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Inside: Continuing Education Examination

Rotavirus Vaccine for the Prevention of Rotavirus Gastroenteritis Among Children

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
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Rotavirus Vaccine for the Prevention of Rotavirus Gastroenteritis Among Children

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

These recommendations represent the first statement by the Advisory Committee on Immunization Practices (ACIP) on the use of an oral, live rotavirus vaccine licensed by the Food and Drug Administration on August 31, 1998, for use among infants. This report reviews the epidemiology of rotavirus, describes the licensed rotavirus vaccine, and makes recommendations regarding its use for the routine immunization of infants in the United States. These recommendations are based on estimates of the disease burden of rotavirus gastroenteritis among children in the United States and on the results of clinical trials of the vaccine.

Rotavirus affects virtually all children during the first 5 years of life in both developed and developing countries, and rotavirus infection is the most common cause of severe gastroenteritis in the United States and worldwide. In the United States, rotavirus is a common cause of hospitalizations, emergency room visits, and outpatient clinic visits, and it is responsible for considerable health-care costs. Because of this large burden of disease, several rotavirus vaccines have been developed. One of these vaccines — an oral, live, tetravalent, rhesus-based rotavirus vaccine (RRV-TV) — was found to be safe and efficacious in clinical trials among children in North America, South America, and Europe and on the basis of these studies is now licensed for use among infants in the United States.

The vaccine is an oral, live preparation that should be administered to infants between the ages of 6 weeks and 1 year. The recommended schedule is a three-dose series, with doses to be administered at ages 2, 4, and 6 months. The first dose may be administered from the ages of 6 weeks to 6 months; subsequent doses should be administered with a minimum interval of 3 weeks between any two doses. The first dose should not be administered to children aged ≥7 months because of an increased rate of febrile reactions after the first dose among older infants. Second and third doses should be administered before the first birthday. Implementation of these recommendations in the United States should prevent most physician visits for rotavirus gastroenteritis and at least two-thirds of hospitalizations and deaths related to rotavirus.

CLINICAL AND EPIDEMIOLOGIC FEATURES OF ROTAVIRUS DISEASE

Rotavirus is the most common cause of severe gastroenteritis in infants and young children in the United States. Worldwide, rotavirus is a major cause of childhood death. The spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe, dehydrating diarrhea with vomiting and fever, which results in death (*1–5*). Virtually all children become infected in the first 3–5 years of life, but severe diarrhea and dehydration occur primarily among children aged 3–35 months.

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted by the fecal-oral route, both through close person-to-person contact and through fomites (*6*). Rotaviruses also might be transmitted by other modes, such as respiratory droplets (*7*). In the United States, rotavirus causes seasonal peaks of gastroenteritis from November to May each year, with activity beginning in the Southwest United States and spreading to the Northeast (*8–10*).

Rotavirus appears to be responsible for approximately 5%–10% of all diarrheal episodes among children aged <5 years in the United States, and for a much higher proportion of severe diarrheal episodes (*2,11*). Although rotavirus gastroenteritis results in relatively few deaths in the United States (approximately 20 per year among children aged <5 years) (*12*), it accounts for more than 500,000 physician visits (*13,14*) and approximately 50,000 hospitalizations each year among children aged <5 years (*4,9,15*). Rotavirus is responsible for 30%–50% of all hospitalizations for diarrheal disease among children aged <5 years, and more than 50% of hospitalizations for diarrheal disease during the seasonal peaks (*11,16–18*). Among children aged <5 years in the United States, 72% of rotavirus hospitalizations occur during the first 2 years of life, and 90% occur by age 3 years (*15*).

In the first 5 years of life, four out of five children in the United States will develop rotavirus diarrhea (*2,19*); one in seven will require a clinic or emergency room visit; one in 78 will require hospitalization; and one in 200,000 will die from rotavirus diarrhea (*4,14*). The risk for rotavirus diarrhea and its outcomes do not appear to vary by geographic region within the United States. Limited data suggest that children from disadvantaged socioeconomic backgrounds and premature infants have an increased risk for hospitalization from diarrheal disease, including rotavirus diarrhea (*20*). In addition, some children and adults who are immunocompromised because of congenital immunodeficiency, hematopoetic transplantation, or solid organ transplantation experience severe, prolonged, and sometimes fatal rotavirus diarrhea (*21–23*). Rotavirus is also an important cause of nosocomial gastroenteritis (*1,11,16,24,25*). Among adults in the United States, rotavirus infection infrequently causes diarrhea in travelers, persons caring for children with rotavirus diarrhea, and the elderly (*26*). Each year in the United States, rotavirus diarrhea results in $264 million in direct medical costs and more than $1 billion in total costs to society (*14*). Direct medical costs are primarily the result of hospitalizations for severe diarrhea and dehydration, and societal costs are attributable primarily to loss of work time among parents and other caregivers.

Several reasons exist to adopt immunization of infants as the primary public health intervention to prevent rotavirus disease in the United States. First, similar rates of illness among children in industrialized and less developed countries indicate that

clean water supplies and good hygiene have not decreased the incidence of rotavirus diarrhea in developed countries, so further improvements in water or hygiene are unlikely to have a substantial impact (*2,27–31*). Second, in the United States, a high level of rotavirus morbidity continues to occur despite currently available therapies. For example, hospitalizations for diarrhea in young children declined only 16% from 1979 to 1992 (*9*), despite the widespread availability of oral rehydration solutions and recommendations by experts, including the American Academy of Pediatrics, for the use of oral rehydration solutions in the treatment of dehydrating gastroenteritis (*32–34*). Third, studies of natural rotavirus infection indicate that initial infection protects against subsequent severe diarrheal disease, although subsequent asymptomatic infections and mild disease might still occur (*30,35*). 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 diarrhea and its sequelae (e.g., dehydration, physician visits, and hospitalizations).

Laboratory Testing for Rotavirus

Because the clinical features of rotavirus gastroenteritis are nonspecific, confirmation of rotavirus infection in children with gastroenteritis by laboratory testing of fecal specimens will be necessary for reliable rotavirus surveillance and could be useful in clinical settings (*1,36*). The most available method is antigen detection by enzyme immunoassay directed at a group antigen common to all Group A rotaviruses. Several commercial enzyme immunoassay test kits are available that are inexpensive, easy to use, rapid, and highly sensitive (approximately 90% compared with detection by electron microscopy); these properties make rapid antigen detection kits suitable for use in rotavirus surveillance systems. Other techniques — including electron microscopy, reverse transcription-polymerase chain reaction, nucleic acid hybridization, polyacrylamide gel electrophoresis, and culture — are used primarily in research settings.

Serologic methods that detect a rise in serum antibodies, primarily enzyme immunoassay for rotavirus serum immunogloblulin G (IgG) and immunogloblulin A (IgA) antibodies, have been used to confirm recent infections. In vaccine trials, detection of rotavirus-specific IgA and neutralizing antibodies to vaccine strains have been used to study the immunogenicity of rotavirus vaccines (*37*).

Morphology, Antigen Composition, and Immune Response

Rotaviruses are 70-nm nonenveloped RNA viruses in the family *Reoviridae*. The viral nucleocapsid is composed of three concentric shells that enclose 11 segments of double-stranded RNA. The outermost layer contains two structural proteins: VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein). These two proteins define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies that might be important for protection (*38,39*). Because the two gene segments that encode these proteins can, in theory, segregate independently, a typing system has been developed to specify each protein; 14 VP7 (G) serotypes and 20 VP4 (P) genotypes have been described. Only viruses containing four distinct combinations of G and P proteins are known to commonly circulate in the United States — G1P1A, G2P1B, G3P1A, G4P1A (*40*); these strains are generally designated by their G serotype specificity (serotypes 1–4). In

some areas of the United States, recent surveillance has detected strains with additional combinations — G9P6 and G9P8 (serotype 9) (*41*). In addition to these human strains, animal strains of rotavirus that are antigenically distinguishable are found in many species of mammals; these strains only rarely appear to cause infection in humans.

Although children can be infected with rotavirus several times during their lives, initial infection after age 3 months is most likely to cause severe diarrhea and dehydration (*30,42,43*). After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhea from a subsequent rotavirus infection, and 88% are protected against severe diarrhea. Second, third, and fourth infections confer progressively greater protection (*30*).

The immune correlates of protection from rotavirus infection and disease are not completely understood. Both serum and mucosal antibodies are probably associated with protection from disease, and in some studies, serum antibodies against VP7 and VP4 have correlated with protection. However, in other studies, including vaccine studies, correlation between serum antibody and protection has been poor (*44*). The first infection with rotavirus elicits a predominantly homotypic, serum-neutralizing antibody response to the virus, and subsequent infections elicit a broader, heterotypic response (*1,45*). The influence of cell-mediated immunity is less clearly understood, but likely is related both to recovery from infection and to protection against subsequent disease (*44,46*).

ROTAVIRUS VACCINE

Background

Research to develop a safe, effective rotavirus vaccine began in the mid-1970s when investigators demonstrated that previous infection with animal rotavirus strains protected laboratory animals from experimental infection with human rotaviruses (*47*). During the past two decades, two types of rotavirus vaccines have been evaluated, and one vaccine has been licensed for use in the United States.

Monovalent vaccines. The first candidate rotavirus vaccines were derived from monovalent rotavirus strains isolated from either bovine or rhesus hosts. Trials, often with a single dose, demonstrated that these live, oral vaccines were safe and could prevent rotavirus diarrhea in young children (*48–51*). However, the efficacy of these vaccines varied in trials. Because these vaccines had relied on heterotypic protection, researchers postulated that a multivalent vaccine that provided serotype-specific immunity against all common human rotavirus strains might be more effective.

Multivalent vaccines. Multivalent vaccine candidates were developed in 1985 by using gene reassortment (*52*). This process produces vaccine virus strains that have been modified from parent animal strains by single gene reassortment so that each strain contains 10 genes from the animal strain along with a single gene from a human rotavirus strain; this single gene encodes the VP7 protein. In theory, a reassortant strain maintains the attenuation of the parent animal strain in the human host but also has the neutralization specificity of a major G serotype of human rotavirus (*53*). The only rotavirus vaccine currently licensed by the Food and Drug Administration for

use in the United States is rhesus-based rotavirus vaccine-tetravalent. A reassortant vaccine that is based on a bovine rotavirus parent strain (WC-3) is undergoing clinical trials (*54*).

Rhesus-based rotavirus vaccine-tetravalent (RRV-TV). The licensed tetravalent vaccine RRV-TV (RotaShield™) is produced by Wyeth-Lederle Vaccines and Pediatrics. RRV-TV is a live, oral vaccine that incorporates rhesus rotavirus strain MMU 18006 (with human serotype G3 specificity) and three single-gene human-rhesus reassortants: D x RRV (human serotype G1), DS-1 x RRV (human serotype G2), and ST3 x RRV (human serotype G4). The parent rhesus rotavirus strain MMU 18006 was isolated from a rhesus monkey with diarrhea at the California Regional Primate Center in Davis and was passed nine times in monkey kidney cells and seven times in normal fetal rhesus diploid cells (FRhL-2) cells. The vaccine virus strains are grown in FRhL-2 cells.

RRV-TV is supplied as a lyophilized pink solid. Because the vaccine strains are acid-labile, RRV-TV is reconstituted with 2.5 mL of irradiated sterile diluent containing citrate-bicarbonate. When reconstituted, the vaccine might contain a fine precipitate, and it usually is yellow-orange in color but occasionally is purple. Each dose of vaccine contains 1 x 10^5 plaque-forming units (pfu) of each component rotavirus strain. Trace amounts of fetal bovine serum, neomycin sulfate, and amphotericin B are present in the vaccine (<1 μg per dose). The vaccine does not contain preservatives.

Studies to evaluate the safety, immunogenicity, and efficacy of RRV-TV have involved 17,963 infants in the United States, Venezuela, and Finland. The efficacy of this vaccine has been evaluated in four field trials, two in the United States (*55,56*) and one each in Venezuela (*57*) and Finland (*58*). Three additional trials have been conducted with lower doses of RRV-TV in the United States (*59*), Brazil (*60*), and Peru (*61*).

Immunogenicity

The immunogenicity of rotavirus vaccines is generally measured by detecting rotavirus group-specific serum IgA seroconversion or by detecting serum-neutralizing antibodies to vaccine strains and to prevalent human strains. In industrialized countries, immunogenicity studies of RRV-TV have produced consistent and reproducible results similar to those found in U.S. trials (Table 1) (*55*) (unpublished data, Wyeth-Lederle, 1997). In all studies, vaccinated children developed significantly higher IgA enzyme-linked immunosorbent assay (ELISA) and neutralizing antibodies to rotavirus than did children who received placebo ($p<0.01$). In the three U.S. efficacy trials, >90% of children who received RRV-TV demonstrated a serologic response to vaccination that included a neutralizing antibody response to rhesus rotavirus (83%–90%) or at least a fourfold rise in rotavirus-specific IgA titers (56%–93%) (*55,56,59*). Neutralizing antibody responses to human rotavirus strains were less common (14%–43%).

When administered simultaneously, a three-dose series of RRV-TV does not diminish the immune response to oral poliovirus vaccine (OPV) (*62*), diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DPT) (*63*), *Haemophilus influenzae* type b conjugate (Hib) vaccine (*63*), inactivated poliovirus vaccine (IPV), or hepatitis B vaccine (unpublished data, Wyeth-Lederle, 1998). Studies of simultaneous administration of RRV-TV with diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) have not yet been completed, but no diminished immune response is expected on the

TABLE 1. Geometric mean titers and seroconversion rates for children participating in an efficacy trial and a large-scale consistency lot trial of rhesus-based rotavirus vaccine-tetravalent (RRV-TV) — United States

Trial	Geometric mean titer (seroconversion rate as % with ≥4-fold rise in antibody titer)					
	ELISA* antirotaviral serum IgA	Neutralization antibody assay†				
		RRV	G1 (Wa)	G2 (DS-1)	G3 (P)	G4 (ST3)
Efficacy trial no. 312§						
Vaccinated children¶	82.6 (56%)	691.5 (90%)	20.4 (14%)	21.6 (31%)	29.0 (29%)	10.8 (14%)
Children receiving placebo**	17.7 (2%)	7.1 (2%)	10.4 (1%)	6.6 (0%)	7.6 (1%)	6.3 (2%)
Consistency lot trial no. 325††						
Vaccinated children (n=1,186)	70.1 (52%)	582.8 (86%)	22.9 (13%)	18.0 (24%)	36.6 (26%)	17.2 (23%)

*ELISA, enzyme-linked immunosorbent assay.
†RRV is rhesus rotavirus; Wa, DS-1, P, and ST3 are human strains of serotypes G1, G2, G3, and G4, respectively.
§Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines — report of the National Multicenter Trial. Pediatrics 1996;97:7–13 (*55*). All comparisons between vaccine and placebo recipients showed differences that were statistically significant (p<0.01).
¶In mean titer calculation, n=142 for vaccinated children; in calculation of seroconversion rate, n=185 for vaccinated children.
**In mean titer calculation, n=108 for children receiving placebo; in calculation of seroconversion rate, n=193 for children receiving placebo.
††Unpublished data, Wyeth-Lederle Vaccines and Pediatrics, 1997.

basis of findings regarding the administration of RRV-TV with DTP. Concurrent administration of RRV-TV with OPV does not affect the immunogenicity and efficacy of a three-dose series of rotavirus vaccine (*64,65*). Breastfeeding does not appear to significantly diminish either the immune response to or the efficacy of the three-dose series (p>0.9) (*64,66,67*).

Efficacy

Four efficacy trials of RRV-TV have been completed in the United States and Finland: three trials with the 4 x 10^5 pfu dose submitted for licensure (*55,56,58*) and one trial with a lower dose (4 x 10^4 pfu) (Table 2) (*59*). The findings of all four studies were similar; the vaccine demonstrated 49%–68% efficacy against any rotavirus diarrhea, 69%–91% efficacy against severe diarrhea, and 50%–100% efficacy in preventing doctor visits for evaluation and treatment of rotavirus diarrhea. The vaccine was also effective in reducing the duration of rotavirus diarrhea. The trial in Finland was large enough to examine the vaccine's efficacy in preventing rotavirus hospitalizations: protection was 100% (13 children in the placebo group were hospitalized compared with zero children in the vaccine group) (*58*). In this study, vaccinated children also were protected from nosocomially acquired rotavirus diarrhea. Extended follow-up in the study in Finland demonstrated that protection against severe disease persisted

TABLE 2. Efficacy of rhesus-based rotavirus vaccine-tetravalent (RRV-TV) — United States and Finland*

Country	Range of ages at which infants received doses 1–3	Number of children vaccinated vs. number in placebo group	Outcome			
			All rotavirus diarrhea		Severe rotavirus diarrhea†	
			Efficacy (95% CI)§	Incidence (V vs. P)§	Efficacy (95% CI)§	Incidence (V vs. P)§
United States¶	4–26 weeks	332 vs. 330	57% (29,74)	10% vs. 22%	82% (-9,97)	1% vs. 4%
United States**	5–25 weeks	398 vs. 385	49% (31,63)	13% vs. 25%	80% (56,91)	2% vs. 9%
United States††	6–24 weeks	347 vs. 348	50% (26,67)	11% vs. 23%	69% (29,88)	2% vs. 8%
Finland§§	6–29 weeks	1,127 vs. 1,146	68% (57,76)	5% vs. 15%	91% (82,96)	1% vs. 7%

* All studies used RRV-TV in a three-dose regimen.
† A 20-point scoring system was used in trials. Severity scores varied slightly between trials, but all scores were based on the duration of diarrhea and vomiting, the maximum number of stools and episodes of vomiting in a 24-hour period, the presence of dehydration or fever, and whether a child required medical care. Severe rotavirus diarrhea was defined as an episode with a score of ≥15 points for the U.S. studies and of ≥11 points for the trial in Finland.
§ CI, confidence interval; V, vaccine recipients; P, placebo recipients.
¶ Bernstein DI, Glass RI, Rodgers G, Davidson BL, Sack DA, the US Rotavirus Vaccine Efficacy Group. Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children. JAMA 1995;273:1191–6 (*59*). Vaccinated children received 4×10^4 plaque-forming units (pfu) of vaccine; all other trials listed used the 4×10^5 pfu dose contained in the currently licensed vaccine.
** Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines — report of the National Multicenter Trial. Pediatrics 1996;97:7–13 (*55*).
†† Santosham M, Moulton LH, Reid R, et al. Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations. J Pediatr 1997;131:632–8 (*56*).
§§ Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205–9 (*58*). The 2-year study in Finland showed that the vaccine was 100% effective in preventing hospitalizations for rotavirus (13 children were hospitalized in the placebo group vs. zero children in the vaccine group).

through three rotavirus seasons (*68*). Because infections with serotype G1 viruses have predominated in most studies, the efficacy of RRV-TV against this serotype is well established. In studies conducted in the United States and Finland, RRV-TV was also effective in preventing nonserotype G1 disease (*55,56,58*). In each study, the efficacy of the vaccine was high despite low neutralizing antibody responses to human strains among the vaccinated children — a finding that illustrates the variable correlation between serologic responses and efficacy. No data are available on the efficacy of administration of fewer than three doses of RRV-TV.

Transmission of Attenuated Rotavirus Vaccine Strains

In studies performed in U.S. day care centers, no evidence of seroconversion to, or shedding of, vaccine strains was observed among unvaccinated children (*69–73*). However, in a large vaccine trial in Venezuela (*57*), stool samples from study children who had rotavirus diarrhea were tested by multiple methods. Wild-type rotavirus was found in high concentration in all samples. In addition, rotavirus vaccine strains were detected by polymerase chain reaction in stool samples from 15% of vaccinated and 13% of nonvaccinated children in concentrations too low to be detected by enzyme immunoassay or polyacrylamide gel electrophoresis. These data support the possibility that vaccine strains spread to some unvaccinated children but indicate that the vaccine strains alone were not the cause of diarrhea.

Vaccine Distribution, Handling, and Storage

Each dose of RRV-TV is approximately 2.5 mL in volume, supplied as a lyophilized vaccine containing 4 x 10^5 pfu total virus and one dispette of buffer diluent for reconstitution; the diluent contains 9.6 mg/mL of citric acid and 25.6 mg/mL of sodium bicarbonate. Neither vaccine nor diluent contain preservatives. Before reconstitution, RRV-TV is stable for at least 24 months when stored at room temperatures <25 C (77 F). The lyophilized vaccine and diluent may be refrigerated at temperatures between 2 C and 8 C (36 F and 45 F) **but should not be frozen**. Once reconstituted, the vaccine is stable for up to 60 minutes at room temperature (23– 27 C [73– 81 F]) and up to 4 hours at refrigeration temperature (2–8 C [36– 45 F]), after which the reconstituted product must be discarded.

Cost-Effectiveness of a Universal Childhood Immunization Program to Prevent Rotavirus

In a recent study 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 three doses of RRV-TV are administered at ages 2, 4, and 6 months would result in 227,000 fewer physician visits, 95,000 fewer emergency room visits, 34,000 fewer hospitalizations, and 13 fewer deaths per year (*14*). After revising this study model by incorporating the costs of adverse events, researchers estimated that a national rotavirus immunization program would yield savings in direct medical costs if the vaccine cost $8 or less per dose and would yield savings in total societal costs if the vaccine cost $41 or less per dose (CDC, unpublished data, 1998).

Note: The Advisory Committee on Immunization Practices (ACIP) has summarized the following rotavirus vaccine recommendations, contraindications, and precautions (see Summary Table on page 23). To provide further guidance to practitioners, the ACIP has rated the evidence for each recommendation.

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Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Rotavirus Vaccine for the Prevention of Rotavirus Gastroenteritis Among Children: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

OBJECTIVE

This *MMWR* provides recommendations regarding rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. These recommendations were developed by CDC staff members and the Rotavirus Working Group of the ACIP. This report is intended to guide clinical practice and policy development related to administration of the rotavirus vaccine to infants. Upon completion of this educational activity, the reader should be able to describe the disease burden of rotavirus in the United States; describe the characteristics and use of rhesus-based rotavirus vaccine-tetravalent (RRV-TV); identify the contraindications and precautions for the use of RRV-TV; and recognize the most common adverse events that can occur after administration of RRV-TV.

ACCREDITATION

Continuing Medical Education (CME) Credit: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through CDC. CDC is accredited by the ACCME to provide continuing medical education for physicians. CDC awards 1.0 hour of category 1 credit toward the AMA Physician's Recognition Award for this activity. Each physician should claim only those hours he/she actually spent in the educational activity.

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EXPIRATION — March 19, 2000

The response form must be completed and returned electronically, by fax, or by mail, **postmarked no later than 1 year from the publication date of this report**, for eligibility to receive continuing education credit.

INSTRUCTIONS

1. Read this MMWR *(Vol. 48, RR-2*), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for Continuing Medical Education (CME) credit, Continuing Education Unit (CEU) credit, *or* Continuing Nursing Education (CNE) credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer *all* of the questions. Questions with more than one answer will instruct you to "indicate all that are true."
5. Sign and date the response form.
6. Return the response form, or a photocopy of the form, no later than **March 19, 2000**, to CDC by one of the following methods:

   Fax: 404-639-4198
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   Mail: MMWR CE Credit
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   1600 Clifton Road, N.E.
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   If you answer all of the questions, you will receive an award letter for 1.0 hour of CME credit, 0.1 hour of CEU credit, or 1.2 hours of CNE credit within 90 days. No fees are charged for participating in this continuing education activity.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

To receive continuing education, please answer all of the following questions.

1. Which of the following statements is NOT true concerning the burden of rotavirus disease in the United States among children aged <5 years?

A. Rotavirus diarrhea results in more than 500,000 physician visits per year.

B. Rotavirus diarrhea is responsible for an estimated 50,000 hospitalizations per year.

C. Rotavirus accounts for 5%–10% of all diarrhea episodes.

D. Rotavirus accounts for 30%–50% of hospitalizations for diarrheal disease.

E. More than 100 deaths per year are attributed to rotavirus diarrhea.

2. Which of the following statements is true concerning rotavirus infection in children?

A. Children can be infected with rotavirus several times during their lives.

B. The first infection with rotavirus after 3 months of age is usually the most severe.

C. After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus.

D. Subsequent infections with rotavirus confer progressively greater protection from rotavirus infection.

E. All the above statements are true.

3. What is the recommended route of administration of rhesus-based rotavirus vaccine-tetravalent (RRV-TV)?

A. Intramuscular injection

B. Subcutaneous injection

C. Subdermal injection

D. Oral

E. Intranasal spray

4. Concurrent administration of RRV-TV reduces the immune response to which of the following vaccines?

A. *Haemophilus influenzae* type b (Hib) vaccine

B. Hepatitis B vaccine

C. Diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP)

D. Inactivated polio vaccine

E. None of the vaccines listed above

5. What is the recommended schedule for RRV-TV?

A. 4 doses at 2, 4, 6, and 12-15 months of age

B. 3 doses at 2, 4, and 6 months of age

C. 3 doses at birth, 1 month, and 6 months of age

D. 2 doses at 12 months and 4-6 years of age

E. 1 dose at 12 months of age

6. What is the maximum age for administering the first dose of RRV-TV?

A. 3 months

B. 6 months

C. 12 months

D. 24 months

E. 59 months

7. Which of the following conditions is NOT a stated contraindication or precaution for the use of RRV-TV?

A. Recent administration of antibody-containing blood product (e.g., whole blood or immune globulin)

B. Immunodeficiency

C. Persistent vomiting

D. Infection with human immunodeficiency virus

E. Severe allergy to a component of the vaccine

8. What is the recommended course of action if an infant regurgitates or spits up all or part of a dose of RRV-TV rotavirus vaccine?

A. Repeat the dose immediately, but only if more than half of the dose was regurgitated.

B. Repeat the dose immediately regardless of the amount that was regurgitated.

C. Request that the child return the next day, and repeat the dose at that time.

D. Do not repeat the dose, and administer the remaining doses on the usual schedule.

E. Do not repeat the dose, and discontinue the vaccination series.

9. What is the most common adverse event following RRV-TV rotavirus vaccine?

A. Diarrhea

B. Vomiting

C. Fever

D. Generalized maculopapular rash

E. Decreased appetite

10. Indicate your work setting.

A. State/local health department

B. Other public health setting

C. Hospital clinic/private practice

D. Managed care organization

E. Academic institution

F. Other

11. Which best describes your professional activities?

A. Patient care — emergency/urgent care department

B. Patient care — inpatient

C. Patient care — primary care clinic

D. Laboratory/pharmacy

E. Administration/public health

12. I plan to use these guidelines as the basis for . . . (*Indicate all that apply.*)

A. health education materials.

B. insurance reimbursement policies.

C. local practice guidelines.

D. public policy.

E. other.

13. Each month, approximately how many children with rotavirus do you treat or provide parental counseling for?

A. None

B. 1–5

C. 6–15

D. 16–25

E. 26 or more

14. How much time did you spend reading this report and completing the exam?

A. 1–1½ hours

B. >1½ hours but <2 hours

C. ≥2 hours

15. Overall, this report met the stated objectives.

A. Strongly agree

B. Agree

C. Neither agree nor disagree

D. Disagree

E. Strongly disagree

16. The tables and figures are useful.

A. Strongly agree

B. Agree

C. Neither agree nor disagree

D. Disagree

E. Strongly disagree

17. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree

B. Agree

C. Neither agree nor disagree

D. Disagree

E. Strongly disagree

18. These recommendations will affect my practice.

A. Strongly agree

B. Agree

C. Neither agree nor disagree

D. Disagree

E. Strongly disagree

Answer guide for questions 1–9

1. E; 2. E; 3. D; 4. E; 5. B; 6. B; 7. A; 8. D; 9. C.

MMWR RESPONSE FORM for CME/CEU/CNE Credit
MMWR Vol. 48/No. RR-2. March 19, 1999

Rotavirus Vaccine for the Prevention of Rotavirus Gastroenteritis Among Children
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Fill in the appropriate block(s) to indicate your answer(s).
To receive continuing education credit, you must answer all of the questions.

1.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
2.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
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4.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
5.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
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15.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
16.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
17.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F
18.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F

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RECOMMENDATIONS FOR THE USE OF ROTAVIRUS VACCINE

Routine Administration

Routine immunization with three oral doses of RRV-TV is recommended for infants at ages 2, 4, and 6 months. Because natural rotavirus infections occur early in life, RRV-TV should be incorporated into the routine childhood immunization schedule. The first dose should be administered at age 2 months, the second dose at age 4 months, and the third dose at age 6 months. However, RRV-TV vaccination can be initiated at any time between the ages of 6 weeks and 6 months, with second and third doses following the preceding dose by a minimum of 3 weeks. Vaccination should not be initiated for children aged ≥7 months because these older infants might have an increased risk of fever occurring 3–5 days after receiving the first dose of vaccine (*74–76*). All doses of vaccine should be administered during the first year of life because data regarding the safety and efficacy of RRV-TV among children aged ≥1 year are lacking. Special efforts should be made to vaccinate children before onset of the winter rotavirus season. Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still complete the three-dose schedule because the initial infection frequently provides only partial immunity.

RRV-TV is recommended for children who are breastfed. Although breastfeeding can slightly decrease the child's humoral immune response to RRV-TV after a first dose, no significant decrease in immune response or in overall efficacy has been observed among breastfed babies compared with nonbreastfed babies after three doses ($p>0.9$) (*64,66,77,78*).

RRV-TV can be administered together with DTP (or DTaP), Hib vaccine, OPV, IPV, and hepatitis B vaccine. RRV-TV is safe and effective when administered with other vaccines. Available evidence suggests that the vaccine does not interfere significantly with the immune response to DTP, Hib vaccine, IPV, or hepatitis B vaccine, and interference with DTaP is not expected to occur (*63*) (unpublished data, Wyeth-Lederle, 1998). Some children who receive RRV-TV and OPV concurrently have slightly decreased immune responses to RRV-TV and serotype 1 poliovirus after the first dose of vaccine, but no decrease is evident after three doses of these vaccines (*56,62,64*). No decrease in efficacy against rotavirus has been found among children receiving OPV compared with children not receiving OPV, although the sample size in this study was limited (*64*).

Like other vaccines, RRV-TV can be administered to infants with transient, mild illnesses, with or without low-grade fever.

Contraindications

Altered Immunity

RRV-TV is not recommended for infants who have known or suspected immunodeficiency. Children with primary immunodeficiency disorders and both children and adults who have received hematopoetic, hepatic, or renal transplants are at risk for severe or prolonged rotavirus gastroenteritis and can shed rotavirus for prolonged periods (*20–22,79–81*). One study also identified rotavirus infection of liver and kidney tissue in a small number of severely immunodeficient children (*79*). Because the

safety and efficacy of RRV-TV is not established in these populations, RRV-TV should not be administered to infants with compromised immune status because of immunosuppressive disease or therapies, leukemia, lymphoma, or other malignancies. The safety of RRV-TV has not been established in children with chronic granulomatous disease and other primary disorders of neutrophil function, but no evidence of increased severity of rotavirus infection has been observed in these children. RRV-TV should not be administered to infants born to mothers with human immunodeficiency virus (HIV) infection, unless a clinician has established that the infant is not HIV-infected.

Allergy to Vaccine Components

RRV-TV should not be administered to persons who have hypersensitivity to any component of the vaccine (e.g., aminoglycoside antibiotics, monosodium glutamate, or amphotericin B) or who have experienced an anaphylactic reaction to a previous dose of RRV-TV.

Acute Gastrointestinal Disease

RRV-TV should not be administered to infants with acute, moderate to severe vomiting or diarrhea until the condition resolves; however, vaccination might be warranted for infants with mild gastrointestinal illness. RRV-TV has not been studied among infants with concurrent gastrointestinal disease. Although RRV-TV is probably safe for infants with gastrointestinal disease, immunogenicity and efficacy can theoretically be compromised. For example, infants who receive OPV during an acute diarrheal illness might have diminished poliovirus antibody responses to OPV (*82*). Although similar studies with RRV-TV have not been reported, health-care providers should be aware of the theoretical potential for diminished immunogenicity and efficacy among infants with diarrhea. Therefore, RRV-TV should be withheld from infants with acute, moderate to severe vomiting or diarrhea. Vaccination of infants with mild gastrointestinal illness might be warranted if the delay in vaccination against rotavirus is expected to be substantial. Otherwise, infants with acute gastroenteritis should be vaccinated as soon as the condition resolves.

Moderate to Severe Febrile Illness

Infants with moderate to severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness (*83*). 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.

Precautions and Special Situations

Premature Infants (i.e., those born at <37 weeks' gestation)

Practitioners should consider the potential risks and benefits of vaccinating premature infants against rotavirus. Limited data suggest that premature infants are at increased risk for hospitalization from diarrheal disease during their first year of life. The ACIP supports immunization of prematurely born infants if they a) are at least 6 weeks of age, b) are being or have been discharged from the hospital nursery, and

c) are clinically stable. However, the number of premature infants studied in clinical trials is insufficient to confidently establish the safety and efficacy of RRV-TV for all premature infants. The lower level of maternal antibody to rotaviruses in very-low–birthweight, premature infants theoretically could increase the risk of fever from rotavirus vaccine. Until further data are available, the ACIP considers that the benefits of RRV-TV vaccination of premature infants outweigh the theoretical risks.

Exposure of Immunocompromised Persons to Vaccinated Infants

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. Most experts believe the protection of the immunocompromised household member afforded by immunization of young children in the household probably outweighs the small risk of transmitting vaccine virus to the immunocompromised household member and any subsequent theoretical risk of vaccine virus-associated disease. To minimize potential virus transmission, all members of the household should employ measures such as good hand washing after contact with the feces of the vaccinated infant (e.g., after changing a diaper).

Recent Administration of Antibody-Containing Blood Products

No restrictions are necessary regarding the timing of administering RRV-TV and antibody-containing blood products. Although no data are available concerning the efficacy of RRV-TV administered simultaneously with antibody-containing blood products, data from studies of OPV indicate that simultaneous administration of OPV with these products does not affect OPV immunogenicity.

Preexisting Chronic Gastrointestinal Disease

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants. Infants with preexisting chronic gastrointestinal conditions might benefit from RRV-TV vaccination. However, the safety and efficacy of RRV-TV have not been established for infants with these preexisting conditions (e.g., congenital malabsorption syndromes, Hirschsprung's disease, short-gut syndrome, or persistent vomiting of unknown cause).

Regurgitation of Vaccine

The practitioner should not readminister a dose of vaccine to an infant who regurgitates, spits out, or vomits during or after administration of vaccine. The infant can receive the remaining recommended doses of RRV-TV at appropriate intervals outlined previously (see Routine Administration). Data are limited regarding the safety of administering a dose of RRV-TV 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.

Late or Incomplete Immunization

Pending additional data, initial vaccination of children aged ≥7 months or administration of any dose of RRV-TV to children on or after their first birthday is not recommended. If a child fails to receive RRV-TV on the recommended schedule of 2, 4,

and 6 months together with other routine immunizations, the child can receive the first dose of vaccine at any time after age 6 weeks but before age 7 months. Second and third doses of RRV-TV can be administered at any time during the first year of life as long as at least a 3-week interval separates doses. Data from the efficacy trials regarding administration of second and third doses are limited to children aged ≤8 months.

Hospitalization After Vaccination

If a recently vaccinated child is hospitalized for any reason, no precautions other than routine universal precautions need be taken to prevent the spread of vaccine virus in the hospital setting.

Latex Hypersensitivity

Health-care workers with a history of latex sensitivity should handle this vaccine with caution because its packaging contains dry natural rubber.

ADVERSE EVENTS AFTER ROTAVIRUS VACCINATION

Serious adverse events that occur after administration of rotavirus vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS). The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report to VAERS any serious adverse events that occur after vaccination, but persons other than health-care workers can also report adverse events. Adverse events that must be reported after rotavirus vaccination are those described in the manufacturer's package insert as contraindications to additional doses of vaccine (*84*). Other adverse events occurring after administration of a vaccine, especially events that are serious or unusual, also should be reported to VAERS, regardless of the provider's opinion about whether the association is causal. VAERS reporting forms and information can be requested 24 hours a day by calling (800) 822-7967 or by accessing the VAERS World-Wide Web site at <http://www.cdc.gov/nip/vaers.htm>.

RRV-TV has been administered to almost 7,000 infants aged 6–28 weeks in three doses of at least 4 x 10^5 pfu, including 2,208 infants in placebo-controlled studies (*55,56,58,76*) (unpublished data, Wyeth-Lederle, 1997), and 4,740 infants in three studies that were not placebo-controlled (unpublished data, Wyeth-Lederle, 1997). The vaccine has been associated with a statistically significant excess of fever following the first dose compared with placebo (>38 C [100.4 F], 21% versus 6% [p<0.001]; >39 C [102.2 F], 2% versus 1% [p<0.001]), with fever usually occurring 3–5 days after administration (Figures 1 and 2, Table 3). Decreased appetite, irritability, and decreased activity also were reported following the first dose of vaccine in some trials; these symptoms were highly associated with the presence of fever in both vaccine and placebo recipients (*85*). A statistically significant excess of fever >38 C (100.4 F, 11% versus 9% [p<0.05]) also was noted after the second dose of RRV-TV; no increase in any symptoms was noted after the third dose of RRV-TV.

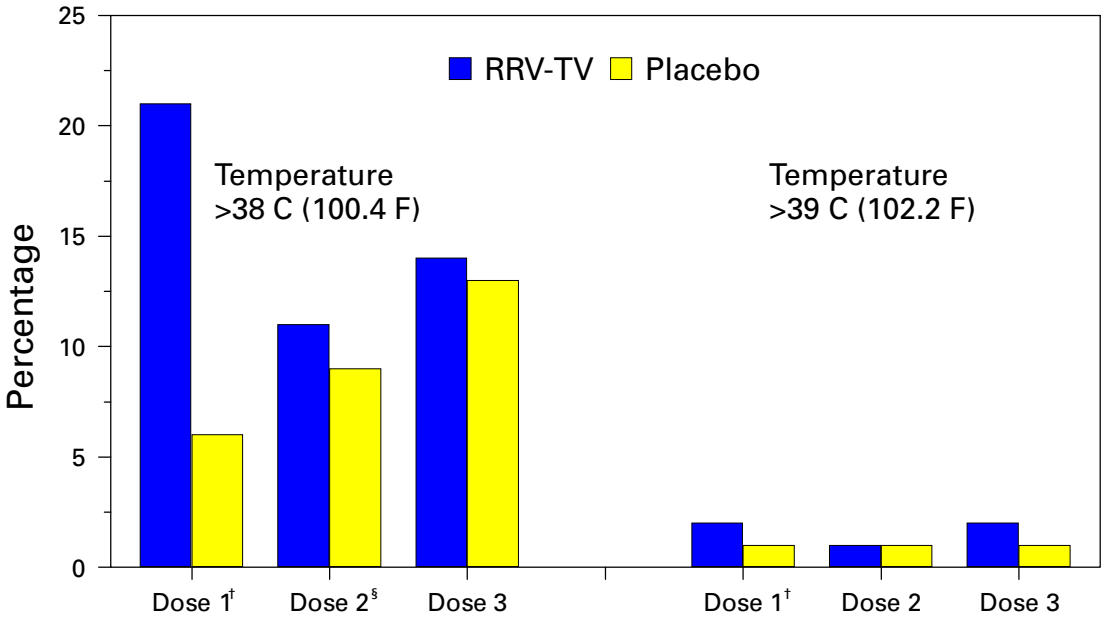
In the placebo-controlled trials, investigators found no overall difference in the rate of diarrhea (*55,56,58,76*) (unpublished data, Wyeth-Lederle, 1997). However, in the efficacy study in Finland (*58*), vaccinated children had a significantly increased rate of diarrhea after the first dose of vaccine compared with placebo recipients (2.8% versus

1.4% [p<0.05]) (Table 3); the diarrhea was associated with the presence of fever (*85*). No evidence exists that RRV-TV causes vomiting.

Initial reports noted failure to thrive or growth delay rarely but more frequently among RRV-TV recipients than among placebo recipients in the Finland and U.S. efficacy trials (18/2,015 [0.9%] among vaccinated children versus 6/2,023 [0.3%] among recipients of placebo [p=0.02]) (unpublished data, Wyeth-Lederle, 1997). On blinded expert review, most cases were found to represent normal variation in growth rates; five cases (three among vaccinated children and two among placebo recipients) were suspected of representing abnormal growth delays.

In all studies of rhesus rotavirus vaccines combined, intussusception was noted in five of 10,054 (0.05%) recipients of any reassortant rhesus vaccine (two of these five children received RRV-TV) compared with one of 4,633 placebo recipients. The difference between the rates of intussusception in these groups was not statistically significant (p=0.92 for children receiving vaccine; p=0.45 for children receiving placebo), and the rates observed among vaccinated children were similar to those seen in comparison populations (*86*). Although the association of these events with RRV-TV appears to be temporal rather than causal, postlicensure surveillance is needed for these and other rare adverse events that might occur.

FIGURE 1. Percentage of children with fever, by dose, during placebo-controlled trials of rhesus-based rotavirus vaccine-tetravalent (RRV-TV) — United States and Finland*

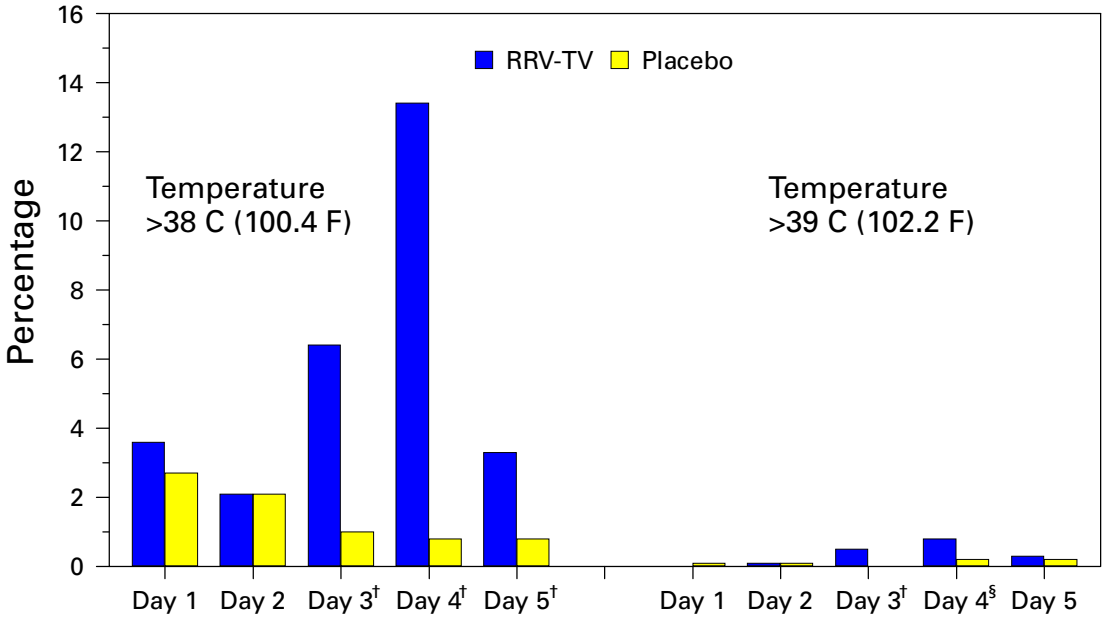


*Data are pooled from separate studies of RRV-TV in the 4 x 10^5 plaque-forming unit dose (Wyeth-Lederle Vaccines and Pediatrics, 1997). Temperatures were taken for the first 5 days after administration of RRV-TV or placebo and were either rectal or axillary, depending on the study.
†p<0.001.
§p<0.05.

Data are limited on adverse events after RRV-TV is administered to premature infants. Of 23 premature infants who were ≤35 weeks' gestational age and who received RRV-TV, one infant developed fever (38.6 C on day 2 after vaccination) and two infants developed diarrhea (one infant on days 2 and 5 after vaccination and the other infant on days 6 and 12) (unpublished data, Wyeth-Lederle, 1997).

The recommendation for routine rotavirus immunization is made in view of the high morbidity associated with rotavirus gastroenteritis and the favorable cost-effectiveness of immunization. Among approximately 20,000 children immunized to date, the vaccine has been found to be generally safe and well tolerated. As with any new vaccine, rare adverse events might be identified when many more children are immunized, and postlicensure surveillance will be required to identify such rare events.

FIGURE 2. Percentage of children with fever, by day, after the first dose of placebo or vaccine during placebo-controlled trials of rhesus-based rotavirus vaccine-tetravalent (RRV-TV) — United States and Finland*



*Data are pooled from separate studies of RRV-TV in the 4 x 10^5 plaque-forming unit dose (Wyeth-Lederle Vaccines and Pediatrics, 1997). Temperatures were taken for the first 5 days after administration of RRV-TV or placebo and were either rectal or axillary, depending on the study.
†$p<0.001$.
§$p<0.05$.

TABLE 3. Percentage of children with adverse reactions after receiving the first dose during placebo-controlled efficacy trials of rhesus-based rotavirus vaccine-tetravalent (RRV-TV) — United States and Finland*

Trial	Adverse effect			
	Fever >38 C	Fever >39 C	Diarrhea	Vomiting
United States†				
Vaccinated children (n=305)	14	2.2	8	7
Children receiving placebo (n=296)	7§	0.6	10	7
United States¶				
Vaccinated children (n=398)	7	0.2	7	4
Children receiving placebo (n=385)	4	0.2	6	5
United States**				
Vaccinated children (n=396)	21	2.3	7	6
Children receiving placebo (n=391)	17	1.4	6	7
Finland††				
Vaccinated children (n=1,184)	29	2.2	3	4
Children receiving placebo (n=1,197)	4§	0.4§	1§	4

*Includes all efficacy studies performed in developed countries. Additional data presented in this table that are not in the published reports were supplied by Wyeth-Lederle Vaccines and Pediatrics.

†Bernstein DI, Glass RI, Rodgers G, Davidson BL, Sack DA, the US Rotavirus Vaccine Efficacy Group. Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children. JAMA 1995;273:1191–6 (*59*). Vaccinated children received 4 x 10^4 plaque-forming units (pfu) of vaccine; all other trials listed used the 4 x 10^5 pfu dose contained in the currently licensed vaccine.

§$p<0.05$.

¶Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines — report of the National Multicenter Trial. Pediatrics 1996; 97:7–13 (*55*).

**Santosham M, Moulton LH, Reid R, et al. Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations. J Pediatr 1997;131:632–8 (*56*).

††Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205–9 (*58*).

FUTURE NEEDS IN ROTAVIRUS SURVEILLANCE, RESEARCH, EDUCATION, AND IMPLEMENTATION

Surveillance

Incidence of Rotavirus Gastroenteritis

Rotavirus gastroenteritis is not a reportable disease, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Therefore, additional efforts will be needed to establish rotavirus disease surveillance systems that are adequately sensitive and specific to document the effectiveness of immunization programs. Current national surveillance systems include a) review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses and b) reports of rotavirus isolation from a sentinel system of laboratories. Additional systems will be needed to provide the timely representative data necessary

for monitoring the effectiveness of a national immunization program. At state and local levels, additional surveillance efforts — by enhanced surveillance at sentinel hospitals or by review of hospital discharge databases — will be necessary to monitor program effectiveness.

Detection of Unusual Strains of Rotavirus

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

Research

Future research should include studies to determine the safety and efficacy of RRV-TV administered to infants born prematurely, infants with immune deficiencies, infants who live in households with immunocompromised persons, infants with chronic gastrointestinal disease, and children aged >1 year. Postlicensure studies also should be conducted to determine the relative efficacy of fewer than three doses of vaccine and to address the cost-effectiveness of vaccination programs in various settings.

Education of Health-Care Providers and Parents

The success of a rotavirus immunization program depends on the acceptance and enthusiasm of physicians and other health-care providers who care for children. Vaccination program personnel will benefit from education about rotavirus disease and rotavirus vaccine. Parental education on rotavirus diarrhea and on the vaccine also will be essential to establish and maintain public confidence in this vaccine and to avoid confusion by cases of diarrhea in early childhood resulting from nonrotaviral etiologies not preventable by RRV-TV.

Implementation

Physicians and health-care providers will require time and resources to incorporate this new vaccine into practice. Therefore, full implementation of these recommendations will not be achieved immediately. During the period of implementation, postmarketing surveillance should be conducted to further delineate the benefits and risks of rotavirus vaccine.

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Summary Table. Recommendations and Quality of Evidence

Rotavirus Vaccine Recommendations
Advisory Committee on Immunization Practices, 1999

Recommendations	Level of Evidence*	Strength of Evidence†
Provide routine vaccination at 2, 4, and 6 months of age.	I	A
Administer to breastfed infants.	I	A
Administer with DTP (or DTaP), Hib vaccine, OPV, IPV, and hepatitis B vaccine.	I	A
Administer to infants with mild illnesses.	I	B
Not recommended for		
Infants with known or suspected immunodeficiency	III	C
Infants with hypersensitivity to vaccine components	III	B
Infants with acute gastrointestinal disease	III	C
Infants with moderate to severe febrile illness	III	C
Precautions and special situations		
Premature infants (<37 weeks gestational age)	III	C
Infants living in households with immunocompromised persons	III	C
Timing of administration of antibody-containing blood products and rotavirus vaccination	III	C
Infants with preexisting chronic gastrointestinal illnesses	III	C
Vaccine that is regurgitated	III	C
Late or incomplete immunization	III	C
Children hospitalized after vaccination	III	C

***Level of Evidence**
I Evidence from randomized, controlled trials
II Evidence from other epidemiologic studies
III Opinions of authorities

†Strength of Evidence
A Good evidence to support recommendation
B Fair evidence to support recommendation
C Insufficient evidence

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