**
The first rotavirus vaccines were derived from either bovine (cow) or rhesus (monkey) origin. Studies demonstrated that these live oral vaccines could prevent rotavirus diarrhea in young children, but efficacy varied widely. Because immunity to G (VP7) or P (VP4) proteins was associated with disease
protection and recovery, new live virus vaccines were developed that incorporated G proteins or both G and P proteins for each of the predominant serotypes.

In 1998, a rhesus-based tetravalent rotavirus vaccine (RRV-TV, Rotashield) was licensed and recommended for routine immunization of U.S. infants. However, RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception. The risk of intussusception was most elevated (more than a 20-fold increase) within 3 to 14 days after receipt of the first dose of RRV-TV, with a smaller (approximately 5-fold) increase in risk within 3 to 14 days after the second dose. Overall, the risk associated with the first dose of RRV-TV was estimated to be about one case per 10,000 vaccine recipients. Some researchers have suggested that the risk of intussusception associated with RRV-TV was age-dependent and that the absolute number of intussusception events, and possibly the relative risk of intussusception associated with the first dose of RRV-TV, increased with increasing age at vaccination.

**Characteristics**

There are currently two rotavirus vaccines licensed for use in the United States. RV5 (RotaTeq) is a live oral vaccine manufactured by Merck and licensed by the Food and Drug Administration in February 2006. RV5 contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains. Each 2-mL vial of vaccine contains approximately $2 \times 10^6$ infectious units of each of the five reassortant strains. The vaccine viruses are suspended in a buffer solution that contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, and tissue culture media. Trace amounts of fetal bovine serum might be present. The vaccine contains no preservatives or thimerosal.

Fecal shedding of vaccine virus was evaluated in a subset of persons enrolled in the phase III trials. Vaccine virus was shed by 9% of 360 infants after dose 1, but none of 249 and 385 infants after doses 2 and 3, respectively. Shedding was observed as early as 1 day and as late as 15 days after a dose. The potential for transmission of vaccine virus was not assessed.

RV1 (Rotarix), a live oral vaccine manufactured by GlaxoSmithKline, was licensed by the FDA in April 2008. RV1 contains one strain of live attenuated human strain 89-12 (type G1P1A[8]) rotavirus. RV1 is provided as a lyophilized powder that is reconstituted before administration. Each 1-mL dose of reconstituted vaccine contains at least $10^6$ median cell culture infective units of virus. The vaccine contains amino acids, dextran, Dulbecco’s modified Eagle
medium, sorbitol and sucrose. The diluent contains calcium carbonate, sterile water and xanthan. The vaccine contains no preservatives or thimerosal.

Fecal shedding of rotavirus antigen was evaluated in all or a subset of infants from seven studies in various countries. After dose 1, rotavirus antigen shedding was detected by ELISA in 50% to 80% (depending on the study) of infants at approximately day 7 and 0 to 24% at approximately day 30. After dose 2, rotavirus antigen shedding was detected in 4% to 18% of infants at approximately day 7, and 0 to 1.2% at approximately day 30. The potential for transmission of vaccine virus to others was not assessed.

### Vaccine Effectiveness

**Rotavirus Vaccine Effectiveness**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any rotavirus gastroenteritis</td>
<td>74%-87%</td>
</tr>
<tr>
<td>Severe gastroenteritis</td>
<td>85%-98%</td>
</tr>
<tr>
<td>Both vaccines significantly reduced physician visits for diarrhea, and reduced rotavirus-related hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

**Phase III clinical trials of RV5 (Rotateq) efficacy** have involved more than 70,000 infants 6 through 12 weeks of age in 11 countries.

After completion of a three-dose RV5 regimen, the efficacy of rotavirus vaccine against rotavirus gastroenteritis of any severity was 74%, and against severe rotavirus gastroenteritis (defined by severity of fever, vomiting, diarrhea and changes in behavior) was 98%. Vaccine efficacy varied by rotavirus serotype.

In a large study, the efficacy of RV5 vaccine against rotavirus gastroenteritis requiring office visits was evaluated among 5,673 children, and efficacy against rotavirus gastroenteritis requiring ED visits and hospitalizations was evaluated among 68,038 children during the first 2 years of life. RV5 vaccine reduced the incidence of office visits by 86%, ED visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%. The efficacy of fewer than three doses is not known.

**Phase III clinical trials of RV1 (Rotarix) efficacy** have involved more than 21,000 infants 6 through 12 weeks of age, primarily in two studies in Latin America and Europe.

After completion of a two-dose RV1 regimen, the efficacy of rotavirus vaccine against severe rotavirus gastroenteritis (Latin America study) was 85%, and against any rotavirus gastroenteritis (Europe study) was 87%. RV1 reduced hospitalization for rotavirus gastroenteritis by 85% to 100% (depending on the study). The efficacy of fewer than two doses is not known.

### Duration of Immunity

The duration of immunity from rotavirus vaccine is not known. Efficacy through 2 rotavirus seasons has been studied for both vaccines. In general efficacy is lower in the second season than in the first.
Vaccination Schedule and Use
Revised ACIP recommendations for the use of rotavirus vaccine were published in MMWR in February 2009. Because of similar estimates of efficacy and safety, neither The Advisory Committee on Immunization Practices (ACIP) nor the Academies of Pediatrics or Family Physicians state a preference for one vaccine versus the other.

ACIP recommends routine rotavirus vaccination of all infants without a contraindication. The vaccine should be administered as a series of either two or three oral doses, for RV1 and RV5, respectively, beginning at 2 months of age. The vaccination series for both vaccines may be started as early as 6 weeks of age. Subsequent doses in the series should be separated from the previous dose by 1 to 2 months. Rotavirus vaccine should be given at the same visit as other vaccines given at these ages.

The maximum age for any dose of RV1 approved by the FDA is 24 weeks, while the maximum FDA-approved age for any dose of RV5 is 32 weeks. This difference, as well as the different number of doses in the series could complicate decisions by clinicians who encounter children who received a brand of rotavirus vaccine other than the brand the clinician has in stock. There are currently no data on schedules that include both RV1 and RV5.

The ACIP developed age recommendations that vary from those of the manufacturers. ACIP recommendations state that the maximum age for the first dose of both vaccines is 14 weeks 6 days. This is an off-label recommendation for RV5 since the approved maximum age for the first dose of that vaccine is 12 weeks. The minimum interval between doses of both rotavirus vaccines is 4 weeks. The maximum age for any dose of either rotavirus vaccine is 8 months 0 days. No rotavirus vaccine should be administered to infants older than 8 months 0 days of age. This is an off-label recommendation for both vaccines, because the labeled maximum age for RV1 is 24 weeks, and the labeled maximum age for RV5 is 32 weeks.

ACIP did not define a maximum interval between doses. It is preferable to adhere to the recommended interval of 8 weeks. But if the interval is prolonged, the infant can still receive the vaccine as long as it can be given on or before the 8-month birthday. It is not necessary to restart the series or add doses because of a prolonged interval between doses.

There are few data on the safety or efficacy of giving more than one dose, even partial doses, close together. ACIP recommends that providers not repeat the dose if the infant spits out or regurgitates the vaccine. Any remaining doses should be administered on schedule. Doses of rotavirus vaccine should be separated by at least 4 weeks.
ACIP recommends that the rotavirus vaccine series should be completed with the same product whenever possible. However, vaccination should not be deferred if the product used for a prior dose or doses is not available or is not known. In this situation, the provider should continue or complete the series with the product that is available. If any dose in the series was RV5 (RotaTeq) or the vaccine brand used for any prior dose in the series is not known, a total of three doses of rotavirus vaccine should be administered.

Breastfeeding does not appear to diminish immune response to rotavirus vaccine. Infants who are being breastfed should be vaccinated on schedule.

There are at least 5 serotypes of rotavirus that may cause diarrheal disease in the United States. In addition, infants may experience multiple episodes of rotavirus diarrhea because the initial infection may provide only partial immunity. Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still begin or complete the 2- or 3-dose schedule.

**Contraindications and Precautions to Vaccination**

Rotavirus vaccine is contraindicated for infants who are known to have had a severe allergic reaction (anaphylactic) to a vaccine component or following a prior dose of vaccine. Latex rubber is contained in the RV1 oral applicator, so infants with a severe allergy to latex should not receive RV1. The RV5 dosing tube is latex free.

Some, but not all, postmarketing studies of the currently licensed vaccines have detected an increased risk for intussusception following rotavirus vaccine administration, particularly during the first week following the first dose of vaccine. As a result, in October 2011, ACIP added a history of intussusception as a contraindication to rotavirus vaccination.

In response to reported cases of vaccine-acquired rotavirus infection in infants with severe combined immunodeficiency (SCID) following rotavirus vaccine administration, ACIP added SCID as a contraindication to rotavirus vaccination in June 2010.

Children who are immunocompromised because of congenital immunodeficiency, or hematopoietic stem cell or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis. However, no safety or efficacy data are available regarding administration of rotavirus vaccine to infants who are, or are potentially immunocompromised due to either disease or drugs. Clinicians will need to use their judgment in this situation.
There are no data on the use of rotavirus vaccine among infants who are exposed to or infected with HIV. However, two considerations support vaccination of these infants. First, the HIV diagnosis might not be established in infants born to HIV-infected mothers by the time they reach the age of the first rotavirus vaccine dose. Only 3% percent or less of HIV-exposed infants in the United States will be determined to be HIV infected. Second, vaccine strains of rotavirus are considerably attenuated, and exposure to an attenuated rotavirus is preferable to exposure to wild-type rotavirus.

Rotavirus vaccine should generally not be administered to infants with acute, moderate or severe gastroenteritis, or other acute illness until the condition improves. However, infants with mild acute gastroenteritis or other mild acute illness can be vaccinated, particularly if the delay in vaccination will delay the first dose of vaccine beyond 15 weeks 0 days of age.

No data are available on the immune response to rotavirus vaccine in infants who have recently received a blood product. In theory, infants who have recently received an antibody-containing blood product might have a reduced immunologic response to a dose of oral rotavirus vaccine. However, 2 or 3 doses of vaccine are administered in the full rotavirus vaccine series, and no increased risk for adverse events is expected. ACIP now recommends that rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product.

Available data suggest that preterm infants (i.e., infants born at less than 37 weeks’ gestation) are at increased risk for hospitalization from rotavirus during the first 1 to 2 years of life. In clinical trials, rotavirus vaccine appeared to be generally well tolerated in preterm infants, although a relatively small number of preterm infants have been evaluated. ACIP considers the benefits of rotavirus vaccination of preterm infants to outweigh the risks of adverse events. ACIP supports vaccination of a preterm infant according to the same schedule and precautions as a full-term infant, provided the following conditions are met: the infant’s chronological age is at least 6 weeks, the infant is clinically stable, and the vaccine is administered at the time of discharge or after discharge from the neonatal intensive care unit or nursery. Although the lower level of maternal antibody to rotavirus in very preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, ACIP believes the benefits of vaccinating the infant when age eligible, clinically stable, and no longer in the hospital outweigh the theoretic risks.

Vaccine strains of rotavirus are shed in the feces of vaccinated infants. So if an infant were to be vaccinated with rotavirus vaccine while still needing care in the hospital, a theoretic
risk exists for vaccine virus being transmitted to infants in the same unit who are acutely ill, and to preterm infants who are not age eligible for vaccine. ACIP considers that, in usual circumstances, the risk from shedding outweighs the benefit of vaccinating an infant who will remain in the hospital and recommends that these infants not be vaccinated until they meet the conditions described above.

Although rotavirus is shed in the feces of vaccinated infants, transmission of vaccine virus has not been documented. Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. ACIP believes that the indirect protection of the immunocompromised household member provided by vaccinating the infant in the household, and thereby preventing wild-type rotavirus disease, outweighs the small risk for transmitting vaccine virus to the immunocompromised household member.

Infants living in households with pregnant women should be vaccinated according to the same schedule as infants in households without pregnant women. Because the majority of women of childbearing age have preexisting immunity to rotavirus, the risk for infection by the attenuated vaccine virus is considered to be very low. Although transmission of vaccine virus has not been documented, it is prudent for all members of the household to employ measures such as good hand washing after changing a diaper or otherwise coming in contact with the feces of the vaccinated infant.

**Adverse Reactions Following Vaccination**

**Intussusception**

The phase 3 clinical trials of both vaccines were very large, primarily to be able to study the occurrence of intussusception in both vaccine and placebo recipients. The RV1 trials included more than 63,000 infants, of whom half received vaccine and half received a placebo. In the 30 days following either vaccine dose, there were 7 cases of intussusception among the vaccine recipients and 7 cases diagnosed among the placebo recipients. The RV5 clinical trials included more than 69,000 infants, of whom half received vaccine and half received a placebo. In the 42 days after vaccination, 6 cases of intussusception were diagnosed among the vaccinated infants and 5 cases were diagnosed among the placebo recipients.

These data indicate the background incidence of intussusception in infants, as evidenced by its occurrence in infants who received a placebo. They also show that while intussusception is to be expected in recipients of rotavirus vaccine.
vaccine, the risk is no higher than among children who are not vaccinated.

**Other Adverse Events**
A variety of other adverse reactions were reported during the 7 or 8 days after rotavirus vaccination in the clinical trials, including vomiting in 15% to 18%, diarrhea in 9% to 24%, irritability in 13% to 62%, and fever in 40% to 43%. However, the rate of these symptoms in vaccinated children was similar to the rate in unvaccinated children. No serious adverse reactions attributable to rotavirus vaccine have been reported.

**Vaccine Storage and Handling**
Both rotavirus vaccines must be stored at refrigerator temperatures (35°–46°F [2°–8°C]) and protected from light. RV1 diluent may be stored at room temperature. The vaccines must not be frozen. The shelf life of properly stored vaccine is 24 months. RV5 should be administered as soon as possible after being removed from refrigeration. RV1 should be administered within 24 hours of reconstitution. Reconstituted RV1 may be stored at refrigerator or room temperature.

Healthcare personnel may be concerned about exposure to vaccine virus during administration of rotavirus vaccine or contact with vaccinated infants. Hand hygiene using soap and water or alcohol-based hand cleaners should already be standard practice wherever vaccines are being administered. This practice should minimize the risk of transmission of rotavirus vaccine virus during administration. Therefore, there are no restrictions on immunosuppressed or pregnant healthcare personnel administering the vaccine.

**Rotavirus Surveillance**
Rotavirus gastroenteritis is not a reportable disease in the United States. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at three sites that participate in the New Vaccine Surveillance Network, and reports of rotavirus detection from a sentinel system of laboratories. At the state and local levels, surveillance efforts at sentinel hospitals or by review of hospital discharge databases can be used to monitor the impact of the vaccine program. Special studies (e.g., case-control studies and retrospective cohort studies) will be used to measure the effectiveness of rotavirus vaccine under routine use in the United States. CDC has established a national strain surveillance system of sentinel laboratories to monitor circulating rotavirus strains before and after the introduction...
of rotavirus vaccine. This system is designed to detect new or unusual strains causing gastroenteritis that might not be prevented effectively by vaccination, which might affect the success of the vaccination program.

**Selected References**


CDC. Addition of severe combined immunodeficiency as a contraindication for administration of rotavirus vaccine. *MMWR* 2010;59(No. 22):687–8.


