ROTAVIRUS DISEASE AND PREVENTION THROUGH VACCINATION

GUEST EDITOR
Gary S. Marshall, MD

This CME supplement is jointly sponsored by Boston University School of Medicine and Med Learning Group. Publication of this supplement is supported by an educational grant from Merck & Co., Inc.

The Pediatric Infectious Disease Journal®
Copyright © 2009 by Lippincott Williams & Wilkins, Inc.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

CME Overview

Rotavirus Disease and Prevention Through Vaccination

Program Overview
Rotavirus is the most common cause of acute infectious gastroenteritis in children and is associated with substantial morbidity in the United States and morbidity and mortality in the developing world. Two orally administered vaccines, a live bovine reassortant vaccine (RV5; licensed in 2006) and a live attenuated human vaccine (RV1; licensed in 2008), are now being employed in a universal infant vaccination program in the United States. There is already ecological evidence and data from post-licensure effectiveness studies that this program will be an unequivocal success in reducing the impact of rotavirus disease. This overview presents the structure, pathogenesis, and mechanisms of natural immunity to rotavirus, key concepts in understanding the rationale behind vaccine-induced protection. The history of rotavirus vaccine development is also included, along with a discussion of the safety, efficacy, and recommended use of the approved vaccines.

CME Release Date: April 1, 2009

CME Expiration Date: March 31, 2010

Estimated Time to Complete: 1.0 Hour

Jointly sponsored by Boston University School of Medicine and Med Learning Group

Supported by an educational grant from Merck & Co., Inc.

Faculty Advisor Content Editor:
Gary S. Marshall, MD
Chief, Division of Pediatric Infectious Diseases
Kosair Children's Hospital
Professor of Pediatrics
University of Louisville School of Medicine
Louisville, KY

Faculty Course Director:
Stephen Pelton, MD
Chief, Division of Pediatric Infectious Diseases
Boston Medical Center
Professor of Pediatrics
Boston University School of Medicine
Boston, MA

Target Audience
This activity has been designed to meet the educational needs of physicians, nurses, and physician assistants who wish to learn about vaccination strategies for the prevention of rotavirus.

Learning Objectives
1. Outline the epidemiology of rotavirus infection, including transmission, seasonality, and year-to-year serotype variation.
2. Calculate rotavirus disease burden in the United States, including outpatient episodes of gastroenteritis and hospitalizations for dehydration.
3. Compare and contrast available rotavirus vaccines.
4. Summarize the ACIP recommendations for rotavirus vaccination.

Disclosure Policy Statement
Boston University School of Medicine asks all individuals involved in the development and presentation of Continuing Medical Education (CME) activities to disclose all relationships with commercial interests. This information is disclosed to CME activity participants. Boston University School of Medicine has procedures to resolve apparent conflicts of interest. In addition, faculty members are asked to disclose when any discussion of an unapproved use of pharmaceuticals and devices is being discussed.

Disclosures of Conflicts of Interest
Gary S. Marshall, MD, receives grant/research support from GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur and is an ad-hoc consultant for GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur. He is on the

speaker's bureau for GlaxoSmithKline, Merck & Co., Inc., and sanofi pasteur. Dr. Marshall receives support for the CME activities from GlaxoSmithKline, MedImmune, Inc., and Merck & Co., Inc.

Stephen Pelton, MD, receives grant/research support from GlaxoSmithKline and Wyeth. He is a consultant for GlaxoSmith-Kline, Novartis, and Wyeth. Dr. Pelton is on the speaker's bureau for sanofi pasteur and Medimmune, Inc.

Jason Worcester, MD, of Boston Medical Center has nothing to disclose in regards to commercial support.

Elizabeth Gifford of Boston University School of Medicine has nothing to disclose.

Tara Hun-Dorris, MMC, ELS, is a consultant for Salix Pharmaceuticals, Inc., and Victory Pharma.

Kelly Kraines of Med Learning Group has nothing to disclose.

Disclosure of Off-Label Use
Unlabeled/investigational uses of commercial products will be discussed in this activity.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Boston University School of Medicine and Med Learning Group. Boston University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Course Code: **E.ROTAMLGM08**

Credit Designation
Boston University School of Medicine designated this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation
There are no fees for participating and CME credit for this activity. During the period of April 1, 2009 and March 31, 2010, participants must:

1. Read the educational objectives and faculty disclosures.
2. Study all parts of the educational activity.
3. Complete the posttest by recording the best answer to each question in the answer key on the evaluation form. CME credit will be awarded if a score of 70% or better is achieved.
4. Submit the answer sheet form via mail or fax to: Boston University School of Medicine, Continuing Medical Education, E.ROTAMLGM08, 72 East Concord Street, A305, Boston, MA 02118, Fax 617.638.4905. Your certificate will be mailed to you in 4–6 weeks. Or participate online to receive your certificate instantly, at www.bucmetest.com. Enter E.ROTAMLGM08 in the Test Code Search field. If you submit your test online or by fax, please do not mail the original evaluation form.
5. For CME questions, please contact BUSM CME at 617.638.4605.

Disclaimer
THESE MATERIALS AND ALL OTHER MATERIALS PROVIDED IN CONJUNCTION WITH CONTINUING MEDICAL EDUCATION ACTIVITIES ARE INTENDED SOLELY FOR THE PURPOSE OF SUPPLEMENTING CONTINUING MEDICAL EDUCATION PROGRAMS FOR QUALIFIED HEALTH CARE PROFESSIONALS. ANYONE USING THE MATERIALS ASSUMES FULL RESPONSIBILITY AND ALL RISK FOR THEIR APPROPRIATE USE. TRUSTEES OF BOSTON UNIVERSITY MAKE NO WARRANTIES OR REPRESENTATIONS WHATSOEVER REGARDING THE ACCURACY, COMPLETENESS, CURRENTNESS, NONINFRINGEMENT, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE MATERIALS. IN NO EVENT WILL TRUSTEES OF BOSTON UNIVERSITY BE LIABLE TO ANYONE FOR ANY DECISION MADE OR ACTION TAKEN IN RELIANCE ON THE MATERIALS. IN NO EVENT SHOULD THE INFORMATION IN THE MATERIALS BE USED AS A SUBSTITUTION FOR PROFESSIONAL CARE.

© 2009 Lippincott Williams & Wilkins

Rotavirus Disease and Prevention Through Vaccination

Gary S. Marshall, MD

Abstract: Rotavirus is the most common cause of acute infectious gastroenteritis in children and is associated with substantial morbidity in the United States and morbidity and mortality in the developing world. Two orally administered vaccines, a live bovine reassortant vaccine (RV5; licensed in 2006) and a live attenuated human vaccine (RV1; licensed in 2008), are now being used in a universal infant vaccination program in the United States. There is already ecologic evidence and data from post-licensure effectiveness studies that this program will be an unequivocal success in reducing the impact of rotavirus disease. This overview presents the structure, pathogenesis, and mechanisms of natural immunity to rotavirus, key concepts in understanding the rationale behind vaccine-induced protection. The history of rotavirus vaccine development is also included, along with a discussion of the safety, efficacy, and recommended use of the approved vaccines.

Key Words: rotavirus, gastroenteritis, RV5, RV1

(*Pediatr Infect Dis J* 2009;28: 355–362)

Since its discovery in 1973, rotavirus has come to be recognized as the most common cause of acute infectious gastroenteritis in children.[1] Morbidity because of rotavirus in the United States is significant, and morbidity and mortality in the developing world are staggering. Fortunately, there is already evidence that universal vaccination programs have the potential to curtail this burden of disease.

Virus Structure

Rotavirus, named from the Latin "rota" for its wheel-like appearance (Fig. 1),[2] is a nonenveloped virus in the Reoviridae family.[2,3] The particle contains 11 segments of double-stranded RNA in its core[2,3]; each strand codes for a different viral protein (VP), but only 6 proteins are incorporated into the virion. The core of the virus is contained within an inner capsid, comprised mostly of VP6.[2,3] This is surrounded by an outer capsid, primarily comprised of VP7, which forms a Wiffle-ball-like shell around the virion; and VP4, which forms spikes that protrude from the particle.[2,3] VP7 and VP4 are the major targets of neutralizing antibodies.

From the Division of Pediatric Infectious Diseases, University of Louisville School of Medicine, Louisville, KY.

Supported by an educational grant from Merck & Co., Inc. Jointly sponsored by Boston University School of Medicine and Med Learning Group.

Disclosures: G.S.M. receives grant/research support from GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur and is an ad-hoc consultant for GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur. He is on the speaker's bureau for GlaxoSmithKline. Merck & Co., Inc, and sanofi pasteur and receives support for CME activities from GlaxoSmithKline, MedImmune, Inc., and Merck & Co., Inc.

Address for correspondence: Gary S. Marshall, MD, 571 S. Floyd St., Suite 321, Louisville, KY 40202. E-mail: gsmars01@louisville.edu.

Copyright © 2009 by Lippincott Williams & Wilkins

ISSN: 0891-3668/09/2804-0355
DOI: 10.1097/INF.0b013e318199494a

Rotavirus is classified according to antigenic specificities by serogroup, subgroup, and serotype.[2] Seven infectious serogroups of rotavirus, labeled A through G, infect various species.[2,3] However, only groups A, B, and C are human pathogens.[2,3] These groups are distinguished by antigenic differences within the virus core and by migration of RNA gene segments.[3] Group A is the primary pathogenic type for humans worldwide and is responsible for the majority of outbreaks.[2,3] Epidemic infection caused by group B has been limited to Asia and the Indian subcontinent.[2,3] Endemic infections caused by group C are generally not detectable by commercial assays and often go unrecognized.[2,3]

Serogroup and subgroup specificities are determined by VP6, which is abundantly represented in the virion.[2] This also happens to be the antigen most commonly detected by diagnostic assays.[2,3]

Rotaviruses are also classified by their VP7 and VP4 antigens.[2,3] VP7, also referred to as the G protein (for "glycoprotein"), occurs in at least 14 different serotypes, 10 of which are important for humans.[4] These serotypes are referred to as Arabic numerals (G1, G2, G3, etc.); those numerals simultaneously designate genotypes. The most common G type in the United States and worldwide is G1 (Fig. 2).[5]

VP4, also referred to as the P protein (for "protease-sensitive"), also occurs in at least 14 different serotypes, 9 of which are important for humans.[4] These serotypes are referred to by Arabic numerals and lowercase letters (P1a, P1b, etc.); unlike G types, the genotype is referred to by a separate Arabic numeral in brackets (P1a[8], P1b[4], etc.). In this article, only the genotype will be referenced to avoid confusion. The most common P type in the United States and worldwide is P[8] (Fig. 2). Proteolytic cleavage of VP4 enhances rotavirus infectivity, and although VP4 plays a role in virulence, increased disease severity has not been linked to any particular serotype.[2,3]

The G and P proteins segregate independently as the gene segments that encode them reassort.[4] Although various combinations of G and P types are possible, there seems to be a preferential association between particular G and P types. Thus, serotypes G1, G3, and G4 are most often associated with P[8] and G2 is most often associated with P[4].[3] The mechanism of this segregation is not well understood.

Pathophysiology

After ingestion, rotavirus particles are carried to the small intestine, where they attach to enterocytes via glycolipids on the cell surface[3] and enter directly or through calcium-dependent endocytosis.[2,3,6] Replication occurs in mature enterocytes, allowing new rotavirus particles to infect distal portions of the small intestine or be excreted in the stool.[2,3] Viral replication leads to notable pathophysiologic changes, including mitochondrial swelling; distension of the endoplasmic reticulum; denudation of microvilli; mononuclear cell infiltration; shortening, flattening, and atrophy of the villi; and decreased disaccharidase activity.[2,3] These changes lead to an increased osmotic load in the gut lumen because of decreased absorption of salt and water, as well as the failure to process and absorb complex sugars. Symptoms may resolve as mature villous epithelial cells are replaced by less mature enterocytes, which may be less susceptible to rotavirus infection.[2,3]

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

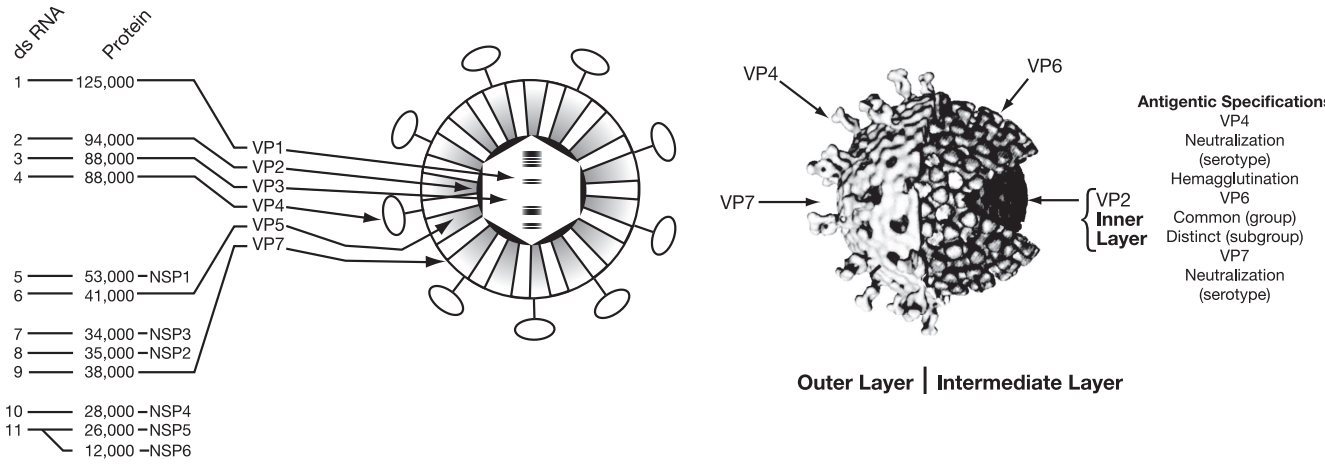
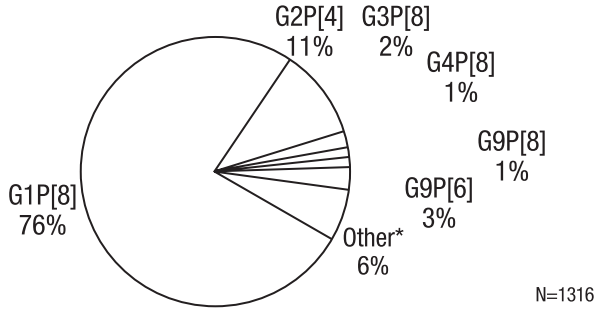


FIGURE 1. Structure of rotavirus. Left: Schematic representation of the rotavirus particle. Right: Surface representations of the 3D structures of the outer layer of the complete particle (*left*) and the particle (*right*) in which the outer layer and a small triangular portion of the intermediate layer have been removed, exposing the inner layer (Modified from Reference 260, with permission. The 3D figure on the right is courtesy of B.V.V. Prasad.)



*Other includes typed uncommon strains, mixed infections, and nontypeable infections.

FIGURE 2. Distribution of human rotavirus serotypes in the United States, November 1997–March 1999 (Adapted from Griffin). Serotypes G1, G3, and G4 with genotype P[8] and serotype G2 with genotype P[4] represented approximately 90% of the strains that were analyzed.

Nonstructural protein 4, an endoplasmic reticulum-specific glycoprotein, that is produced in cells but is not packaged into the mature virion, acts as an enterotoxin and contributes to the genesis of diarrhea.[2,3] It is hypothesized that nonstructural protein 4 interacts with a cellular receptor in the gut epithelium,[2] stimulating a calcium-dependent signal transduction pathway that increases plasma membrane chloride permeability and potentiates chloride secretion, leading to secretory diarrhea.[2] Stimulation of the enteric nervous system also may enhance fluid secretion.

Disease Burden

Most rotavirus infections in infants are symptomatic. After a 2-day incubation period, symptoms begin with fever and vomiting followed shortly thereafter by diarrhea. The whole illness lasts about 3 or 4 days, but loose stools can persist for weeks.[7,8] Early on, vomiting may be rate limiting in terms of attempts at oral rehydration.

Most children have experienced at least 1 rotavirus infection by their second birthday,[7] and almost all are infected in the first 5 years of life.[9] The virus is highly infectious and spreads by the fecal-oral route.[2,3,7] The amount of rotavirus excreted by infected children is very high, more than 10^{10} to 10^{11} viral particles per gram of feces.[2,3] This, combined with the fact that children begin shedding before they are symptomatic and for up to 2 weeks after onset of symptoms[7,10] and that infants do not have good stool hygiene, helps to explain why rotavirus spreads so quickly through daycare centers, families, and communities. The peak incidence of disease is between 6 months and 2 years of age; neonates may be relatively protected by maternal antibody.[3]

Estimates hold that rotavirus is responsible for 111 million worldwide episodes of gastroenteritis, 25 million clinician office visits, 2 million hospitalizations, and 440,000 deaths annually in children <5 years of age.[9] By 5 years of age, 1 in 5 children will have visited a clinic for treatment of rotavirus disease, and 1 in 65 will have been hospitalized. One in 293 children will have died of rotavirus-induced dehydration before the fifth birthday.

In the United States, mortality associated with rotavirus is much lower. Eighty percent of children contract rotavirus by their fifth birthday.[11] Of these, 1 in 200,000 children will die of the disease.[11] However, rotavirus morbidity is still high. Annual direct and indirect costs of rotavirus disease in the United States are estimated at $1 billion.[11] One in 7 children require a clinic or an emergency department (ED) visit because of rotavirus, and 1 in 70 will be hospitalized.[11] Interestingly, the proportion of hospital cases of acute gastroenteritis caused by rotavirus is approximately the same in the developed world as it is in the developing world. This emphasizes the importance of person-to-person transmission, as opposed to water- or food-borne transmission, in the epidemiology of rotavirus infection.

Rotavirus is responsible for at least 18% of pediatric hospital admissions associated with gastroenteritis in the United States, according to retrospective analysis of National Hospital Discharge Survey data from 1993 to 2002.[12] Survey data also indicate that the number of rotavirus hospitalizations has steadily increased from 15.4% during 1993 to 1995 to 20.8% during 2000 to 2002, whereas the rates of all-cause gastroenteritis-associated hospitalizations remained stable at 95 per 10,000 children <5 years of age. Children hospitalized for rotavirus also had significantly longer hospital stays (3.2 vs. 2.9 days).

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

In a separate analysis, the Kids' Inpatient Database was used to estimate the number of diarrhea- and rotavirus-related hospitalizations in US children <5 years of age in 1997 and 2000.[13] Diarrhea was associated with 173,220 and 150,465 hospitalizations in 1997 and 2000, respectively, accounting for about 13% of all hospitalizations in that age group. This suggests that 1 out of every 23 to 27 children <5 years of age will be hospitalized for diarrhea. Most (62%) hospitalizations were of unspecified etiology; however, 35% were identified as viral, and rotavirus was specifically identified in 18% and 19% of cases in 1997 and 2000, respectively. Annual costs for rotavirus hospitalizations in 1997 and 2000 were estimated to be between $140 and $180 million. The authors concluded that a rotavirus vaccine would likely decrease hospitalizations for diarrhea by about 30% for children <5 years of age.

Even when it doesn't result in hospitalization, rotavirus places a tremendous burden upon caregivers and the healthcare system.[8] An analysis of 5 independent prospective cohort studies found that 40% of 284 stool samples collected from outpatients <36 months of age with acute gastroenteritis were positive for rotavirus.[8] The proportion of patients with follow-up medical care was similar among those with rotavirus and those with some other cause of acute gastroenteritis; 57% of patients had a follow-up visit, 8% were seen in an ED, and 5% were hospitalized. However, the data suggested that rotavirus gastroenteritis was more severe than other forms of gastroenteritis: caregivers of patients with rotavirus were more likely to make follow-up calls to healthcare providers (73% vs. 57%); twice as many children with rotavirus required ≥4 healthcare contacts (28% vs. 14%); patients with rotavirus missed significantly more daycare; and in turn, caregivers of children with rotavirus missed significantly more work. Median lost work time was 2 days for caregivers of children with rotavirus, but there was no lost work time for caregivers of children with gastroenteritis that was caused by an agent other than rotavirus.

Given the clinical significance of rotavirus infection, understanding the risk factors for severe disease is important. A case-control study nested within a surveillance study was conducted at Cincinnati Children's Hospital Medical Center, Children's Hospital of New Orleans, and Hasbro Children's Hospital.[14] Data from 349 children ≤59 months of age admitted for rotavirus gastroenteritis from April 1, 2000, through June 31, 2001, were compared with 1242 controls selected from birth certificate registries (Cincinnati and Providence [Hasbro]) and a large-practice consortium patient registry (New Orleans). Breastfeeding was found to protect against hospitalization in infants <6 months of age, although breastfeeding likely postponed rotavirus disease rather than prevented it. Factors associated with hospitalization of children <24 months of age included birth weight <2500 g (odds ratio [OR], 2.8), being a Medicaid recipient or lacking health insurance (OR, 2.1), living with another child <24 months of age (OR, 1.6), and daycare attendance the month before hospitalization (OR, 1.5).

Seasonality

In temperate climates such as the continental United States, rotavirus occurs in predictable seasonal epidemics.[3] An analysis of rotavirus samples reported weekly by the National Respiratory and Enteric Virus Surveillance System from July 1991 to June 1996 found that, in general, rotavirus season began from late November to late December, peaked in mid-February to mid-March, and ended by May, with a mean duration of 23 weeks.[15] Activity tends to begin and peak earlier in the southwest United States and later in the northeast United States (Fig. 3).[15,16]

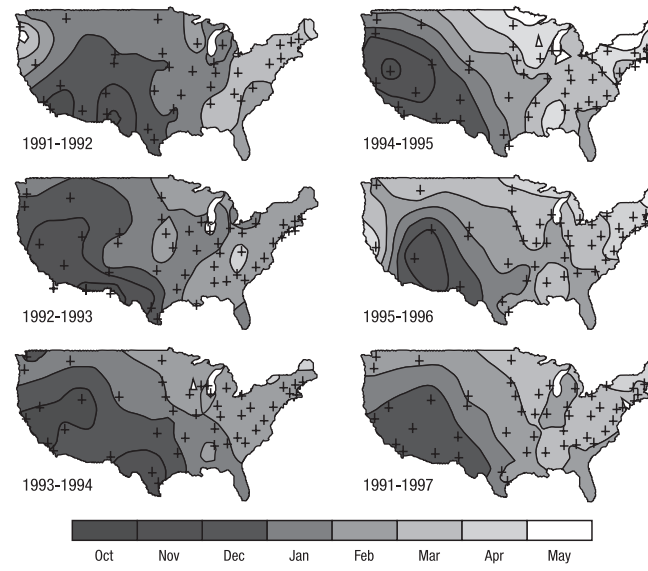


FIGURE 3. Rotavirus activity: United States, July 1991–June 1997 National Respiratory and Enteric Virus Surveillance System. Reprinted with permission from Tõrõk TJ, et al. Pediatr Infect Dis J. 1997;16:941–946.

Strain Prevalence

In a study of 45,571 samples collected worldwide between 1973 and 2003, G1P[8], G2P[4], G3P[8], and G4P[8] strains were found to be responsible for most (89%) of episodes of rotavirus infection in children.[4] However, the predominant serotypes varied by continent. In North America, for example, 73% of infections were caused by G1P[8] strains, and G1, G2, G3, and G4 strains collectively accounted for 98% of infections. G9P[6], originally detected in Philadelphia, Pennsylvania, represented 4% of global rotavirus infections and is believed to be persistent in the United States and emergent worldwide.[4,5]

Another study looked at samples collected from 1981 to 1989 from hospitalized children in the north-central United States (Ohio, New York, Pennsylvania, West Virginia, Kentucky, Indiana, and Michigan) and samples collected from 1979 to 1989 in Harris County (Houston) and other parts of Texas.[16] G1 strains were identified in 61% of infections, followed by G3 (23%), G4 (7%), G2 (4%), and a small number of nontypeable and mixed specimens. Serotype prevalence also varied by season, but the prevalent serotype tended to predominate early in each season. No significant differences in serotypes were noted in different age groups. However, geographic differences were marked. The ratio of G1:G3 was about 10:1 in the north central states compared with about 1:1 in Harris County and 2:1 in other parts of Texas. G4 was also significantly more prevalent in Texas than in the north central states. When this trend was mapped, G3 and G4 decreased in prevalence from the southwest to the northeast.

Natural Infection Confers Protection

After rotavirus infection, children develop serum and intestinal antibody responses that protect against severe diarrhea upon reinfection.[6] Viral antigens are transported to Peyer patches, where they are processed by macrophages and dendritic cells and presented to B cells and helper T cells.[2,3] The end result is the generation of rotavirus-specific B cells and expansion of cytotoxic T lymphocytes.[2,3]

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Protection is thought to be largely due to humoral immunity.[2,3] In infants and young children, rotavirus-specific IgM can be detected in duodenal fluid and serum during the first week of illness.[3] Months later, rotavirus-specific IgG and IgA can be detected in duodenal fluid, and rotavirus-specific IgG and monomeric IgA can be detected in serum.[3] One year postinfection, rotavirus-specific IgG but not IgA can be detected in the serum.[3] Serum IgG antibody against rotavirus is considered the most consistent marker of rotavirus immunity, although definitive correlates of protection have not been established.[2,3,6] Fecal or duodenal IgA is considered an excellent marker for recent primary infection or reinfection.[3]

The initial antibody response to rotavirus is serotype specific, and production of cross-protective antibodies is limited.[2,3,6] However, cross-reactive antibodies arise after repeated infections.[2,3,6] In this regard, it is important to differentiate homotypic from heterotypic antibody responses. Infection with a G1P[8] strain would be expected to protect against subsequent infections with G8 strains as well as other G serotypes associated with P[8]; this is an example of homotypic immunity. Protection against infection with a G2P[4] strain, if present, would be mediated by heterotypic immunity or cross-reactive antibodies.

In a classic prospective cohort study, 200 newborns in Mexico City were followed through 2 years of age. Home visits were made and stool samples were collected each week.[17] Additional stool samples were collected when children had symptoms of diarrhea. This study clearly demonstrated that natural infection was protective against reinfection. As shown in Figure 4,[17] the cumulative probability of 1 rotavirus infection by age 2 was nearly 100%, testifying to the universality of infection in childhood. However, the cumulative probability of a second infection was lower, and a third infection even lower, implying a protective effect of the prior infections. Subsequent infections were also less severe than prior infections; in fact, no child who had 2 rotavirus infections had a third infection that was judged to be moderate to severe. This was true even if the prior infections were asymptomatic. The implications of this study were clear: a vaccine that could mimic natural infection in an immunologic sense would be expected, after multiple doses, to protect against moderate-to-severe rotavirus gastroenteritis.

Vaccine Development

Given the disease burden described above, development of a rotavirus vaccine has been considered an important public health initiative for several decades. Rhesus rotavirus vaccine, tetravalent (RRV-TV), licensed in 1998 under the trade name RotaShield (Wyeth), was the first rotavirus vaccine approved in the United States. The vaccine was based on a G3P[3] rhesus rotavirus strain that was naturally attenuated for humans. The vaccine was comprised of 4 live viruses: 3 reassortants, each the parental rhesus virus with 1 gene segment substitution from a human strain leading to expression of either G1, G2, or G4, and the native G3P[3] strain. The vaccine was administered as a 3-dose series given orally at 2, 4, and 6 months of age. Efficacy against severe rotavirus gastroenteritis was 70% to 95%.[18]

Use of RRV-TV was short-lived. Within a year, the vaccine was found to be associated with intussusception and the recommendation for universal use was withdrawn.[19] The attributable risk of intussusception to the vaccine is now estimated to be somewhere around 1 in 11,000 vaccine recipients,[20–22] with most cases occurring in the first 2 weeks after dose 1, the time of peak viral replication. The mechanism by which RRV-TV caused intussusception is not fully understood, but is believed to be related to biologic characteristics of the native rhesus strain.

Two newer generation rotavirus vaccines are now available in the United States. Rotavirus vaccine, 5-valent (RV5), licensed under the trade name RotaTeq (Merck) in February 2006, is a live, oral, bovine reassortant vaccine.[23] Rotavirus vaccine, monovalent (RV1), licensed under the trade name Rotarix (GlaxoSmithKline) in April 2008, is a live, attenuated, oral vaccine made from a human strain of rotavirus.[24] Both vaccines were tested in more than 70,000 infants before approval.

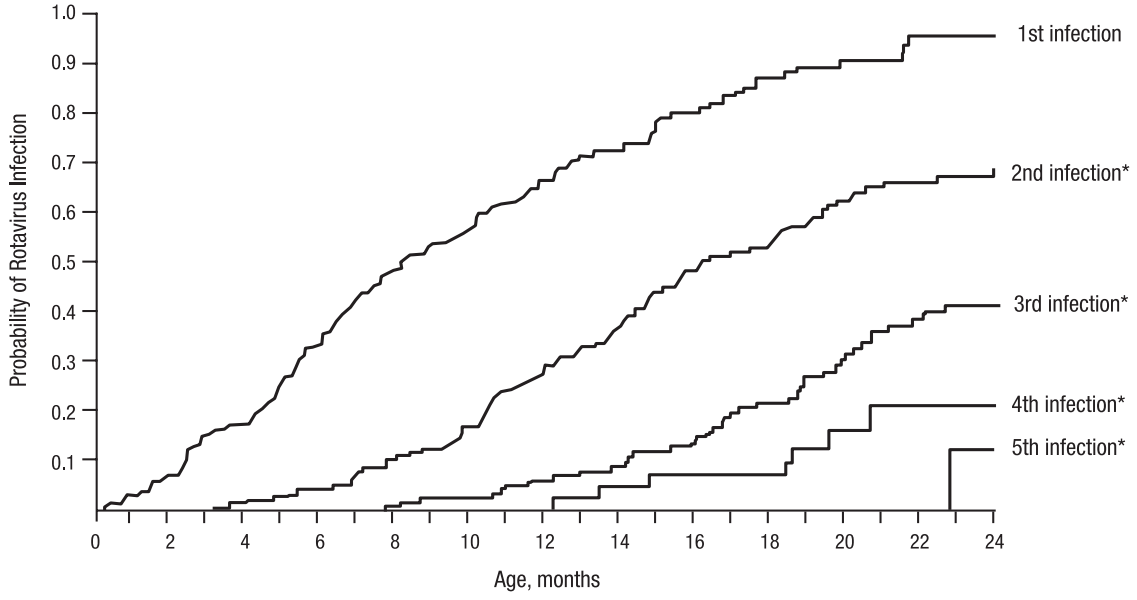


FIGURE 4. Cumulative probability of first and future rotavirus infection during the first 2 years of life. *Subsequent infections were usually caused by a different serotype. Reprinted with permission from Velaquez FR, Matson DO, Calva JJ, et al. *N Engl J Med.* 1996;335:1022–1028. Copyright 1996 Massachusetts Medical Society.

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

RV5 Efficacy and Safety

RV5 was developed from the bovine rotavirus strain WC3, a G6P[5] virus that is attenuated for humans. WC3 was reassorted with human strains to yield the 5 viruses that comprise the licensed vaccine: each the parental bovine virus with 1 gene segment substitution from a human strain, leading to expression of either G1, G2, G3, or G4, each with the bovine P[5], or P[8] along with the bovine G6.

The pivotal phase 3 study called REST (*R*otavirus *E*fficacy and *S*afety *T*rial) was conducted primarily in the United States and Finland, but with other sites worldwide.[25] A total of 70,301 healthy infants were enrolled; 34,644 were assigned to receive RV5 and 34,630 were assigned to receive placebo. A total of 3 doses were given: the first doses at 6 to 12 weeks of age and subsequent doses at 4 to 10 week intervals. Among infants who received at least 1 dose, 67,756 were followed for 42 days after their last dose. Six RV5 recipients and 5 placebo recipients had confirmed cases of intussusception within the 42-day period after any dose (relative risk, 1.6; 95% confidence interval [CI], 0.4–6.4). No cases of intussusception were reported within 42 days after the first dose, the highest risk period that was noted for RRV-TV. These results met the study's prespecified safety criteria for no association with intussusception. The incidence of serious adverse events was similar between RV5 and placebo recipients (2.4% vs. 2.5%). Forty-four deaths occurred during the study, mostly attributable to sudden infant death syndrome. No deaths were considered related to RV5 administration.

In a detailed safety substudy, the incidence rates of fever, vomiting, diarrhea, and hematochezia were similar for RV5 (n = 4806) and placebo (n = 4799) recipients within 42 days after any dose. However, the incidence of the following solicited adverse events was higher for vaccinees versus placebo recipients: vomiting (6.7% vs. 5.4%) and diarrhea (10.4% vs. 9.1%) after dose 1, and diarrhea (8.6% vs. 6.4%) after dose 2.[23] This is perhaps not surprising for an orally administered, live-attenuated vaccine.

In a detailed efficacy cohort nested within the Rotavirus Efficacy and Safety Trial that compared approximately 2800 vaccinees and placebo recipients, efficacy against rotavirus gastroenteritis of any severity (caused by serotypes G1 through G4) was 74% (95% CI, 66.8–79.9) through 1 season and 71.3% (95% CI, 64.7–76.9) through 2 seasons. Efficacy against severe rotavirus gastroenteritis through 1 season was 98.0% (95% CI, 88.3–100.0) and in the second season only was 88.0% (95% CI, 49.4–98.7). The numbers were similar when efficacy was considered without regard to serotype. The large-scale efficacy study looking at health resource utilization involved approximately 28,000 to 34,000 vaccinees and equal numbers of placebo recipients. Hospitalizations due to rotavirus serotypes G1 through G4 during the 2 years after dose 3 were reduced by 95.8% among vaccinees and ED visits were reduced by 93.7%.

RV1 Efficacy and Safety

RV1 was developed from a human strain of rotavirus (G1P[8]) isolated from a child in Cincinnati in 1989. The virus was serially passaged in tissue culture to achieve attenuation. The vaccine is considered monovalent because it contains only 1 strain of virus; in fact, 2 major neutralizing proteins—G1 and P[8]—are included.

The pivotal clinical trial was conducted primarily in Latin America and Finland; 6 to 13 week old healthy infants were enrolled and scheduled to receive vaccine or placebo at approximately 2 and 4 months of age.[26] In all, 31,673 infants received RV1 and 31,552 received placebo. Six RV1 recipients and 7 placebo recipients had definite intussusception within 31 days, after either dose (respective incidence rates, 1.89 and 2.21 per 10,000 infants; difference in risk −0.32 per 10,000 infants; 95% CI, −2.91 to 2.18). There was no statistically significant difference between RV1 and placebo recipients in intussusception occurring within 31 days of vaccine (relative risk, 0.85), after the 31-day window (3 vs. 9), or during the entire safety surveillance period (9 vs. 16). These results met the study's prespecified safety criteria for no association with intussusception.

Significantly fewer RV1 recipients experienced serious adverse events than placebo recipients (293.0 vs. 331.8 events per 10,000 infants). Ninety-nine deaths occurred during the study. Although overall mortality did not differ between RV1 and placebo recipients, more RV1 recipients died of pneumonia (16 vs. 6). However, the distribution of pneumonia-related deaths within 31 days of vaccine administration did not differ between groups, and further analyses did not detect a difference in pneumonia-related serious adverse events. There were no differences in the incidence of solicited adverse events between RV1 and placebo.[24] However, RV1 recipients did experience significantly more irritability (11.4% vs. 8.7%) and flatulence (2.2% vs. 1.3%).[24]

Efficacy was evaluated in 9009 infants who received RV1 and 8858 infants who received placebo, and were followed until they were 1 year old.[26] Efficacy against severe rotavirus gastroenteritis was 84.7% (95% CI, 71.7–92.4) and efficacy against hospitalization for severe rotavirus gastroenteritis was 85.0% (95% CI, 69.6–93.5).

Efficacy against severe rotavirus gastroenteritis caused by G1P[8] strains (homotypes of the vaccine strain) was 91.8% (95% CI, 74.1–98.4). For severe rotavirus gastroenteritis caused by strains with heterotypic G types (G3, G4, and G9) but with homotypic P types (P[8]), efficacy was 87.3% (95% CI, 64.1–96.7). Efficacy against rotavirus gastroenteritis caused by G2P[4], which does not share any antigens with the vaccine strain, was 41.0% (95% CI, −79.2 to 82.4); the small number of cases here is responsible for the wide confidence interval.

Efficacy also was assessed in a separate double-blind trial of RV1 limited to Europe.[27] The primary end point was vaccine efficacy against rotavirus gastroenteritis of any severity. Subjects were followed through the end of the second rotavirus season after vaccination. Overall, 2646 subjects received RV1 and 1348 subjects received placebo; 3883 infants (97%) completed the follow-up visit. RV1 efficacy against rotavirus gastroenteritis of any severity was 78.9% (95% CI, 72.7%–83.8%); efficacy against severe gastroenteritis was 90.4% (95% CI, 85.1%–94.1%). Efficacy against rotavirus gastroenteritis of any severity due to G1, G3, G4, G9, and G2 was 89.8%, 84.8%, 83.1%, 72.9%, and 58.3%, respectively. Efficacy against severe rotavirus gastroenteritis due to the same strains was 96.4%, 93.7%, 95.4%, 85.0%, and 85.5%.

Vaccine Comparison

Both RV5 and RV1 were found to be safe and effective in these large-scale clinical trials, and each has been licensed in many countries, including the United States. Table 1 presents a comparison of RV5, RV1, and the discontinued RRV-TV.[28] It is important to note that the vaccines have not been directly compared in head-to-head controlled clinical trials.

Evidence of Effectiveness of the US Rotavirus Vaccination Program

The recommendation to immunize all infants in the United States against rotavirus disease was issued in August 2006, shortly after the licensure of RV5.[11] The Centers for Disease Control and Prevention (CDC) recently analyzed data from the National

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

TABLE 1. Comparison of Rotavirus Vaccines (The Vaccine Quarterly)*

Characteristic	Vaccines		
	No Longer Available	Currently Licensed in the United States	
	Rhesus Rotavirus Vaccine-Tetravalent	Pentavalent Rotavirus Vaccine	Human Rotavirus Vaccine
Common abbreviation	RRV-TV	RV5 (rotavirus vaccine, 5-valent)	RV1 (rotavirus vaccine, monovalent)
Trade name	RotaShield	RotaTeq	Rotarix
Manufacturer	Wyeth	Merck	GlaxoSmithKline
Licensure	1998	2006	2008
Description	Live rhesus rotavirus reassortant	Live bovine rotavirus reassortant	Live attenuated human rotavirus
Method of attenuation	Heterologous host	Heterologous host serial in vitro passage	Serial in vitro passage
Cell type used for production	Fetal rhesus diploid cells	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells
Serotypes actually contained in the vaccine (origin)	G1 (human) G2 (human) G3-like (rhesus) G4 (human) P5[3] (rhesus)	G1 (human) G2 (human) G3 (human) G4 (human) G6 (bovine) P1[8] (human) P7[5] (bovine)	G1 (human) P1[8] (human)
Serotypes for which vaccine is labeled as protective	G1, G2, G3, G4	G1, G2, G3, G4	G1, G3, G4, G9
Route	Oral	Oral	Oral
Dose	2.5 mL	2 mL	1 mL
Presentation	Lyophilized in a single-dose vial Reconstitution required using plastic ampoule containing liquid diluent	Liquid in a single-dose, squeezable, plastic tube	Lyophilized in a single-dose vial Reconstitution required using oral applicator containing liquid diluent
Dosing schedule	2, 4, 6 mos of age	2, 4, 6 mos of age	2, 4 mos of age
Age at first dose according to the package insert	≥6 wks	6–12 wks	≥6 wks
Age at first dose according to the 2009 ACIP recommendations	N/A	6 wk–14 wk 6 days	6 wk–14 wk 6 days
Minimum interval between doses	3 wks	4 wks	4 wks
Maximum age for last dose according to the package insert	6 mos	32 wks	24 wks
Maximum age for last dose according to the ACIP recommendations	N/A	8 mos 0 days	8 mos 0 days
Storage	Vials and diluent stored in refrigerator or room temperature Reconstituted vaccine stable for 1 h at room temperature and 4 h in refrigerator	Refrigerator	Vials in refrigerator and diluent at room temperature Reconstituted vaccine stable for 24 h at room temperature or in refrigerator
Approximate number of children involved in mature pre-licensure trials	11,000	72,000	72,000
Efficacy against any rotavirus disease through the first season	49%–83%	73%–74%	87%
Efficacy against severe rotavirus disease through the first season	70%–95%	98%–100%	85%–96%
Shedding and transmission	50% of vaccines Low-level horizontal transmission documented	9% after first dose only Horizontal transmission not evaluated	26% Horizontal transmission not evaluated
Solicited adverse events statistically higher than placebo during first week	Fever Decreased appetite Irritability Decreased activity	Slight excess of vomiting and diarrhea	None
Risk of intussusception attributable to the vaccine	1 in 11,000 vaccinees	No attributable risk detected	No attributable risk detected

*Data on safety and efficacy are based on information provided in the respective package inserts. It is important to point out that the vaccines were not compared to each other in a head-to-head clinical trial.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

© 2009 Lippincott Williams & Wilkins

Respiratory and Enteric Virus Surveillance System and the New Vaccine Surveillance Network to see if there has been an impact of the rotavirus vaccine program.[29] On average, the rotavirus seasons between 1991 and 2006 began in mid-November and peaked in early February (Fig. 5).[29] During the height of the season, about 40% of stool specimens submitted were positive for rotavirus. The 2007–2008 season was very different—the onset was delayed and the season peaked around April. What's more, at the height of the season, <20% of tests were positive. Several additional studies presented in abstract form at the recent Infectious Diseases Society of America/International Conference on Antimicrobial Agents and Chemotherapy meeting confirm these observations and suggest that the rotavirus program is working. Investigators have reported dramatic reductions in hospitalizations and positive laboratory tests[30–35]; these benefits have been seen despite the fact that only 1 vaccine has been in general use since 2006, and fewer than half of infants have received all 3 doses. A formal postlicensure effectiveness study[36] among 33,135 fully-vaccinated infants and 27,954 control infants who were not vaccinated demonstrated a 100% reduction in hospitalizations and ED visits and a 96% reduction in physician visits for rotavirus gastroenteritis.

Recommendations

The following recommendations were recently published by the Advisory Committee for Immunization Practices (ACIP).[37] There are some important differences between the information in the respective package inserts and the ACIP recommendations, particularly with respect to the timing of doses (Table 1). In practice, ACIP recommendations generally trump product labeling, although in a technical sense, the timing suggested by the ACIP is off-label.

All infants should be vaccinated against rotavirus. There is no preference for 1 vaccine over the other, and either vaccine can be given concomitantly with the other vaccines recommended in infancy. The usual schedule for RV5 is 3 oral doses at 2, 4, and 6 months of age and the usual schedule for RV1 is 2 oral doses at 2 and 4 months of age. The first dose of either product should be given between 6 weeks and 14 weeks 6 days of age. The last dose (second dose of RV1 or third dose of RV5) should be given before 8 months 0 days of age. Effort should be made to complete the series with the same product; however, vaccination should not be deferred if the same product is not available or not known. If any dose in the series is RV5 or is unknown, a total of 3 doses should be given. If the infant spits up a dose, repeat administration is not necessary (although the RV1 package insert says that a single replacement dose at the same visit may be considered).

Vaccination is recommended in the following circumstances:

- Infants who have already had an episode of rotavirus gastroenteritis
- Infants who are breastfed
- Premature infants who are clinically stable and are being or have been discharged from the nursery (infants who remain in the nursery should not be vaccinated)
- Infants living in the home of immunocompromised or pregnant individuals (standard precautions should be followed to minimize horizontal transmission)

Vaccine should not be given to infants who have had an allergic reaction to a previous dose or any vaccine components. Rotavirus vaccine should be used with precaution (this means weighing the risks and benefits) in infants with moderate or severe acute illness; moderate or severe acute gastroenteritis; immunodeficiency or immunosuppression (infants with or at risk for HIV infection may be vaccinated); pre-existing gastrointestinal disease such as congenital malabsorption syndromes, chronic diarrhea and failure to thrive, previous abdominal surgery, Hirschsprung's disease, short-gut syndrome, persistent vomiting of unknown cause (history of uncorrected congenital malformation of the gastrointestinal tract that might predispose to intussusception [eg, Meckel diverticulum] is listed in the package insert as a contraindication for RV1); and previous history of intussusception. In addition, whereas receipt of an antibody-containing blood product could impair the immune response to the vaccine, vaccination should not be deferred in this situation.

Routine vaccination of infants against rotavirus is considered the most effective public-health intervention for reducing the burden of rotavirus disease.[38]

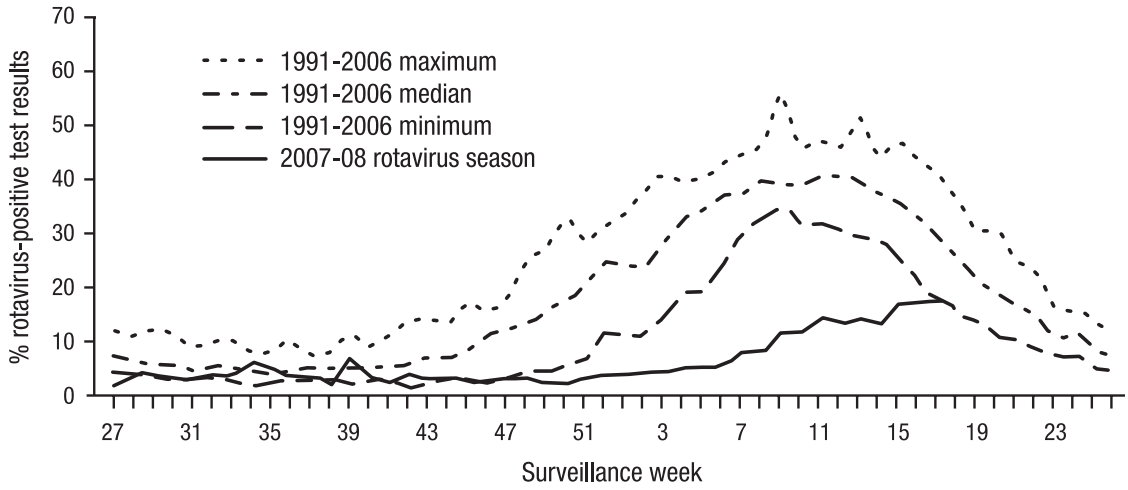


FIGURE 5. Percentage of rotavirus tests with positive results from participating laboratories, by week of the year—-National Respiratory and Enteric Virus Surveillance System, United States; 1991–2006 rotavirus seasons and 2007–2008 rotavirus season* (*MMWR* 6/27/08). *2008 data current through week ending May 3, 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) baseline data.

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

ACKNOWLEDGMENTS

The author thanks Tara Hun-Dorris, MMC, ELS, of THD Editorial, Inc., for assistance in preparation of this manuscript.

REFERENCES

1. Anderson EJ, Weber SG. Rotavirus infection in adults. *Lancet Infect Dis*. 2004;4:91–99.
2. Kapikian AZ, Hoshino Y, Chanoock RM. Rotaviruses. In: Knipe DM, Howley PM, eds. *Fields Virology*. Philadelphia, PA: Lippincott Williams and Wilkins; 2001:1787–1808.
3. Offit PA, Clark HF. Rotavirus. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Disease*. Philadelphia, PA: Churchill Livingstone; 2000:1696–1703.
4. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implications for the development and implementation of an effective rotavirus vaccine. *Rev Med Virol*. 2005;15:29–56.
5. Griffin DD, Kirkwood CD, Parashar UD, et al. Surveillance of rotavirus strains in the United States: identification of unusual strains. *J Clin Microbiol*. 2000;38:2784–2787.
6. Jiang B, Gentsch JR, Glass RI. The role of serum antibodies in the protection against rotavirus disease: an overview. *Clin Infect Dis*. 2002;34: 1351–1361.
7. Musher DM, Musher BL. Contagious acute gastrointestinal infections. *N Engl J Med*. 2004;351:2417–2427.
8. Coffin SE, Elser J, Marchant C, et al. Impact of acute rotavirus gastroenteritis on pediatric outpatient practices in the United States. *Pediatr Infect Dis J*. 2006;25:584–589.
9. Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and death caused by rotavirus disease in children. *Emerg Infect Dis.* 2003;9:565–572.
10. Pickering LK, Bartlett AV, Reves RR, et al. Asymptomatic excretion of rotavirus before and after rotavirus diarrhea in children in day care centers. *J Pediatr*. 1988;112:361–365.
11. Parashar UD, Alexander JP, Glass RI, Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-12):1–13.
12. Charles MD, Holman RC, Curns AT, et al. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993 to 2002. *Pediatr Infect Dis J*. 2006;25:489–493.
13. Maleck MA, Curns AT, Holman RC, et al. Diarrhea- and rotavirus-associated hospitalization among children less than 5 years of age: United States, 1997 and 2000. *Pediatrics*. 2006;117:1887–1892.
14. Dennehy PH, Cortese MM, Begue RE, et al. A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in US children. *Pediatr Infect Dis J*. 2006;25:1123–1131.
15. Török TJ, Kilgore PE, Clarke MJ, et al. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. *Pediatr Infect Dis J*. 1997;16:941–945.
16. Matson DO, Estes MK, Burns JW, et al. Serotype variation of human group A rotaviruses in two regions of the USA. *J Infect Dis.* 199;162:605–614.
17. Velazquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med*. 1996;335:1022–1028.
18. RotaShield prescribing information. Philadelphia, PA: Wyeth-Ayerst; August 1998.
19. Centers for Disease Control and Prevention. Suspension of rotavirus vaccine after reports of intussusception—United States, 1999. *MMWR.* 2004; 53:786–789.
20. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344:564–572.
21. Kramarz P, France EK, DeStefano F, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J*. 2001;20: 410–416.
22. Simonsen L, Viboud C, Elixhauser A, et al. More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis*. 2005;192(suppl 1):S36–S43.
23. RotaTeq prescribing information. Whitehouse Station, NJ: Merck and Co. Inc; 2008.
24. Rotarix prescribing information. Research Triangle Park, NC: GlaxoSmith-Kline; 2008.
25. Vesikari T, Matson DO, Dennehy P, et al; the Rotavirus Efficacy and Safety Trial Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23–33.
26. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354:11–22.
27. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants, randomized, double-blind controlled study. *Lancet*. 2007; 370:1757–1763.
28. Marshall GS. Rotavirus vaccines. *Vaccine Quart*. 2008;2:17.
29. Centers for Disease Control and Prevention. Delayed onset and diminish magnitude of rotavirus activity—United States, November 2007–May 2008. *MMWR.* 2008;57:697–700.
30. Clark HF, Lawley D, Mallette L, et al. Decline in rotavirus (RV) gastroenteritis (GE) presenting to the Children's Hospital of Philadelphia (CHOP) after introduction of pentavalent rotavirus vaccine (PRV). Poster (G1-413) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
31. Daskalaki I, Wood SJ, Inumerable YM, et al. Epidemiology of rotavirus-associated hospitalizations pre- and post-implementation of immunization: North Philadelphia, 2000–2008. Poster (G1-432) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
32. Harrison CJ, Jackson M, Olson-Burgess C, et al. Fewer 2008 hospitalizations for rotavirus (RV) in Kansas City, two years post RV vaccine. Poster (G1-435) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
33. Hatch S, Fontecchio S, Gibson L, et al. Rapid decline in pediatric rotavirus cases following introduction of rotavirus vaccine. Poster (G1-436) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
34. Lieberman JM, Huang X, Koski E, et al. Decline in rotavirus cases in the US after licensure of a live, oral rotavirus vaccine. Poster (G1-437) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
35. Patel JA, Loeffelholz M. Reduction of severe rotavirus gastroenteritis following the routine use of live, oral, pentavalent rotavirus vaccine. Poster (G1-434) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
36. Mast T, Wang F, Goli V, et al. Post-licensure effectiveness of RotaTeq in preventing gastroenteritis. Poster (G1-433) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
37. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2009;58(RR-2):1–25.
38. Rotavirus vaccination coverage and adherence to the Advisory Committee on Immunization Practice (ACIP)-recommended vaccination schedule—United States, February 2006–May 2007. *MMWR.* 2008;57:398–401.

© 2009 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

CME Posttest

Rotavirus Disease and Prevention Through Vaccination

1. Which of the following rotavirus serogroups are human pathogens?
    a. A
    b. D
    c. F
    d. All of the above
    e. None of the above

2. Which protein is the "glycoprotein" in rotavirus?
    a. VP4
    b. VP6
    c. VP7
    d. NSP4
    e. None of the above

3. When is the peak incidence of rotavirus infection?
    a. <6 months of age
    b. 6 months to 1 year of age
    c. 6 months to 2 years of age
    d. 6 months to 5 years of age
    e. Birth to 5 years of age

4. Which of the following statements is true regarding the disease burden of rotavirus in the United States?
    a. Annual direct and indirect costs associated with rotavirus are estimated at $100 million
    b. 1 in 20,000 children will die from rotavirus
    c. Children hospitalized for rotavirus have significantly shorter hospital stays
    d. Rotavirus is responsible for at least 18% of pediatric hospitalizations
    e. All children will contract rotavirus by their fifth birthday

5. Natural rotavirus infection does not confer protection against future disease.
    a. True
    b. False

6. Which of the following is true about the seasonality of rotavirus in the United States?
    a. Rotavirus activity tends to begin in the southwest
    b. The season begins in late November/early December
    c. The season peaks in mid-February/mid-March
    d. None of the above
    e. All of the above

7. Which rotavirus strain tends to be most prevalent in North America?
    a. G1P[8]
    b. G2P[4]
    c. G3P[8]
    d. G4P[8]
    e. None of the above

8. There is evidence that the rotavirus vaccine program is working.
    a. True
    b. False

9. According to ACIP, which of the following infants can receive the rotavirus vaccine?
    a. Prior rotavirus gastroenteritis
    b. Breastfeeding
    c. Clinically stable premature infants who are/have been discharged from the nursery
    d. None of the above
    e. All of the above

10. How did the RRV-TV vaccine differ from the currently approved rotavirus vaccines?
    a. It was tested in a smaller population in clinical trials prior to approval
    b. It caused shedding in approximately 50% of patients
    c. It was associated with a higher risk of intussusception attributable to vaccine
    d. None of the above
    e. All of the above

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Evaluation - please complete

Rotavirus Monograph Journal Supplement
Rotavirus Disease and Prevention Through Vaccination

To participate in this activity please read the monograph and take the test. Fill in the answer sheet and submit it to BUSM CME before March 31, 2010. CME credit will be awarded if a score of 70% or better is achieved. Submit the answer sheet form via mail or fax to: Boston University School of Medicine, Continuing Medical Education, (E.ROTAMLGM08), 72 East Concord Street, A305, Boston, MA 02118, Fax 617.638.4905. Your certificate will be mailed to you in 4-6 weeks. Or participate online to receive your certificate instantly, at: **www.bucmetest.com** Enter "E.ROTAMLGM08" in the Test Code Search field. If you submit your test online or by fax, please do not mail the original. For questions please contact BUSM CME at 617.638.4605.

Request for Credit

Name_____ Degree _____
Organization _____ Specialty _____
Address _____ City/State/Zip_____
Telephone _____ Fax _____ Email _____
Signature _____ Date _____

For Physicians Only: I certify my actual time spent to complete this educational activity to be:
__ I participated in the entire activity and claim 1.0 credits.
__ I participated in only part of the activity and claim ___ credits.

Posttest Answer Key

__	__	__	__	__	__	__	__	__	__
1	2	3	4	5	6	7	8	9	10

1. How would you rate this educational activity overall?
(5 = excellent, 1 = poor, please circle one) 5 4 3 2 1

2. In your opinion, did you perceive any commercial bias in any of the presentations?
☐ Yes If yes, please explain:
☐ No

3. Do you plan on making any changes in your practice as a result of this activity?
☐ Yes If yes, please explain:
☐ No

4. Do you feel each of the following objectives were met?
I am now better able to:

• Outline the epidemiology of rotavirus infection, including transmission, seasonality, and year-to-year serotype variation.	☐Yes ☐No ☐Partially ☐N/A
• Calculate rotavirus disease burden in the United States, including outpatient episodes of gastroenteritis and hospitalizations for dehydration.	☐Yes ☐No ☐Partially ☐N/A
• Compare and contrast available rotavirus vaccines.	☐Yes ☐No ☐Partially ☐N/A
• Summarize the ACIP recommendations for rotavirus vaccination.	☐Yes ☐No ☐Partially ☐N/A

5. Do you feel that the information presented was based on the best evidence available?
☐ Yes
☐ No If no, please explain:

6. Which of the following competency areas do you feel have been improved as a result of this activity? (Check all that apply)
☐ Patient Care ☐ Professionalism ☐ Practice Based Learning
☐ Medical Knowledge ☐ System Base Practice ☐ Communication Skills

7. Please suggest topics for future activities.

_____

8. Please rate the quality of the content. (5 = Excellent, 1 = Poor)
Rotavirus Disease and Prevention Through Vaccination 5 4 3 2 1
Comments:

General Comments:

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.