Prevention of Rotavirus Disease: Guidelines for Use of Rotavirus Vaccine

ABSTRACT. Virtually all children experience rotavirus (Rv) infection before school entry. In the United States and other temperate countries, Rv disease peaks in the winter and during this time is responsible for the majority of episodes of diarrhea in infants and young children. Data collected by the Centers for Disease Control and Prevention from 1979 through 1992 indicate that approximately 50,000 hospitalizations attributable to Rv occur annually in the United States, a number that approximates about 1 in 78 children being hospitalized with Rv diarrhea by 5 years of age.

RotaShield (Wyeth-Lederle Vaccines and Pediatrics, Philadelphia, PA) was licensed by the Food and Drug Administration on August 31, 1998, for oral administration to infants at 2, 4, and 6 months of age. The rationale for using Rv immunization for prevention or modification of Rv disease is based on several considerations. First, the rate of illness attributable to Rv among children is comparable in industrialized and developing countries, which indicates that improved public sanitation is unlikely to decrease the incidence of disease. Second, although implementation of oral rehydration programs to prevent dehydration has improved in the United States, widespread use is inadequate to prevent significant morbidity. Third, trials of rhesus rotavirus-tetavalent (Rv) vaccine in the United States, Finland, and Venezuela show efficacy rates of approximately 80% for prevention of severe illness and 48% to 68% against Rv-induced diarrheal episodes. These results are similar to the protection observed after natural Rv infection, which also confers better protection against subsequent episodes of severe disease than against mild illness. This statement provides recommendations regarding the use of Rv vaccine in infants in the United States.

EPIDEMIOLOGY OF ROTAVIRUS INFECTION

Rotavirus (Rv) is present in high concentrations in stools of infected children and may be excreted 2 days before and as many as 10 days after onset of symptoms in immunocompetent hosts. Rv can persist on fomites that may serve as reservoirs for infection, which is especially important in child care centers. Transmission occurs by the fecal-oral route, and common source outbreaks with person-to-person transmission have been reported. Data proving transmission by other routes are lacking. The incubation period is usually 1 to 3 days. Rv infections occur in many animals but animal-to-human transmission has not been documented.

Various epidemiologic studies have estimated that Rv causes greater than 3 million cases of diarrhea, 50,000 hospitalizations, and 20 to 40 deaths annually in the United States. The peak incidence of Rv infection in the United States and other temperate countries occurs in winter, with early activity in the southwest late in the fall and progressive geographic and temporal movement of activity to the northeast and east. More than 50% of diarrheal episodes requiring in-hospital care during the peak of the winter Rv season is attributable to Rv disease; virtually all children will have had at least one Rv infection by 4 years of age. Disease tends to be most severe between 3 and 24 months of age, although 25% of the cases of severe disease occur after 2 years of age. Infants younger than 3 months of age are relatively protected against Rv disease; breastfeeding and transplacental antibody may decrease the likelihood and severity of infection. In neonates generally are asymptomatic.

The incidence of Rv disease in countries 10 degrees above or below the equator is less seasonal than in temperate countries. Worldwide, Rv is estimated to cause more than 125 million cases of diarrhea annually in children younger than 5 years of age. Eighteen million cases are considered at least moderately severe, with approximately 600,000 deaths per year.

Because the clinical features and stool characteristics of diarrhea caused by Rv are nonspecific, confirmation of the diagnosis of Rv infection in children with diarrhea by laboratory testing is necessary in some clinical settings and surveillance activities. The most frequently used method is antigen detection in stool by enzyme immunoassay (EIA) directed at a group antigen common to all group A Rvs, including those in the Rv vaccine. Stool specimens from children immunized with Rv vaccine may test positive by EIA for several weeks after immunization.
CLINICAL MANIFESTATIONS

Primary Rv infection of infants and toddlers may be asymptomatic or result in diarrhea, usually preceded or concomitant with emesis and fever. In one study of 72 hospitalized patients with proven Rv infection, emesis and a temperature greater than 37.8°C occurred in 96% and 77% of patients, respectively. Accompanying dehydration usually is isotonic and can be severe with concomitant acidosis. Infection also can be associated with upper respiratory tract symptoms, such as coryza and cough. Neurologic symptoms occur in severe cases and may be attributable to electrolyte imbalance or central nervous system involvement. Second episodes are common and generally mild or asymptomatic, but severe illness does occur during reinfection.

Infection of children with significant T-lymphocyte abnormalities such as those associated with severe combined immune deficiency can result in a persistent infection associated with multisystem abnormalities, particularly hepatic and renal involvement. Data indicate that the majority of deaths attributable to diarrhea in the United States occurs in premature infants, but data specifically linking death and Rv infection are not available.

IMMUNITY

Protective Efficacy After Natural Infection

Children may be infected with Rv several times during their lives. After an initial natural infection, 38%, 77%, and 87% of children are protected against any subsequent infection, diarrhea, and severe diarrhea, respectively. The components of the immune response necessary to provide protection against Rv have not been completely defined. Rv-specific fecal and salivary immunoglobulin A (IgA), serum IgA and immunoglobulin G (IgG), G type-specific antibody, and cell-mediated immunity reflect natural infection and illness. In adult volunteers, prospectively monitored children, and animal models, preexisting serum antibody and fecal Rv IgA antibody have been associated with protection against infection or disease. Antibody responses to first infections are primarily homotypic (to the infecting G type); antibody responses to subsequent infections are broader and reflect a heterotypic response.

Immunologic Correlates of Protection in Vaccine Studies

Studies have demonstrated variable associations between serum Rv antibody concentrations and protection. Specificity of Rv-neutralizing antibodies after Rv immunization has not correlated with protection. Studies that evaluate homotypic and heterotypic epitope-specific antibody responses may provide clarification.

EFFECT OF ORAL REHYDRATION

Oral rehydration therapy has been recommended by both the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) for prevention and treatment of dehydration resulting from diarrhea in infants and children, but oral rehydration is underutilized in the United States. The principles of oral rehydration therapy include early adequate rehydration using an appropriate solution, replacement of ongoing fluid losses from vomiting and diarrhea with oral rehydration solution (ORS), and frequent feeding as soon as dehydration is corrected. Early initiation of oral rehydration therapy in children with diarrhea reduces morbidity and mortality associated with diarrhea and dehydration in children. Most children with diarrhea should receive an appropriate ORS.

PREVENTION

Vaccine

Initial vaccine candidates, developed in the 1980s, were monovalent vaccines derived from animal strains. These vaccines were tested under different conditions and efficacy results were inconsistent from trial to trial.

The recently licensed vaccine is a live-attenuated orally administered product derived from four group A Rvs. Three of the Rvs are single gene reassortants of the VP7 gene of human origin (types G1, G2, and G4); the fourth strain is rhesus Rv (type G3), which is antigenically similar to human G3. This quadrivalent vaccine formulation contains one unaltered rhesus Rv strain and three reassortant strains. Each reassortant contains the gene encoding the G protein of its parent human Rv and the remaining 10 genes are from the parent rhesus Rv.

1. Manufacturing, handling, and storage. Each dose of the Rv vaccine is given orally as a 2.5-mL volume that contains approximately 1 × 10^3 plaque-forming units (PFU) of each of the four strains. The viruses are grown in a fetal rhesus diploid cell line. Fetal bovine serum from US herds free of bovine spongiform encephalitis, neomycin sulfate, amphotericin B, and monosodium glutamate are present during cell culture growth. This vaccine is supplied in single-dose vials as a lyophilized preparation with one pouch of buffer diluent for reconstitution containing 9.6 mg/mL of citric acid and 25.6 mg/mL of sodium bicarbonate to neutralize stomach acidity and protect the acid-labile virus from inactivation. Neither vaccine nor diluent contains preservatives.

2. Administration, dosage, and schedule. This Rv vaccine is recommended by the manufacturer for oral administration to infants at 2, 4, and 6 months of age. Each dose should be separated
from another dose by at least 3 weeks, and all three doses should be administered by 6 months of age. According to the product label, administration as late as 12 months of age is acceptable if at least one dose has been given between 6 weeks and 6 months of age. Administration of the first dose of vaccine to children older than 6 months of age may result in a higher rate of fever and is not recommended currently.12,14,15 A period between doses of longer than 2 months is not an indication for restarting the three-dose series. Insufficient safety and efficacy data are available to support administration of Rv vaccine to children older than 12 months of age. Because the safety of administering a dose of vaccine higher than the recommended dose is not known, a second dose of vaccine should not be administered to an infant who vomits or spits up during or after administration of Rv vaccine. The infant should receive the remaining doses of vaccine according to the recommended schedule.

3. Immunogenicity. Studies of Rv vaccine demonstrate that more than 88% of children respond to three doses of the vaccine as indicated by either a fourfold or greater rise in serum IgA titers as measured by either EIA or neutralizing antibody assays to vaccine strains (Table 1).12–16 In Venezuela, the number of responses after the third vaccine dose was not significantly different from that after 2 doses.15 Children in the placebo groups of the studies had IgA antibody responses ranging from 4% to 29% after the third placebo dose,12–16 indicating exposure to wild-type Rv during the course of these studies.

4. Efficacy. Studies with Rv vaccine containing 4 \times 10^4 PFU12 involving more than 3000 children in the United States, Finland, and Venezuela demonstrated efficacy rates of 48% to 68% in preventing diarrhea caused by Rv, 38% to 91% in preventing moderate disease, and 70% to 100% in preventing severe disease (Table 2).12–16 In Venezuela Rv vaccine prevented dehydration and hospitalization in 75% and 70% of recipients, respectively; in Finland rates of prevention of dehydration and hospitalization were 97% and 100%, respectively. In Finland the protective rate against physician visits, hospital outpatient clinic visits, diarrhea more than 5 days, vomiting more than 2 days, a temperature above 39°C, and acidosis was greater in the vaccine group when compared with the placebo group (P < .001). In a US trial, none of the children in the vaccine group compared with 13 of 385 (3%) children in the placebo group became dehydrated.13 In this same study, physician intervention occurred for 16 of 398 (4%) children in the vaccine group and 58 of 385 (15%) in the placebo group (73% efficacy, 95% confidence interval [CI] 54,84). In a second US study, medical visits for diarrhea and vomiting occurred for 27 (9%) children in the placebo group compared with 6 (2%) in the vaccine group (78% efficacy, 95% CI 38,93).12

In several of the studies, episodes of rotaviral diarrhea were serotyped.12–15 Most of these wild-type Rv strains were of the G1 serotype and, therefore, several studies could not determine the efficacy of the vaccine against other serotypes of Rv.12,13,15 In one US study, the vaccine was protective against G3, which was the predominant serotype.16 In the study conducted in Finland, protection against G1 serotype (70%, 95% CI 58% to 78%) was similar to protection against the G4 serotype (76%, 95% CI 29% to 92%).14 No data are available to indicate whether this Rv vaccine protects against diarrhea attributable to rotavirus strains not contained in the vaccine.

5. Duration of protection. In Finland Rv vaccine was 68% effective in preventing rotaviral diarrhea and 90% effective for prevention of severe disease during two seasons of surveillance.14 Vaccine efficacy was greater during the first than during the second analysis period.14

6. Effect of breastfeeding on immunogenicity. Although breastfeeding has been demonstrated to decrease the immunogenicity of single doses of Rv vaccine,15–16 no overall effect has been noted on immune response or efficacy after administration of 3 doses of Rv vaccine.15

7. Adverse effects. Approximately 10,000 infants 6 to 28 weeks of age have received rhesus Rv vaccine at doses ranging from 4 \times 10^4 to 4 \times 10^5 PFU12–16,60–63 including approximately 3200 infants who received Rv vaccine in five placebo-controlled studies.12–16 The Rv vaccine appears to be safe at doses of 4 \times 10^4 PFU12 and 4 \times 10^5 PFU (Table 3).13–16 The major side effects reported in the five placebo-controlled trials were an increase in tem-

**TABLE 1.** Antibody Responses after 1, 2, or 3 Doses of Rhesus Rotavirus Tetravalent Vaccine or Placebo*

<table>
<thead>
<tr>
<th>Location of Study</th>
<th>Years</th>
<th>Dose</th>
<th>Antibody Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vaccine (%)</td>
</tr>
<tr>
<td>Venezuela15</td>
<td>1992–1995</td>
<td>1</td>
<td>43/63 (68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>41/43 (95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>35/40 (88)</td>
</tr>
<tr>
<td>Finland14</td>
<td>1993–1995</td>
<td>1</td>
<td>70/93 (75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>83/93 (89)</td>
</tr>
<tr>
<td>United States12</td>
<td>1989–1990</td>
<td>3</td>
<td>144/155 (93)</td>
</tr>
<tr>
<td>United States16</td>
<td>1992–1994</td>
<td>3</td>
<td>201/217 (93)</td>
</tr>
</tbody>
</table>

* P < .001 for comparison with the vaccine group. NA indicates data not available.
† Determined by a fourfold or greater rise in serum IgA titers using EIA or neutralizing antibody assay to vaccine strains. Dose of vaccine administered in these studies was 4 \times 10^4 PFUs or 4 \times 10^5 PFUs.12–16
An increase in temperature ≥38°C, an increase in temperature >39°C, decreased appetite, irritability and decreased activity, all of which occurred more often in the immunized infants than in the placebo group during the first 3 to 5 days after the first dose. Temperature ≥38°C was observed more frequently in immunized infants than in placebo recipients in the 5 days after the second dose of vaccine. No significant differences were demonstrated between the vaccine and placebo groups in the occurrence of vomiting, coughing, rhinitis, or other clinical signs or symptoms in these studies. In the one US study in which serum alanine aminotransferase levels were measured, no difference was demonstrated between the two groups. In all five studies no significant differences were noted in side effects between the two groups after the third dose of vaccine or placebo.

<table>
<thead>
<tr>
<th>Location of Study</th>
<th>No.</th>
<th>Episodes of Diarrhea</th>
<th>Dehydration</th>
<th>Hospitalization for Gastroenteritis</th>
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<tr>
<td>Venezuela</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>1112</td>
<td>70 (6)</td>
<td>32 (3)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>1095</td>
<td>135 (12)</td>
<td>60 (5)</td>
<td>25 (2)</td>
</tr>
<tr>
<td>Efficacy (95% CI)</td>
<td></td>
<td>48 (33, 61)</td>
<td>47 (20, 66)</td>
<td>88 (61, 96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .001</td>
<td>P &lt; .05</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>1127</td>
<td>54 (5)</td>
<td>8 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>1146</td>
<td>172 (15)</td>
<td>92 (8)</td>
<td>24 (2)</td>
</tr>
<tr>
<td>Efficacy (95% CI)</td>
<td></td>
<td>68 (57, 76)</td>
<td>91 (82, 96)</td>
<td>100</td>
</tr>
<tr>
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<td>P &lt; .001</td>
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<td>United States</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>398</td>
<td>51 (13)</td>
<td>24 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>385</td>
<td>97 (25)</td>
<td>72 (19)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Efficacy (95% CI)</td>
<td></td>
<td>49 (31, 63)</td>
<td>68 (50, 79)</td>
<td>80 (56, 91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>305</td>
<td>13 (4)</td>
<td>11 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>296</td>
<td>35 (12)</td>
<td>25 (9)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Efficacy (95% CI)</td>
<td></td>
<td>64 (24, 83)</td>
<td>59 (5, 82)</td>
<td>82 (9, 97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>347</td>
<td>39 (11)</td>
<td>31 (9)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>348</td>
<td>81 (23)</td>
<td>54 (16)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Efficacy (95% CI)</td>
<td></td>
<td>52 (31, 66)</td>
<td>38 (7, 60)</td>
<td>70 (35, 86)</td>
</tr>
</tbody>
</table>

* Data in each trial are based on a point scoring system. Scores were based on duration of diarrhea and vomiting, the maximum number of stools and episodes of vomiting in a 24-hour period, presence of dehydration or fever, and whether a child required medical care. Efficacy data are derived from first season in all studies except the study conducted in Finland in which efficacy data are determined over 2 years. Immunized children received 4 × 10⁵ PFUs (dose of currently licensed vaccine) except children in one US trial in which 4 × 10⁴ PFUs was used.

<table>
<thead>
<tr>
<th>Location of Study</th>
<th>No.</th>
<th>Temperature</th>
<th>Diarrhea</th>
<th>Vomiting</th>
</tr>
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<tbody>
<tr>
<td>Venezuela</td>
<td></td>
<td>≥38°C</td>
<td>≥39°C</td>
<td></td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td>1112</td>
<td>167 (15)</td>
<td>NA</td>
<td>100 (9)</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td>1095</td>
<td>77 (7)*</td>
<td>NA</td>
<td>77 (7)†</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td>1184</td>
<td>345 (29)</td>
<td>26 (2)</td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td></td>
<td>1197</td>
<td>44 (4)*</td>
<td>5 (0.4)*</td>
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<tr>
<td>Placebo (%)</td>
<td></td>
<td>398</td>
<td>28 (7)</td>
<td>1 (2.5)</td>
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<tr>
<td>United States</td>
<td></td>
<td>385</td>
<td>15 (4)*</td>
<td>1 (2.5)</td>
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<td>United States</td>
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<td>43 (14)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td></td>
<td>386</td>
<td>21 (7)*</td>
<td>2 (0.6)*</td>
</tr>
<tr>
<td>Placebo (%)</td>
<td></td>
<td>347</td>
<td>74 (21)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>348</td>
<td>21 (6)*</td>
<td>5 (1)*</td>
</tr>
</tbody>
</table>

* Denotes P < .001 for comparison with the vaccine group.
† Denotes not significant.
‡ Denotes P < .05 for comparison with the vaccine group.
§ Denotes P < .01 for comparison with the vaccine group.
immune globulin-containing product parenterally of this Rv vaccine to infants who have received an immunization. Data are not available regarding administration in the past several months; however, data from studies of other orally administered live vaccines indicate that simultaneous administration with immune globulin-containing products does not affect the immunogenicity of the vaccines. Health care professionals with latex sensitivity who administer the vaccine should do so with caution because the packaging contains dry natural rubber.

10. Transmission of Rv vaccine strains. This Rv vaccine consists of live Rv that replicates in the intestine of the recipient and is shed in stool. The documented rate of excretion of Rv in stool depends on the method of detection; polymerase chain reaction (PCR) is more sensitive than EIA, electron microscopy, or polyacrylamide-gel electrophoresis. Although Rv shedding was detected in stool specimens from 125 of 248 (50%) children in eight centers in the United States,66 studies in child care centers have not demonstrated transmission of vaccine strains from vaccine recipients to nonrecipients. In Venezuela with PCR, cell culture, and electrophoresis used to test stool specimens, a vaccine strain was detected in 29 (14%) of the 213 Rv-positive stool specimens from children with diarrhea. Eighteen of the 139 episodes of diarrhea in the placebo group (13%) and 11 of 74 episodes in the vaccine group (15%) yielded a vaccine strain. In all of these episodes the vaccine strain occurred in conjunction with a wild-type Rv strain, indicating that the vaccine strain alone did not cause diarrhea. In addition, the vaccine strains were not detected in stools by EIA, indicating that the virus was shed in low titer.

11. Administration with other vaccines. Studies evaluating the concomitant administration of this Rv vaccine with oral poliovirus vaccine (OPV), inactivated poliovirus vaccine (IPV), Haemophilus influenzae type b vaccine (Hib), diphtheria and tetanus toxoids and pertussis (DTP), and hepatitis B virus vaccines have demonstrated no effect on the immune response to any of the antigens in these vaccines. Infants given OPV concurrently with Rv vaccine may have slightly decreased serum antibody responses to Rv antigens and serotype 1 poliovirus, but this possible interference is not evident after 3 doses of Rv and polio vaccines.

12. Immunization after documented disease. Children with documented Rv infection should complete their Rv immunization schedule because one natural infection may not confer protection against all serotypes of Rv that cause disease.

ECONOMIC IMPACT OF RV DISEASE

In cost-benefit analyses of Rv vaccines, the cost of the vaccine and rates of hospitalization, emergency department (ED) visits, and physician visits contribute to direct medical costs, while time lost from work by parents and other caregivers contribute to societal costs. The cost-effectiveness of giving Rv vaccine to infants in the United States at 2, 4, and 6 months of age has been analyzed in several studies. The study by Tucker and associates used the
most recent assumptions for vaccine efficacy and disease burden. On the basis of a birth cohort of 3.9 million, the authors estimated that annually, Rv results in 50,000 hospitalizations of children between birth and 5 years of age, with a length of hospitalization of 3.4 days, 160,000 ED visits at a cost of $245 per case, and 410,000 physician visits at a cost of $132 per visit. The Rv vaccine was estimated to have an efficacy of 85% against hospitalizations and deaths, 75% against ED visits, and 70% against physician visits. No correction was made for possible herd immunity or for severe adverse effects. With this study, a national Rv immunization program in which 3 doses of this Rv vaccine administered at 2, 4, and 6 months of age would result in 1.08 million fewer episodes of diarrhea, 227,000 fewer physician visits, 95,000 fewer ED visits, 34,000 fewer hospitalizations, and 13 fewer deaths during the first 5 years of life. This decrease would be cost-effective, yielding savings in direct medical costs (primarily the cost of hospitalization) and nonmedical costs (primarily the loss of caregiver earnings), depending on the price of the vaccine. If a different rate of hospitalization is used in these calculations or the variables used are altered, the cost-benefit analysis would be affected.

FACTORS THAT MAY INFLUENCE VACCINE ACCEPTANCE

Many enteric pathogens other than Rv are associated with diarrhea and vomiting. Because children in the United States may have as many as 8 episodes of diarrhea in the first 5 years of life, parents may not appreciate the true impact of the Rv vaccine. The impact should be apparent to office-based pediatricians who may see a decrease in the number of children with office visits for watery diarrhea. In addition, because Rv accounts for approximately 50% of hospitalizations from diarrhea and dehydration during the winter Rv season and because the vaccine is 80% or more effective in preventing these illnesses, a substantial reduction should occur in serious diarrhea and dehydration after widespread use of this vaccine. Similar to many vaccines the magnitude of reduction in disease may need to be realized from aggregative data.

RECOMMENDATIONS

Morbidity from Rv disease in the United States and cost to the health care system and society associated with Rv disease are substantial. These considerations in conjunction with vaccine safety and efficacy justify a nationwide immunization program for prevention or modification of Rv disease in infants and young children. Specific AAP recommendations for use of this FDA-approved Rv vaccine are as follows:

1. Based on safety and efficacy data, Rv vaccine is recommended for use in infants at 2, 4, and 6 months of age for prevention of Rv disease; routine implementation of this recommendation will require reconciliation of related economic issues.

2. The first dose of Rv vaccine may be given to infants as early as 6 weeks of age. For children in whom initiation of vaccine has been delayed, the first dose may be given as late as 6 months of age. Each subsequent dose should be given at an interval of at least 3 weeks. Special efforts should be made to immunize infants before the anticipated annual onset of Rv disease activity in their local communities.

3. Increased rates of fever have been reported in vaccine recipients after the first and second doses, but fevers generally are mild and last less than 24 hours. Initiation of immunization after 6 months of age is not recommended because of the age-related occurrence of fever after receipt of the first dose of vaccine. All three doses of vaccine should be administered during the first 12 months of age because data regarding the safety and efficacy of vaccine administration to older children are not available.

4. The Rv vaccine can be administered at the same time as DTaP (or DTP), Hib, hepatitis B, or IPV/OPV vaccines as recommended in the routine immunization schedule. Modification of timing of administration of Rv vaccine is not necessary after administration of antibody-containing blood products, including blood, plasma, and immune globulin.

5. To ensure maximum immunity, the recommended three-dose Rv immunization schedule should be completed even if a child has had a documented episode of wild-type Rv gastroenteritis.

6. Contraindications to Rv vaccine include the following:
   • Infants with hypersensitivity to aminoglycoside antibiotics, amphotericin B, or monosodium glutamate that are components of the vaccine, should not receive this vaccine. In addition, Rv vaccine should not be administered to persons who have experienced an anaphylactic reaction to a previous dose of Rv vaccine.
   • Infants with moderate or severe febrile illness should not receive the Rv vaccine during the illness, but should be immunized as soon as they have recovered from the acute phase of their illness. The Rv vaccine, like other vaccines, can be given to infants with a low-grade fever.
   • Until further data are available, children who are known or suspected to be immunosuppressed or immunodeficient should not receive this live-attenuated virus vaccine. The vaccine should not be administered to infants born to women known to be HIV-infected until tests for HIV infection in the infant are negative at 2 months or older by PCR or culture.71 Infants living in households with persons known or suspected to be immunocompromised should be immunized.
   • Breastfeeding is not a contraindication to administration of Rv vaccine.
8. This Rv vaccine is not recommended for children with acute vomiting or diarrhea because vaccine efficacy in these circumstances has not been established. Consideration should be given to immunizing children with chronic gastrointestinal tract disease until further data are available to make definitive recommendations for this group.

9. Although data are limited, premature infants may receive Rv vaccine at or after discharge from the hospital nursery if they have achieved a chronological age of at least 6 weeks.

10. If a child is hospitalized after administration of Rv vaccine, he/she can be managed by standard precautions and does not need to be placed in contact precautions unless diarrhea, vomiting, or both occur. Children may attend their child care facilities after administration of Rv vaccine.

**RESEARCH NEEDS AND FUTURE DEVELOPMENTS**

Studies are needed to define more fully the serologic parameters that can be used to predict whether a candidate Rv vaccine will be efficacious. Other candidate Rv vaccines are in different stages of testing and may be approved for use in children in the future. Once any Rv vaccine is introduced, postlicensure surveillance is necessary to define the incidence of rotavirus diarrhea, including monitoring the projected decline in the number of cases of Rv disease and hospitalizations after a Rv vaccine has been introduced to evaluate the cost savings of the vaccine program, to assess potential changes in serotypes associated with disease, to determine if new or unusual strains emerge, and to evaluate adverse effects.

Because none of the clinical trial data extend beyond 2 years, duration of protection beyond this time is uncertain, but protection similar to that after natural infection is expected. Data are needed to establish the safety, immunogenicity, and, if possible, efficacy of the Rv vaccine, and of future Rv vaccines in several populations, including premature infants and children with acute diarrhea, chronic gastrointestinal tract disease, immunosuppression; children in long-term care facilities; and children ages 1 to 3 years. Studies also are needed to determine the efficacy of a two-dose immunization schedule as well as the effect of maternal Rv immunization on maternal milk and serum antibody titers and the protection afforded to nursing infants by these maternal antibodies. The long-term goal of the Rv vaccine program is to prevent rotaviral disease. These recommendations are important steps in achieving this goal.

**REFERENCES**


17. Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after
Prevention of Rotavirus Disease: Guidelines for Use of Rotavirus Vaccine
Committee on Infectious Diseases
*Pediatrics* 1998;102;1483
DOI: 10.1542/peds.102.6.1483

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