

AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Prevention of Rotavirus Disease: Guidelines for Use of Rotavirus Vaccine

ABSTRACT. On February 3, 2006, a bovine-based pentavalent rotavirus vaccine (RotaTeq, Merck & Co Inc, Whitehouse Station, NJ) was licensed by the US Food and Drug Administration for use in infants in the United States. The American Academy of Pediatrics recommends routine immunization of infants with 3 doses of pentavalent rotavirus vaccine administered orally at 2, 4, and 6 months of age. The first dose should be administered between 6 and 12 weeks of age; immunization should not be initiated for infants older than 12 weeks of age. Subsequent doses should be administered at 4- to 10-week intervals, and all 3 doses of vaccine should be administered by 32 weeks of age. Pentavalent rotavirus vaccine can be coadministered with other childhood vaccines. Pentavalent rotavirus vaccine is contraindicated for infants with a serious allergic reaction to any vaccine component or to a previous dose of vaccine.

Key words: rotavirus vaccine, rotavirus gastroenteritis.

ABBREVIATIONS: AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; EIA, enzyme immunoassay; IgA, immunoglobulin A; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; DTaP, diphtheria and tetanus toxoids and acellular pertussis; RRV-TV, rhesus-human rotavirus reassortant-tetravalent vaccine; SIDS, sudden infant death syndrome; OPV, oral poliovirus; VSD, Vaccine Safety Datalink.

PURPOSE OF RECOMMENDATIONS AND RATIONALE

The purpose of this statement is to provide the rationale and recommendations for use of a bovine-based pentavalent rotavirus vaccine (RotaTeq) in US infants. The rationale for using rotavirus immunization for prevention or modification of rotavirus disease is based on several considerations. First, rates of rotavirus illness among children in industrialized and less developed countries are similar, indicating that clean water supplies and good hygiene have little effect on virus transmission, so further improvements in water or hygiene are unlikely to prevent the disease.¹⁻⁵ Second, in the United States, a high level of rotavirus morbidity continues to occur despite currently available therapies. For example, the rate of hospitalizations for gastroenteritis in young children declined only 16% from 1979 to 1995,^{6,7} despite the widespread recommendation by experts, including the American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC),^{8,9} for the use of oral rehydration solutions in the treatment of dehydrating gastroenteritis. Third, studies of natural rotavirus infection indicate that initial infection protects against subsequent severe gastroenteritis, although subsequent asymptomatic infections and mild disease might still occur.^{1,10,11} Finally, trials of pentavalent rotavirus vaccine in the United States and 10 other countries show efficacy rates of 98% for prevention of severe illness and 74% for prevention of rotavirus-induced diarrheal episodes of any severity.¹² These results are similar to the protection observed after natural rotavirus infection. Thus, immunization early in life, which mimics a child's first natural infection, will not prevent all subsequent disease but should prevent most cases of severe rotavirus disease and their sequelae (eg, dehydration, physician visits, hospitalizations, and deaths).

This statement provides recommendations regarding the use of pentavalent rotavirus vaccine in infants in the United States.

EPIDEMIOLOGY OF DISEASE

Rotavirus is a major cause of acute gastroenteritis in the United States, infecting almost all children in the first 3 to 5 years of life, with severe, dehydrating gastroenteritis occurring primarily among children 3 to 35 months of age. In the first 5 years of life, 4 out of 5 children in the United States will develop rotavirus gastroenteritis,^{1,4,13} 1 in 7 will require a clinic or emergency department visit, 1 in 70 will be hospitalized, and 1 in 200 000 will die from this disease.^{14,15}

In the United States, rotaviruses are proven to be responsible for only 5% to 10% of all gastroenteritis episodes among children younger than 5 years. However, infection with rotavirus results in more severe disease than with other pathogens causing gastroenteritis and, thus, accounts for a higher proportion of severe gastroenteritis episodes requiring outpatient or hospital visits.^{16,17} For example, rotavirus is responsible for 30% to 50% of pediatric admissions to hospitals because of gastroenteritis and 20% to 25% of cases of pediatric gastroenteritis in outpatient clinics.¹⁸⁻²¹ During peak rotavirus season, the virus may be the cause of more than 70% of inpatient pediatric admissions for gastrointestinal illness.⁷ Rotavirus is also an important cause of hospital-acquired diarrhea in children^{22,23} and is a major cause of acute gastroenteritis in children attending child care.²⁴⁻²⁶

In the United States, rotavirus causes yearly epidemics of disease from late fall to early spring. The peak of disease varies by region. In the southwest, the peak rotavirus season is in November-December. The peak of the epidemic then travels sequentially across the United States from west to east, concluding in April-May in the northeast.^{6,27,28}

Multiple serotypes of rotavirus are in circulation. Serotype is defined by 2 surface proteins, VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein),

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which induce neutralizing antibodies. A typing system has been developed for each protein.²⁹

Ten G serotypes and 11 P serotypes have been identified in humans. Four rotavirus strains (G1, G3, G4 combined with P1A[8], and G2 combined with P1B[4]) make up 96% of the globally identified strains.³⁰ Recently, previously rare G serotypes, such as G9, have emerged.

Predominant serotypes vary from year to year and region to region.

Rotavirus is transmitted from person to person primarily by the fecal-oral route. Children shed more than 100 billion virus particles per gram of stool during the acute illness.^{31,32} Shedding may occur before the development of symptoms and can persist for as long as 10 days after the onset of symptoms in immunocompetent hosts.³³ Spread of rotavirus infections within families is common. Thirty percent to 50% of adult contacts of infected infants become infected, although most are asymptomatic.^{34,35}

Clinical Manifestations of Disease

After an incubation period of 1 to 3 days, rotavirus gastroenteritis begins with acute onset of fever and vomiting followed 24 to 48 hours later by watery diarrhea.³⁶ Typically, there are 10 to 20 bowel movements per day. Symptoms generally persist for 3 to 8 days. Fever occurs in up to half of all infected children and is usually low grade, although up to one third of patients may have a temperature greater than 39°C. Vomiting is nonbilious and occurs in 80% to 90% of infected children. Vomiting is usually brief, lasting 24 hours or less in most children. Dehydration and electrolyte disturbances are the major sequelae of rotavirus infection and occur most often in the youngest children.^{37,38} Rotavirus infection is usually localized to the intestine, but rarely, involvement of extraintestinal sites, including the respiratory tract, liver, kidney, lymph nodes, and central nervous system, has been reported.³⁹⁻⁴²

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In immunocompetent children, disease tends to be most severe in those between 3 and 24 months of age, although 25% of cases of severe disease occur after 2 years of age.⁷ Patients with immunodeficiency, including those with human immunodeficiency virus (HIV) infection, solid organ or bone marrow transplantation, and natural killer cell deficiency, may suffer more severe or prolonged diarrhea.⁴³⁻⁴⁶

Most children are infected with rotavirus more than once. First infections are more likely to result in severe gastroenteritis than are subsequent infections. Protective immunity develops after rotavirus infection and is strongest against moderate to severe disease.¹ Subsequent infections are usually milder or may even be asymptomatic. Adults usually have asymptomatic or mild disease because of immunity from previous exposure.^{34,35}

Most mothers have rotavirus antibody from previous infection that is passed transplacentally, protecting the neonate. As a result, most infected neonates will have asymptomatic or mild disease.¹¹ An exception is the preterm infant, who is at greater risk of severe illness than the term infant because of the lack of transplacental maternal antibodies.⁴⁷

Because the clinical features and stool characteristics of diarrhea caused by rotavirus are nonspecific, confirmation of the diagnosis of rotavirus infection in children with diarrhea by laboratory testing is necessary in some clinical settings and for surveillance. The most frequently used method is antigen detection in stool by enzyme immunoassay (EIA) directed at a group antigen common to all group A rotaviruses, including those in the rotavirus vaccine. Stool specimens from less than 10% of children immunized with rotavirus vaccine may test positive by EIA for up to 2 weeks after the first immunization. Positive stool EIA test results are unlikely after subsequent doses.

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Vaccine

Description

The licensed pentavalent rotavirus vaccine is an oral vaccine that contains 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. The reassortants are propagated in Vero cells using standard tissue culture techniques.

The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. There are no preservatives or thimerosal.

Immunogenicity

The immune correlates of protection from rotavirus infection and disease are not fully understood. In a large phase III clinical trial (see Appendix A for definition of study phase) of pentavalent rotavirus vaccine, an increase in titer of rotavirus group-specific serum immunoglobulin A (IgA) antibodies was used as one of the measures of the immunogenicity of pentavalent rotavirus vaccine. Serum samples were obtained from a subset of study participants before immunization and approximately 2 weeks after the third dose, and seroconversion was defined as a threefold or greater increase in antibody titer from baseline. Seroconversion rates for

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IgA antibody to rotavirus were 95% among 189 vaccine recipients versus 14% in 161 recipients of the placebo.¹²

When administered simultaneously, a 3-dose series of pentavalent rotavirus vaccine does not diminish the immune response to *Haemophilus influenzae* type b (Hib) conjugate vaccine, inactivated poliovirus (IPV) vaccine, hepatitis B vaccine, pneumococcal conjugate vaccine, and the diphtheria and tetanus antigens in diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.⁴⁸ Because validation of the pertussis assays is still under review, insufficient immunogenicity data are available to confirm lack of interference when pentavalent rotavirus vaccine is concomitantly administered with childhood vaccines to prevent pertussis.

Efficacy

The efficacy of pentavalent rotavirus vaccine has been evaluated in 2 phase III trials.^{12,49} In these trials, the efficacy of pentavalent rotavirus vaccine after completion of a 3-dose regimen against rotavirus gastroenteritis of any severity was 74% and against severe rotavirus gastroenteritis was 98% (Table 1). Efficacy was observed against all G1-G4 and G9 serotypes (Table 2), but relatively few non-G1 rotavirus cases were reported.

In a large study,¹² the efficacy of pentavalent rotavirus vaccine in reducing the number of office visits for rotavirus gastroenteritis was evaluated among 5673 subjects and in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis among 68 038 subjects over the first 2 years of life. Pentavalent rotavirus vaccine reduced the incidence of office visits by 86%, emergency department visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96% (Table 3). Efficacy against all gastroenteritis hospitalizations of any etiology was 59%.

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The efficacy of pentavalent rotavirus vaccine in the second rotavirus season after immunization was 63% against rotavirus gastroenteritis of any severity and 88% against severe rotavirus gastroenteritis.¹²

Data on the efficacy of fewer than 3 doses of pentavalent rotavirus vaccine are limited. In the large study, the efficacy of pentavalent rotavirus vaccine in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis was evaluated in children receiving fewer than 3 doses of vaccine.⁵⁰ Although the study included more than 68 000 children, the number receiving fewer than 3 doses of vaccine or placebo was less than 8600. In an analysis assessing vaccine efficacy starting 14 days after each dose and including breakthrough cases of rotavirus gastroenteritis between doses, the estimated rate reduction in hospitalizations and emergency department visits of 1, 2, and 3 doses of vaccine in this study was 83%, 81%, and 95% respectively.

Neither breastfeeding nor concurrent administration of other childhood vaccines appears to diminish the efficacy of a 3-dose series of pentavalent rotavirus vaccine (Merck, unpublished data, 2005). Among 204 immunized infants born preterm (<37 weeks' gestation), the point estimate of vaccine efficacy against G1-G4 rotavirus gastroenteritis of any severity was comparable to that among nonpreterm infants (70%), but the confidence bounds included zero because of the small sample size (Merck, unpublished data, 2005).

Safety

Intussusception

Safety with respect to intussusception was evaluated in 71 725 subjects enrolled in phase III efficacy trials. In a large-scale safety and efficacy trial designed specifically to evaluate the risk of intussusception,¹² parents or legal guardians of all subjects were contacted by telephone

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or home visit on approximately day 7, 14, and 42 after each immunization and every 6 weeks thereafter for up to 1 year after the first dose. Parents were asked about all serious adverse experiences, including intussusception, among enrolled children. Potential intussusception cases were adjudicated according to a prespecified case definition that included radiographic, surgical, and autopsy criteria. For the prespecified 42-day postimmunization endpoint, 6 cases of intussusception were observed in the pentavalent rotavirus vaccine group versus 5 cases of intussusception in the placebo group (multiplicity-adjusted relative risk: 1.6). The data did not suggest an increased risk of intussusception relative to placebo. Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period after the first dose, which was the period of highest risk for the previously licensed rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV) vaccine (Table 4). In addition, no evidence of clustering of cases of intussusception was observed within a 7- or 14-day window after immunization for any dose. For the 1-year follow-up period after administration of the first dose, 13 cases of intussusception were observed in the pentavalent rotavirus vaccine group versus 15 cases of intussusception in the placebo group (multiplicity-adjusted relative risk: 0.9).

Other Adverse Events

Serious adverse events and deaths were evaluated in 71 725 infants enrolled in phase III trials (Table 5). Among pentavalent rotavirus vaccine and placebo recipients, the incidence of serious adverse events, including deaths, was similar. No deaths were attributed to immunization by blinded investigators. The most common cause of death (accounting for 17 of the 52 deaths) was sudden infant death syndrome (SIDS), and deaths from SIDS were equally distributed among pentavalent rotavirus vaccine and placebo recipients (N=8 and N=9, respectively).

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A subset of 11 722 subjects was studied in detail to assess other potential adverse experiences such as fever, diarrhea, and vomiting. In the 42 day period after immunization, vaccinees had a small but significantly ($P < .05$) greater rate of several symptoms compared with placebo recipients, including 1% excess of vomiting (15% vs 14%, respectively), 3% excess of diarrhea (24% vs 21%, respectively), 1% excess of nasopharyngitis (7% vs 6%, respectively), 2% excess of otitis media (15% vs 13%, respectively), and 0.4% excess of bronchospasm (1.1% vs 0.7%, respectively). Among pentavalent rotavirus vaccine and placebo recipients, the incidence of reported episodes of fever (43% vs 43%, respectively) and hematochezia (0.5% vs 0.3%, respectively) was similar.

In the 7-day period after immunization, vaccinees had a small but significantly ($P < .05$) greater rate of diarrhea, with an excess of 1% after dose 1 (10% vs 9%, respectively), 3% after dose 2 (9% vs 6%, respectively), and 3% after any dose (18% vs 15%, respectively). Similarly, vaccinees had a small but significantly ($P < .05$) greater rate of vomiting, with an excess of 2% after dose 1 (7% vs 5%, respectively) and 2% after any dose (12% vs 10%, respectively). The incidence of fever and irritability during the 7-day period after any vaccine dose was similar among pentavalent rotavirus vaccine and placebo recipients.

Safety in Preterm Infants

Pentavalent rotavirus vaccine or placebo was administered to 2070 preterm infants (25 to 36 weeks' gestational age, median 34 weeks) in the phase III trials. All preterm infants were monitored for severe adverse events, and a subset of 308 was monitored in detail for all adverse events. No cases of intussusception were reported among preterm infants. Among preterm infants given pentavalent rotavirus vaccine and placebo, the incidence of serious adverse events (5.5% vs 5.8%, respectively) was similar. Two deaths each were reported among preterm infants

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given pentavalent rotavirus vaccine (1 SIDS and 1 motor vehicle crash) and placebo (1 SIDS and 1 unknown cause).

Shedding and Transmission of Vaccine Strains

Fecal shedding of vaccine virus was evaluated by EIA in a subset of subjects enrolled in the phase III trials by obtaining a single stool sample during days 4 to 6 after each immunization visit and among all children who submitted a rotavirus antigen-positive stool specimen at any time. Vaccine virus was shed in 32 of 360 (8.9%) subjects after dose 1, 0 of 249 (0%) subjects after dose 2, and 1 of 385 (0.3%) subjects after dose 3. In phase III studies, 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 through epidemiologic studies.

Cost-Effectiveness

In a recent analysis that used current estimates of rotavirus disease burden, vaccine efficacy, vaccine coverage rates, and health costs, investigators estimated that a national rotavirus immunization program in which 3 doses of pentavalent rotavirus vaccine are administered at ages 2, 4, and 6 months would result in 255 000 fewer physician visits, 137 000 fewer emergency department visits, 44 000 fewer hospitalizations, and 13 fewer deaths per year in children younger than 5 years. From the health care perspective alone, immunization is likely to be cost saving at total cost per child (including administration costs) of up to \$66 per child (approximately \$22 per vaccine dose). A higher-priced vaccine would be increasingly unlikely to be cost saving, and at a cost of more than \$268 per child (approximately \$89 per dose), a rotavirus immunization program would most likely have a net cost to society (CDC unpublished data, 2006).

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Vaccine Administration and Storage

Pentavalent rotavirus vaccine is provided in a squeezable plastic dosing tube with a twist-off cap designed to allow for the vaccine to be administered directly to infants by mouth. Each tube contains a single 2-mL dose of the vaccine as a liquid buffered-stabilized solution that is pale yellow in color but may have a pink tint. This formulation protects the vaccine virus from gastric acid and stabilizes the vaccine, allowing for storage at refrigerator temperatures (2°C-8°C) for 24 months. Pentavalent rotavirus vaccine should be administered as soon as possible after being removed from refrigeration. For information on stability under conditions other than those recommended, call 1-800-637-2590.

Contraindications and Precautions

Contraindications

Serious Allergic Reaction to a Vaccine Component or a Previous Vaccine Dose

Pentavalent rotavirus vaccine should not be administered to infants who have severe hypersensitivity to any component of the vaccine or who have experienced a serious allergic reaction to a previous dose of pentavalent rotavirus vaccine. (Recommendation. Evidence grade D; expert opinion [see Appendix B].)

Precautions

Altered Immunocompetence

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected altered immunocompetence. (Recommendation. Evidence grade D; expert opinion) Children and adults who are immunocompromised because of congenital immunodeficiency, bone marrow transplantation, or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis. However, no

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safety or efficacy data are available for the administration of rotavirus vaccine to infants who are potentially immunocompromised, including:

- Infants with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system.
- Infants on immunosuppressive therapy (including high-dose systemic corticosteroids).
- Infants with primary and acquired immunodeficiency states, including HIV or acquired immunodeficiency syndrome (AIDS) or other clinical manifestations of infection with HIV; cellular immune deficiencies, and hypogammaglobulinemic and dysgammaglobulinemic states. Data from clinical trials are insufficient to support administration of rotavirus vaccine to infants with indeterminant HIV status who are born to mothers with HIV or AIDS.
- Infants who have received a blood transfusion or blood products, including immune globulins, within 42 days. In general, rotavirus vaccine should be deferred for 42 days following receipt of an antibody-containing product if possible. However, if the 42-day deferral would cause the first dose of rotavirus vaccine to be scheduled for ≥ 13 weeks of age, a shorter deferral interval should be used to ensure the first dose is administered before 13 weeks of age.

Moderate to Severe Acute Gastroenteritis

In usual circumstances, pentavalent rotavirus vaccine should not be administered to infants with acute, moderate to severe gastroenteritis until the condition improves.

(Recommendation. Evidence grade D; expert opinion) However, infants with mild acute gastroenteritis can be immunized, particularly if the delay in immunization may be substantial

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and might make the child ineligible to receive vaccine (eg, older than 12 weeks of age before immunization is initiated).

Pentavalent rotavirus vaccine has not been studied among infants with concurrent acute gastroenteritis, among whom its immunogenicity and efficacy theoretically can be compromised. For example, infants who received oral poliovirus (OPV) vaccine during an episode of acute gastroenteritis, in some instances, had diminished poliovirus antibody responses to OPV.

Moderate to Severe Febrile Illness

Infants with moderate to severe illness should be immunized as soon as they have recovered from the acute phase of the illness. (Recommendation. Evidence grade D; expert opinion) This precaution avoids superimposing adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine.

Preexisting Chronic Gastrointestinal Disease

Practitioners should consider the potential risks and benefits of administering pentavalent rotavirus vaccine to infants with preexisting chronic gastrointestinal disease. (Recommendation. Evidence grade D; expert opinion) Infants with preexisting chronic gastrointestinal conditions and who are not undergoing immunosuppressive therapy should benefit from pentavalent rotavirus vaccine immunization, and the benefits outweigh the theoretic risks. However, the safety and efficacy of pentavalent rotavirus vaccine have not been established for infants with these preexisting conditions (eg, congenital malabsorption syndromes, Hirschsprung disease, short-gut syndrome, or persistent vomiting of unknown cause).

Previous History of Intussusception

After administration of a previously licensed rotavirus vaccine (RRV-TV), an increased risk of intussusception was observed. Available prelicensure data from a large trial of 70 000

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infants show no evidence of an association between intussusception and pentavalent rotavirus vaccine. However, additional postlicensure surveillance data are required to confirm that the vaccine is not associated with intussusception at a lower rate than that would have been detected in prelicensure trials. In addition, some data suggest that infants with a history of intussusception may be at higher risk of a repeat episode than other infants. Therefore, until postlicensure data on safety of rotavirus vaccine are available, the risks and benefits of immunization should be considered when immunizing infants with a previous episode of intussusception.

(Recommendation. Evidence grade D; expert opinion)

RECOMMENDATIONS

Routine Immunization With Pentavalent Rotavirus Vaccine

Infants should receive 3 doses of pentavalent rotavirus vaccine administered orally at 2, 4, and 6 months of age. The first dose should be administered between 6 and 12 weeks of age (ie, on or before 12 weeks, 0 days of age). Subsequent doses should be administered at 4- to 10-week intervals, and all 3 doses of vaccine should be administered by 32 weeks of age (ie, on or before 32 weeks, 0 days). (Strong recommendation. Evidence grade A; well-designed, randomized, controlled trials)

Immunization should not be initiated for infants older than 12 weeks because of insufficient data on safety of the first dose of pentavalent rotavirus vaccine in older infants.

(Recommendation. Evidence grade D; expert opinion)

Vaccine should not be administered after 32 weeks of age because of insufficient data on the safety and efficacy of pentavalent rotavirus vaccine in infants after this age.

(Recommendation. Evidence grade D; expert opinion) Adverse events, such as fever, were

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substantially higher in children who initiated or completed the RRV-TV vaccine series after 6 months of age.⁵¹⁻⁵³

For infants in whom the first dose of pentavalent rotavirus vaccine is inadvertently administered off label at 13 weeks or older, the rest of the rotavirus immunization series should be completed as per the schedule defined above, because timing of the first dose should not affect the safety and efficacy of the second and third dose. (Recommendation. Evidence grade D; expert opinion)

Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus immunizations should still initiate or complete the 3-dose schedule because the initial infection frequently provides only partial immunity. (Recommendation. Evidence grade D; expert opinion)

Infants who are being breastfed can receive pentavalent rotavirus vaccine. The efficacy of pentavalent rotavirus vaccine is similar among breastfed and nonbreastfed infants. (Strong recommendation. Evidence grade A; well-designed, randomized, controlled trials)

Like other childhood vaccines, pentavalent rotavirus vaccine can be administered to infants with transient, mild illnesses, with or without low-grade fever.⁵⁴ (Recommendation. Evidence grade D; expert opinion)

Simultaneous Administration With Other Childhood Vaccines

Pentavalent rotavirus vaccine can be administered together with DTaP, Hib, IPV, hepatitis B, and pneumococcal conjugate vaccines. Available evidence suggests that the vaccine does not interfere with the immune response to the Hib, IPV, hepatitis B, and pneumococcal conjugate vaccines and the diphtheria and tetanus antigens in DTaP vaccine. (Strong recommendation. Evidence grade A; well-designed, randomized, controlled trials) Because

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validation of the pertussis assays is still under review, insufficient immunogenicity data are available to confirm lack of interference of immune responses when pentavalent rotavirus vaccine is concomitantly administered with childhood vaccines to prevent pertussis.

(Recommendation. Evidence grade D; expert opinion)

Special Situations

Preterm Infants (Those Born at <37 Weeks' Gestation)

Practitioners should consider the potential benefits and risks of immunizing preterm infants against rotavirus. Limited data suggest that preterm infants are at increased risk of hospitalization from viral gastroenteritis during their first year of life.⁴⁷ In clinical trials, the safety and efficacy of pentavalent rotavirus vaccine appears to be similar for preterm and term infants, although a relatively small number of preterm infants have been evaluated. The lower concentration of maternal antibody to rotaviruses in very low birth weight, preterm infants theoretically could increase the risk of adverse reactions from pentavalent rotavirus vaccine. The AAP supports immunization of preterm infants under the following conditions: the infant is at least 6 weeks of age, the infant is clinically stable, and the first dose of vaccine is given at the time of discharge or after the infant has been discharged from the hospital nursery. Until further data are available, the AAP considers the benefits of pentavalent rotavirus vaccine immunization of preterm infants to outweigh the theoretic risks. (Recommendation. Evidence grade B; randomized, controlled trials with minor limitations)

Exposure of Immunocompromised Persons to Immunized Infants

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be immunized. (Recommendation. Evidence grade D; expert opinion) Most experts believe the protection of the

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immunocompromised household member afforded by immunization of young children in the household outweighs the small risk of transmitting vaccine virus to the immunocompromised household member and any subsequent theoretic risk of vaccine virus-associated disease. To minimize potential virus transmission, persons having contact with the feces of the immunized infant (eg, after changing a diaper) should employ measures such as good hand washing for at least 1 week after the first dose of pentavalent rotavirus vaccine.

Exposure of Pregnant Women to Immunized Infants

Infants living in households with pregnant women can be immunized. (Recommendation. Evidence grade D; expert opinion) Most women of childbearing age would have preexisting immunity to rotavirus, so the risk of infection and disease from potential exposure to the attenuated vaccine virus strain is very low. In addition, immunization of young children would decrease potential exposure of the pregnant women to wild virus if the unimmunized infant suffers from rotavirus gastroenteritis.

Regurgitation of Vaccine

The practitioner should not readminister a dose of pentavalent rotavirus vaccine to an infant who regurgitates, spits out, or vomits during or after administration of vaccine. (Recommendation. Evidence grade D; expert opinion) The infant can receive the remaining recommended doses of pentavalent rotavirus vaccine at appropriate intervals. Data are limited regarding the safety of administering a dose of pentavalent rotavirus vaccine higher than the recommended dose and on the efficacy of administering a partial dose. Additional data on safety and efficacy are needed to evaluate the benefits and risks of readministration.

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Hospitalization After Immunization

If a recently immunized child is hospitalized for any reason, no precautions other than standard precautions need be taken to prevent the spread of vaccine virus in the hospital setting. (Recommendation. Evidence grade D; expert opinion)

Reporting Adverse Events

Any clinically significant or unexpected adverse events that occur after administration of rotavirus vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). The National Childhood Vaccine Injury Act requires health care professionals to report to VAERS 1) any event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine; or 2) any event listed in the Table of Reportable Events Following Vaccination (see <http://vaers.hhs.gov/reportable.htm>) that occurs within the specified time period after immunization. Pentavalent rotavirus vaccine is covered under the general category of rotavirus vaccines in the table of reportable events, and no specific conditions are listed for reporting. VAERS reporting forms and information can be requested 24 hours a day by calling 800-822-7967 or by accessing the VAERS Web site at <http://vaers.hhs.gov/>.

Enhanced Postlicensure Surveillance for Adverse Events

In prelicensure clinical trials, pentavalent rotavirus vaccine has not been associated with any serious adverse events, including intussusception. Nevertheless, continued monitoring for adverse events after introduction of pentavalent rotavirus vaccine into routine immunization programs is important, particularly in light of the previous experience with RRV-TV vaccine. In addition to manufacturer-sponsored phase IV studies, postlicensure monitoring will include enhanced review of adverse events reported to VAERS. The Vaccine Safety Datalink (VSD) will also be used to monitor intussusception risk associated with pentavalent rotavirus vaccine and to

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evaluate any other possible associations that may be identified through VAERS or in phase IV studies. The VSD project includes information on persons enrolled in 8 large health maintenance organizations, with an annual birth cohort of more than 90 000 infants. Data on all vaccines administered within the study population are recorded and linked with diagnoses from medical encounters to determine rates of potential adverse events resulting from immunization. Recently developed rapid-analysis methods allow the VSD to conduct near “real-time” monitoring for vaccine adverse events.

Given the background rate of natural intussusception among US infants (25-38 cases per 100 000 infants) and the large number of children who potentially are eligible for immunization, some intussusceptions are expected to occur in the 2-week period after immunization by chance alone that will be unrelated to the vaccine. Consequently, intensive postlicensure surveillance will be necessary to assess the safety of pentavalent rotavirus vaccine against this rare event.

Future Needs

Surveillance of Rotavirus Gastroenteritis

Rotavirus gastroenteritis is not a reportable disease in the United States, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Establishing rotavirus disease surveillance systems that are adequately sensitive and specific to document the effectiveness of immunization programs will be necessary. Current national surveillance systems for rotavirus infections include 1) review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses; 2) reports of rotavirus isolation from a sentinel system of laboratories; and 3) surveillance in 3 sites that participate in the New Vaccine Surveillance Network. At state and local levels, additional surveillance efforts—by enhanced surveillance at sentinel hospitals or by review of hospital

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discharge databases—will be necessary to monitor the effectiveness of the vaccine program.

Special studies (eg, case-control studies) will be needed to confirm the effectiveness of pentavalent rotavirus vaccine in routine programmatic use.

Detection of Unusual Strains of Rotavirus

A national strain surveillance system of sentinel laboratories has been established at the CDC to monitor the prevalence of rotavirus strains before and after the introduction of rotavirus vaccines. This system is designed to detect new or unusual strains that might not be effectively prevented by immunization and affect the success of the immunization program.

Research

Future research should include studies to determine the safety and efficacy of pentavalent rotavirus vaccine administered to preterm infants, infants with immune deficiencies, infants who live in households with immunocompromised persons, and infants with chronic gastrointestinal disease. Postlicensure studies also should be conducted to determine the relative efficacy of fewer than 3 doses of vaccine and to address the cost-effectiveness of immunization programs in various settings.

Introduction of Additional Rotavirus Vaccines

A monovalent attenuated human rotavirus vaccine (RotaRix, GSK Biologicals, Belgium) has shown good clinical efficacy and, in a trial of more than 60 000 infants, no increase in intussusception among vaccine as compared with placebo recipients.⁵⁵ As of August 2006, RotaRix is licensed in the European Union and 33 countries in Latin America, Africa, and Asia, but a licensure application has not yet been submitted in the United States.

Factors That May Influence Vaccine Acceptance

The success of a rotavirus immunization program depends on the acceptance and

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enthusiasm of physicians and other health care professionals who care for children and caregivers of infants. In light of the experience with the withdrawal of RRV-TV vaccine because of its association with intussusception, some health care professionals and parents might have concerns about immunization with pentavalent rotavirus vaccine. However, in a study by Iwamoto and colleagues,⁵⁶ 94% of surveyed pediatricians reported that they would use a new rotavirus vaccine if proved to be safer than RRV-TV vaccine and if recommended by the AAP and CDC for routine use among infants. Barriers to reintroducing a rotavirus vaccine were fear of adverse reactions among 95% of pediatricians, followed by potential high vaccine cost (63%) and amount of time required to educate parents (57%).

Immunization program personnel will benefit from education about rotavirus disease and rotavirus vaccine. Parental education on rotavirus gastroenteritis and on the vaccine also will be essential to establish and maintain public confidence in this vaccine and to avoid confusion by cases of gastroenteritis in early childhood resulting from nonrotaviral causes not preventable by pentavalent rotavirus vaccine.

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Table 1. Efficacy of Pentavalent Rotavirus Vaccine Against G1-4 Rotavirus Gastroenteritis by Disease Severity

	Number of Cases*			
	Vaccine (N=3484)	Placebo (N=3499)		
Disease Severity			% Efficacy	95% CI
Any	97	369	73.8	67.2-79.3
Severe [†]	1	57	98.2	89.6-100.0

* Per protocol population (includes only cases that occurred at least 14 days after dose 3)

[†] Severity score >16, as determined by the scoring system of Clark et al.⁵⁸

Table 2. G Serotype-Specific Efficacy of Pentavalent Rotavirus Vaccine Against Rotavirus Gastroenteritis of Any Severity

Serotype	Number of Cases		% Efficacy	95% CI
	Vaccine	Placebo		
	(N=3484)	(N=3499)		
G1	85	339	75.0	68.2-80.5
G2	6	17	63.4	2.7-88.2
G3	3	7	55.6	<0-92.6
G4	3	6	48.1	<0-91.6
G9	1	4	74.1	<0-99.5

Table 3. Efficacy of Pentavalent Rotavirus Vaccine by in Reducing Health Care Utilization for G1-4 Rotavirus Gastroenteritis

Type of Contact	Number of Cases*		% Rate Reduction	95% CI
	Vaccine	Placebo		
Hospitalizations [†]	6	144	95.8	90.5-98.2
ED Visits [†]	14	225	93.7	88.8-96.5
Office Visits [‡]	13	98	86.0	73.9-92.5

* Per protocol population (includes only cases that occurred at least 14 days after dose 3)

[†] N=34 035 vaccine and N=34 003 placebo recipients

[‡] N=2834 vaccine and N=2839 placebo recipients

Table 4. Intussusception Cases by Day Range in Relation to Dose

Day Range	Dose 1*		Dose 2*		Dose 3*		Any Dose*	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
1-7	0	0	1	0	0	0	1	0
1-14	0	0	1	0	0	1	1	1
1-21	0	0	3	0	0	1	3	1
1-42	0	1	4	1	2	3	6	5

* N=34 837 vaccine and N=34 788 placebo recipients

Table 5. Summary of Serious Adverse Events (SAEs) Within 42 Days of Any Dose

	Number (%) of Subjects	
	Vaccine	Placebo
No SAEs	35 289 (97.6)	34 614 (97.4)
SAEs	861 (2.4)	922 (2.6)
Dose-related SAEs	49 (0.1)	79 (0.2)
Deaths	15 (<0.1)	13 (<0.1)
Discontinued due to an SAE	83 (0.2)	72 (0.2)

Appendix A. Definitions of Study Phase

Most clinical trials are designated as phase I, II, or III, based on the type of questions that study is seeking to answer:

- In Phase I clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- In Phase III studies, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

Appendix B. Classification of Evidence-Based Statements*

The AAP definitions for evidence-based statements are listed in Tables B1 and B2.

Table B1. Guideline Definitions for Evidence-Based Statements

Statement	Definition	Implication
Strong Recommendation	A strong recommendation means that the subcommittee believes that the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B). [†] In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation means that the subcommittee believes that the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C). [†] In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (grade D) [†] or that well-done studies (grade A, B, or C) [†] show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set boundaries on alternatives; patient preference should have a substantial influencing role.

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No Recommendation	No recommendation means that there is both a lack of pertinent evidence (grade D) [†] and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.
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* American Academy of Pediatrics, Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874-877

† See Table B2 for the definitions of evidence grades.

Table B2. Evidence Quality for Grades of Evidence

Grade	Evidence Quality
A	Well-designed, randomized, controlled trials or diagnostic studies performed on a population similar to the guideline's target population
B	Randomized, controlled trials or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

* American Academy of Pediatrics, Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874-877