Rotavirus Vaccine

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses rotavirus vaccine.

1. **Medical Necessity**

   Aetna considers Food and Drug Administration-approved rotavirus vaccines (i.e., RotaTeq® and Rotarix®) a medically necessary service for prevention of rotavirus gastroenteritis in infants less than 8 months of age. **Note:** policy is based on recommendations from the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP). See Appendix for additional administration schedule recommendations.

2. **Experimental, Investigational, or Unproven**

   Aetna considers rotavirus vaccines experimental, investigational, or unproven for all other indications because their effectiveness for indications other than the one listed in Section I (above) have not been established.

3. **Policy Limitations and Exclusions**

   Note: Some plans exclude coverage of preventive services. Please check benefit plan descriptions for details.

Dosing Recommendations

U.S. FDA-approved Prescribing Information:

- RotaTeq (RV5) – administered orally starting at 6 to 12 weeks of age with subsequent doses administered at 4- to 10-week intervals. The third dose should not be given after 32 weeks of age. It is recommended that the first dose be administered before 12 weeks of age (Merck, 2020).
- Rotarix (RV1) – administered orally with first dose to infants beginning at 6 weeks of age. Administer second dose after an interval of at least 4 weeks and prior to 24 weeks of age (GlaxoSmithKline, 2019).

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description

Code	Code Description
CPT codes covered if selection criteria are met:	
90680	Rotavirus vaccine, pentavalent (RV5), 3 dose schedule, live, for oral use
90681	Rotavirus vaccine, human, attenuated (RV1), 2 dose schedule, live, for oral use
ICD-10 codes covered if selection criteria are met:	
Z23	Encounter for immunization [rotavirus gastroenteritis]

Background

Rotavirus is a leading cause of severe diarrhea in infants and young children. Virtually all children will experience rotavirus infection; while some children experience mild symptoms of rotavirus, infection can be severe and lead to dehydration that can be fatal. Among children under 5 years of age in the United States (U.S.), it has been estimated that 2.7 million episodes of rotavirus gastroenteritis occur each year, leading to approximately 250,000 emergency room visits and up to 70,000 hospitalizations.

In the U.S., children are at the greatest risk for severe rotavirus disease from 6 to 24 months of age. By the time they are 5 years old, approximately 1 out of every 17 children in the U.S. will visit the emergency room, and 1 out of every 65 children will be hospitalized for rotavirus gastroenteritis.

The U.S. Food and Drug Administration (FDA) has approved 2 oral vaccines for the prevention of rotavirus gastroenteritis: RotaTeq® (Merck & Co., Whitehouse Station, NJ) and Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium).

RotaTeq is a pentavalent live virus vaccine that targets the G1, G2, G3, and G4 strains of rotavirus, which are responsible for more than 90 % of rotavirus disease in the U.S. The FDA approval of RotaTeq is based on data from Merck's phase III clinical trials of more than 70,000 infants, including the Rotavirus Efficacy and Safety Trial (REST). Among infants observed in phase III clinical trials, RotaTeq prevented 98 % of severe cases of rotavirus gastroenteritis and prevented 74 % of rotavirus gastroenteritis cases of any severity caused by serotypes targeted by the vaccine (G1, G2, G3, G4) compared to placebo through the first full rotavirus season after vaccination. In REST, RotaTeq reduced hospitalizations by 96 % and emergency room visits by 94 % for rotavirus gastroenteritis caused by serotypes targeted by the vaccine through the first 2 years after the third dose.

Because intussusception was associated with a previously licensed rotavirus vaccine that was withdrawn from the market in 1999, one of the primary goals of REST was to evaluate the safety of RotaTeq rotavirus vaccine with respect to intussusception. In REST, rotavirus vaccine did not significantly increase the risk of intussusception compared to placebo. Within 1 year after the first dose, there were 13 cases of intussusception in the vaccine group and 15 in the placebo group.

The manufacturer of RotaTeq reports that, in more than 11,000 infants in clinical trials, a Vaccination Report Card was used to report the presence of adverse events for 42 days after each dose. Fever was observed at similar rates in vaccine and placebo recipients. Adverse events that occurred at a statistically higher incidence within 6 weeks of any dose among recipients of rotavirus vaccine as compared with placebo recipients were diarrhea, vomiting, otitis media, nasopharyngitis, and bronchospasm.

The Advisory Committee on Immunization Practices (Parashar et al, 2006) as well as the American Academy of Pediatrics (2007) recommended routine immunization of infants with rotavirus vaccine.

According to the FDA-approved labeling, RotaTeq is indicated for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, and G4. RotaTeq, an oral vaccine, is given in 3 doses administered to infants between the ages of 6 to 32 weeks. It can be given during the current well baby visits 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 RotaTeq should be administered by 32 weeks of age. The FDA-approved labeling of RotaTeq states that the safety and efficacy of the vaccine has not been established in infants less than 6 weeks of age or greater than 32 weeks of age. The labeling states that no safety or efficacy data are available for the administration of RotaTeq to infants who are potentially immunocompromised, including those with certain disorders of the bone marrow or lymphatic system, those on immunosuppressive therapy or with an immunodeficient condition, or those who have received blood products within 6 weeks of vaccination. For infants in whom the 1st dose of RotaTeq is inadvertently administered off-label at age 13 weeks or greater, the rest of the RotaTeq vaccination series should be completed as per the schedule because timing of the 1st dose should not affect the safety and efficacy of the 2nd and 3rd dose. The labeling states that the efficacy of RotaTeq beyond the second season after vaccination was not evaluated. RotaTeq is contraindicated for infants with a serious allergic reaction to any vaccine component or to a previous dose of vaccine.

According to the FDA press release, Rotarix, an oral vaccine, is indicated for the prevention of rotavirus gastroenteritis caused by the G1, G3, G4, and G9 strains. During studies involving more than 24,000 infants, Rotarix was effective in preventing both severe and mild cases of rotavirus-caused gastroenteritis during the first 2 years of life. The most common adverse reactions reported during clinical trials were fussiness, irritability, cough, runny nose, fever, loss of appetite and vomiting.

The manufacturer conducted a study of more than 63,000 infants to evaluate the safety of Rotarix rotavirus vaccine with respect to intussusception. In that study, there was no increase in the risk of intussusception in those who received Rotarix (31,673 infants) compared to those who received placebo (31,552 infants). Increased rates of convulsion and pneumonia-related deaths were observed in the Rotarix recipients in the intussusception study, however these events were not observed in other studies conducted by the manufacturer. Although the FDA has concluded that the available data do not establish that these events are related to the vaccine, the agency has requested the manufacturer to conduct post-marketing safety studies involving more than 40,000 infants to provide additional safety information.

According to product information from the manufacturer's website, the vaccination course for Rotarix consists of 2 doses. The first dose should be given between 6 and 14 weeks of age. The interval between the 2 doses should not be less than 4 weeks. The vaccine course should be completed by the age of 24 weeks as safety has not been assessed in older children. Rotarix is contraindicated in individuals with any history of chronic gastrointestinal disease including any uncorrected congenital malformation (such as Meckel’s diverticulum) of the gastrointestinal tract.

The American Academy of Pediatrics (AAP)'s updated guidelines on the use of rotavirus vaccine for prevention of rotavirus disease (2009) stated that in April 2008, a live, oral, human attenuated rotavirus vaccine (RV1 [Rotarix]) was licensed as a 2-dose series for use in infants in the United States. The AAP does not express a preference for either RV5 or RV1 – RV5 is to be administered orally in a 3-dose series with doses administered at 2, 4, and 6 months of age; while RV1 is to be administered orally in a 2-dose series with doses administered at 2 and 4 months of age. The 1st dose of rotavirus vaccine should be administered from 6 weeks through 14 weeks, 6 days of age. The minimum interval between doses of rotavirus vaccine is 4 weeks. All doses should be administered by 8 months, 0 days of age. The updated guidelines also stated that rotavirus vaccination may be postponed until a subsequent time in children with moderate-to-severe acute gastroenteritis or other moderate-to-severe acute illness. To avoid failing to complete the vaccination series, the rotavirus vaccine should be administered on schedule to children with mild illness.

Guidelines for preventing infections in hematopoietic cell transplant (HCT) recipients by the Center for International Blood & Marrow Transplant Research, National Marrow Donor Program, European Group for Blood and Marrow Transplantation, American Society for Blood and Marrow Transplantation, Canadian Blood and Marrow Transplant Group, Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, Association of Medical Microbiology and Infectious Disease, and the CDC (Ljungman et al, 2009) indicated that rotavirus vaccines must be administered before 12 weeks of age to be safe for hematopoietic cell transplant recipients.

Richardson et al (2010) assessed the effect of vaccination on deaths from diarrhea in Mexican children in 2008 and 2009. These investigators obtained data on deaths from diarrhea, regardless of cause, from January 2003 through May 2009 in Mexican children under 5 years of age. They compared diarrhea-related mortality in 2008 and during the 2008 and 2009 rotavirus seasons with the mortality at baseline (2003 to 2006), before the introduction of the rotavirus vaccine. Vaccine coverage was estimated from administrative data. By December 2007, an estimated 74 % of children who were 11 months of age or younger had received 1 dose of rotavirus vaccine. In 2008, there were 1,118 diarrhea-related deaths among children younger than 5 years of age, a reduction of 675 from the annual median of 1,793 deaths during the 2003 to 2006 period. Diarrhea-related mortality fell from an annual median of 18.1 deaths per 100,000 children at baseline to 11.8 per 100,000 children in 2008 (rate reduction, 35 %; 95 % confidence interval [CI]: 29 to 39; $p < 0.001$). Among infants who were 11 months of age or younger, diarrhea-related mortality fell from 61.5 deaths per 100,000 children at baseline to 36.0 per 100,000 children in 2008 (rate reduction, 41 %; 95 % CI: 36 to 47; $p < 0.001$). As compared with baseline, diarrhea-related mortality was 29 % lower for children between the ages of 12 and 23 months, few of whom were age-eligible for vaccination. Mortality among unvaccinated children between the ages of 24 and 59 months was not significantly reduced. The reduction in the number of diarrhea-related deaths persisted through 2 full rotavirus seasons (2008 and 2009). The authors concluded that after the introduction of a rotavirus vaccine, a significant decline in diarrhea-related deaths among Mexican children was observed, suggesting a potential benefit from rotavirus vaccination.

In A Cochrane review, Soares-Weiser K (2010) evaluated rotavirus vaccines approved for use (Rotarix, RotaTeq, and Lanzhou Lamb Rotavirus (LLR)) for preventing rotavirus diarrhea. In February 2010, these investigators searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (published in The Cochrane Library 2009, Issue 1), MEDLINE, EMBASE, LILACS, and BIOSIS. We also searched the ICTRP (January 2010) and checked reference lists of identified studies. Randomized controlled trials comparing rotavirus vaccines approved for use with placebo, no intervention, or another vaccine in children were selected. Two authors independently assessed trial eligibility, extracted data, and assessed risk of bias. Dichotomous data were combined using the risk ratio (RR) and 95 % CI. A total of 34 trials that included 175,944 participants met the inclusion criteria. They evaluated Rotarix (26 trials; 99,841 participants) and RotaTeq (8 trials; 76,103 participants), and had variable risk of bias (where information provided). None of the identified trials used LLR or compared rotavirus vaccines. Compared to placebo, Rotarix and RotaTeq were both effective at reducing rotavirus diarrhea (severe cases and cases of any severity). They also reduced all-cause diarrhea (severe cases), and hospitalizations and need for medical attention caused by rotavirus diarrhea. However, few data were available for Rotarix and all-cause diarrhea. Versus the placebo groups, participants

in each vaccine group had similar numbers of deaths, serious adverse events, reactogenicity profiles (fever, diarrhea, and vomiting), and adverse events that required discontinuation of the vaccination schedule. Both vaccines were immunogenic (measured by virus shedding in stool and/or seroconversion). Subgroup analyses indicate that both vaccines are effective in countries with different incomes, but few data are available. The authors concluded that Rotarix and RotaTeq are effective vaccines for the prevention of rotavirus diarrhea.

Middleton et al (2022) stated that oral rotavirus vaccines have lower effectiveness in high child mortality settings. In a systematic review, these investigators examined the impact of additional dose(s) schedules of rotavirus vaccine on vaccine immunogenicity and reduction in episodes of gastroenteritis. They searched Medline (via PubMed), Cochrane databases and ClinicalTrials.gov for randomized controlled trials (RCTs) from 1973 to February 2022, examining the immunological and clinical impact of additional dose versus standard dose oral rotavirus vaccine schedules. These researchers extracted immunogenicity (proportion of children with evidence of anti-rotavirus IgA sero-response) as well as clinical (proportion of children with at least 1 episode of severe rotavirus gastroenteritis) outcome data and used random effects meta-analysis where appropriate. They evaluated the methodological quality of the studies using the Cochrane risk of bias tool. These investigators screened 536 items and included 7 clinical trials. The results suggested moderate-to-high level evidence that an additional dose of oral rotavirus vaccine improved IgA vaccine immune response, including additional doses administered as a booster dose schedule more than 6 months old; IgA vaccine sero-response 74.3 % additional dose schedule versus 56.1 % standard dose schedule RR 1.3 (95 % CI: 1.15 to 1.48), and when administered to children who were sero-negative at baseline; IgA vaccine sero-response 48.2 % additional dose schedule versus 29.6 % standard dose schedule RR 1.86 (95 % CI 1.27 to 2.72). Only 1 study examined reduction in gastroenteritis episodes and found little benefit in 1st year of life, 1.8 % versus 2.0 % RR 0.88 (95 % CI: 0.52 to 1.48), or 2nd year of life, 1.7 % versus 2.9 % RR 0.62 (95 % CI: 0.31 to 1.23). The authors concluded that administration of an additional dose of oral rotavirus vaccines is likely to result in an improved vaccine immune response, including when administered as a booster dose to older children. Moreover, these researchers stated that evidence of an impact on diarrheal disease is needed before additional dose rotavirus vaccine schedules can be recommended as vaccine policy.

Appendix

Advisory Committee on Immunization Practices (ACIP) recommendations (Cortese et al, 2009):

- RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months. The minimum age for dose 1 of rotavirus vaccine is 6 weeks; the maximum age for dose 1 is 14 weeks and 6 days. Vaccination should not be initiated for infants aged 15 weeks and 0 days or older because of insufficient data on safety of dose 1 of rotavirus vaccine in older infants. The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set. All doses should be administered by age 8 months and 0 days. The 2009 ACIP statement was revised to change last dose recommendation from "weeks" to "months". The recommendation now states that the maximum age for the last dose of rotavirus vaccine is 8 months and 0 days. Previous recommendation stated 32 weeks.
- For infants to whom dose 1 of rotavirus vaccine is administered inadvertently at age 15 weeks and 0 days or older, the rest of the rotavirus vaccination series should be completed according to the schedule and by age 8 months and 0 days because timing of dose 1 should not affect the safety and efficacy of any subsequent dose(s). Infants who have had rotavirus gastroenteritis before receiving the full series of rotavirus vaccination should still start or complete the schedule according to the age and interval recommendations because the initial rotavirus infection might provide only partial protection against subsequent rotavirus disease.

Centers for Disease Control and Prevention (CDC, 2018) recommendations:

- Two rotavirus vaccines are currently licensed for infants in the United States:
    - RotaTeq® (RV5) is given in 3 doses at ages 2 months, 4 months, and 6 months
    - Rotarix® (RV1) is given in 2 doses at ages 2 months and 4 months
- The first dose of either vaccine should be given before a child is 15 weeks of age. Children should receive all doses of rotavirus vaccine before they turn 8 months old.

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The above policy is based on the following references:

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Policy History

- Last Review 10/24/2024

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  Next Review: 08/14/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes