Chapter 13: Rotavirus

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I. Disease Description

Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Nearly every US child who is not vaccinated against rotavirus as an infant is expected to be infected with rotavirus within the first years of life, and the majority will have symptomatic gastroenteritis. The clinical spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death. Following an incubation period of 1–3 days, the illness often begins abruptly, and vomiting often precedes the onset of diarrhea. Gastrointestinal symptoms generally resolve in 3–7 days. Up to one-third of patients have a temperature of >102°F (>39°C). Severe, dehydrating rotavirus infection occurs primarily among unvaccinated children aged 3–35 months.1,2,3,4,5

Rotaviruses are shed in high concentrations in the stools of infected children and are transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites.7 Rotaviruses also are probably transmitted by other modes, such as fecally contaminated food and water and respiratory droplets.8 Rotavirus is highly communicable, with a small infectious dose of < 100 virus particles.9

During the pre-rotavirus vaccine era, rotavirus caused marked winter seasonal peaks of gastroenteritis in the US, usually beginning in the Southwest during November–December and spreading to the Northeast by April–May. However, since the widespread use of rotavirus vaccines, this seasonality has shifted and this trend in rotavirus peak activity is no longer consistently observed.10,11,12,13 (Figure 1)

Repeated infections occur from birth to old age, but natural immunity renders the majority of infections asymptomatic after the first years of life.14 Additionally, no indication of waning vaccine-induced immunity has yet been observed during the rotavirus vaccine post-licensure period.15,16 Children who are immunocompromised sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis.17,8,19,20 Rotavirus also is an important cause of nosocomial gastroenteritis.3,21,22,23,24,25,26 Among US adults, rotavirus infection can cause gastroenteritis primarily in travelers returning from developing countries, persons caring for children with rotavirus gastroenteritis, immunocompromised persons and older adults.27
II. Background

Burden of disease

During the pre-rotavirus vaccine era, four of five children in the US had symptomatic rotavirus gastroenteritis, one in seven required a clinic or emergency department (ED) visit, one in 70 was hospitalized, and one in 200,000 would die from this disease, within the first 5 years of life. The direct and indirect costs of these 410,000 physician visits, 205-272,000 ED visits, and 55-70,000 hospitalizations was estimated to be approximately $1 billion (Figure 2). Relatively few childhood deaths have been attributed to rotavirus in the US (approximately 20–60 deaths per year among children aged <5 years). However, in developing countries, rotavirus gastroenteritis continues to be a major cause of severe childhood morbidity; responsible for approximately half a million deaths per year among children aged <5 years.

Figure 2. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among United States children aged <5 years during the pre-rotavirus vaccine era [Parashar UD, et al. Emerg Inf Dis J 2003; 9:565-71. /and/ Parashar UD, et al. J Infect Dis 1997;177:13–7.]

Virology

Rotaviruses are nonenveloped RNA viruses belonging to the Reoviridae family. The viral nucleocapsid is composed of three concentric shells that enclose 11 segments of double-stranded RNA. The outermost layer contains two structural viral proteins (VP): VP4, the protease-cleaved protein (P protein) and VP7, the glycoprotein (G 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. Because the two gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed. Several animal species (e.g., primates, cows, horses, pigs, sheep) are susceptible to rotavirus infection and suffer from rotavirus diarrhea, but common animal rotavirus serotypes differ from prevalent human strains. Although human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified, animal-to-human transmission of whole virions appears to be uncommon. Most human rotaviruses having some genetic similarity to animal rotaviruses appear formed by reassortment of one or more animal rotavirus genes into a human rotavirus during a mixed infection in vivo.

III. Vaccination

Descriptions and clinical trial results from high and middle income countries:

In 2006, a live, oral, human-bovine reassortant rotavirus vaccine (RotaTeq®, produced by Merck and Company, Whitehouse Station, New Jersey) was recommended by the Advisory Committee on Immunization Practices (ACIP) for routine vaccination of US infants. Three doses of this vaccine are recommended to be administered at ages 2, 4, and 6 months, concurrently with other vaccines given at this age. RotaTeq® contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains that express human outer capsid proteins of five common circulating strains (G1, G2, G3, G4, and P[8] (subgroup P1A)).

RotaTeq® has been tested in two phase III trials, including a large scale clinical trial of more than 70,000 infants enrolled primarily in the US and Finland. The efficacy of 3 doses of RotaTeq® against G1-G4 rotavirus gastroenteritis of any severity was 74% (95% confidence interval [CI] = 67%, 80%) and against severe G1-G4 rotavirus gastroenteritis was 98% (CI = 88%, 100%). RotaTeq® was observed to be effective against each targeted serotype and reduced the incidence of medical office visits by 86% (CI = 74%, 93%), ED visits by 94% (CI = 89%, 97%), and rotavirus gastroenteritis hospitalizations by 96% (CI = 91%, 98%). Efficacy against all gastroenteritis hospitalizations of any etiology was 59% (CI = 52%, 65%) for the period beginning after dose.

Rotarix® (produced by GlaxoSmithKline Biologicals, Rixensart, Belgium), was recommended for routine vaccination of US infants by the ACIP in 2008. This live vaccine contains the attenuated monovalent G1, P[8] human rotavirus strain and is recommended by the manufacturer to be orally administered in 2 doses to infants at ages 2 and 4 months.

Rotarix® efficacy was evaluated in a large clinical trial of more than 63,000 infants from 11 Latin American countries, and was found to be safe and highly immunogenic. During the first year after vaccination, the efficacy of 2 doses of Rotarix® against hospitalization due to severe rotavirus was 85% and 100% against more severe rotavirus gastroenteritis, as defined by the Vesikari 20-point scoring system. After two years of follow-up the vaccine demonstrated 83% (CI=73%, 90%) efficacy in preventing rotavirus-related hospitalizations. Rotarix® was
protective against hospitalizations due to all causes of gastroenteritis (42% protection for the first year, CI=27%, 54%). Rotarix® provided protection against a broad range of rotavirus serotypes during the study’s 2-year period, including against the less common G9, P[8] strain.

In a randomized, double-blind, placebo-controlled study conducted in 6 European countries, Rotarix® was observed to be highly immunogenic. Efficacy of Rotarix® against any grade of severity of rotavirus gastroenteritis through one rotavirus season was 87% (CI= 80%, 92%) and against severe rotavirus gastroenteritis, as defined by a score ≥11 on the Vesikari scale, through one rotavirus season was 96% (CI=90%, 99%). Rotarix® reduced hospitalizations for all cause gastroenteritis regardless of presumed etiology by 75% (CI= 46%, 89%). The efficacy of Rotarix® against severe rotavirus gastroenteritis through two rotavirus seasons was 90% (CI= 85%, 94%), and the efficacy of Rotarix® in reducing hospitalizations through two rotavirus seasons was 96% (CI= 84%, 100%).

No clinical trial has yet compared the efficacy of Rotarix® against that of RotaTeq®, and ACIP offers no vaccine preference. For harmonization of vaccination administration scheduling, the ACIP now recommends that, for both vaccines, the maximum age for dose 1 is 14 weeks and 6 days (previous recommendation: 12 weeks), and the maximum age for the last dose of rotavirus vaccine is 8 months and 0 days (previous recommendation: 32 weeks).

Post-licensure vaccine effectiveness and impact:

Since the introduction of RotaTeq® in 2006, several field studies have been conducted to determine vaccine effectiveness (VE) in the United States. A case-control study in Texas of 3-dose RotaTeq® VE in children age-eligible to receive vaccination during the 2007-08 and 2008-09 rotavirus seasons showed a combined VE of 84% (CI=70%, 92%). VE was highest during the 2007-2008 season (90%, CI=72%, 96%), and, while slightly decreased, remained significant during the 2008-2009 season (78%, CI=47%, 91%). In a further case-control study of children aged 15 days-23 months enrolled at this Texas clinical setting during February-June 2008, even partial immunization with RotaTeq® provided protection against rotavirus disease, with a VE of 69% (CI=13%, 89%) for a single dose, 81% (CI=13%, 96%) for two doses, and 88% (CI=68%, 96%) for a full course of three doses.

RotaTeq® vaccine effectiveness was evaluated in a multi-site study during the first three years following licensure by the New Vaccine Surveillance Network (NVSN), finding 3-dose efficacy against G1-G4 rotavirus hospitalizations and ED to be 94.5% (CI=91%, 97%), with estimated effectiveness of 91% (CI=73%, 97%) using controls with non-rotavirus acute gastroenteritis and 86% (CI=70%, 94%) using acute respiratory infection controls. Vaccine effectiveness estimates were comparable between the first and second years of life, and these estimates were similar across observed rotavirus strains.

Similar estimates of VE have been observed using different methodologies and in other geographic areas of the country. A case-control study of children aged 8 weeks to 3 years was conducted in Connecticut during January 2006-August 2009. The adjusted VE for a complete 3-dose course of RotaTeq® was 96% (CI=29%, 100%) when calculated using hospitalized controls and 99% (CI=78%, 100%) using community controls. Incomplete vaccination was also found to be highly effective at preventing hospitalization due to rotavirus gastroenteritis, with a VE of 93% (CI=41%, 99%) when calculated using hospitalized controls and 94% (CI=23%, 100%) when using community controls.

Multiple studies have shown that the US rotavirus season has shortened and become less pronounced since the introduction of RotaTeq®. The National Respiratory and Enteric Viruses Surveillance System (NREVSS) is a national, passive laboratory surveillance network to which participating laboratories submit weekly reports of the number of rotavirus antigen detection tests performed and the number positive. The median onset of rotavirus season, defined as the first of two consecutive weeks during which the percentage of positive rotavirus tests exceeds 10%, during the pre-vaccine years of 2000-06 occurred in mid-December. During the 2007-08, the onset of rotavirus season did not occur until early March, approximately 11 weeks later than the median for 2000-06. Onset during the 2008-09 season was again delayed and occurred in
January, approximately 6 weeks later. Median season duration during 2000-06 was 26 weeks (range 25-28). However, this was reduced to 14 weeks during 2007-08 and 17 weeks during 2008-09. During all three time periods, the total number of tests performed each year remained similar at approximately 14,000 tests.44,45 (Figure 4)

In another analysis of hospital discharge data from 18 states (accounting for 49% of the US population), acute, all-cause gastroenteritis hospitalization rates for children aged <5 years were calculated from 2000 to 2008. Compared with the median rate for the 2000–2006 rotavirus seasons the rates for 2007 and 2008 were 16% and 45% lower, respectively, reinforcing the finding that RotaTeq® vaccine introduction was associated with a dramatic reduction in hospitalizations for acute gastroenteritis among US children during the 2008 rotavirus season.46

Figure 4: Rotavirus incidence trends from 2001–2010 using passively reported laboratory rotavirus test data from the National Respiratory and Enteric Virus Surveillance System (NREVSS) [Tate JE, Pediatrics 2009; 124:465-71. and Cortese MM. Presented to the US Advisory Committee on Immunization Practices (ACIP), October 2010, Atlanta, Georgia.]

Indirect protective benefits of rotavirus vaccination to unvaccinated individuals were not studied during the clinical trials of either currently licensed rotavirus vaccine. However, NVSN surveillance from 2006 through 2009 empirically indicated that reductions among older, largely unvaccinated children in 2008 likely resulted from indirect protection conferred by younger, vaccinated children within the household and community. Compared with 2006, a significant reduction in rotavirus hospitalization rates (P<0.001) was observed in 2008 among all age groups (87% reduction in 6 to <12 month olds [vaccine coverage=77%], 96% reduction in 12 to <24 months olds [vaccine coverage=46%], and a 92% reduction in 24 to <36 month olds [vaccine coverage=1%], which far exceeded reductions that would be expected based on vaccine coverage and effectiveness estimates. While rotavirus hospitalization rates among age groups eligible for vaccination remained low in 2009, indirect protective benefits from vaccine disappeared and the median age for rotavirus hospitalizations increased.36

Indirect protective benefits from rotavirus vaccination were likely caused by disrupted rotavirus transmission among household and community contacts following the large increase in vaccination coverage in 2008. Although indirect benefits were not observed in 2009, these effects may re-emerge in future years even within specific communities. Several studies have also suggested that the median and mean ages of hospitalized, rotavirus positive children have increased during the post-licensure period.34,35,36
Mathematical modeling of rotavirus trends:
Several recent mathematical modeling analyses have been conducted to better understand the effects of rotavirus vaccination upon disease trends. Using a deterministic, age-structured model in a developed country setting, Atchinson, et al., calculated that short-term age-specific fluctuations in rotavirus incidence and age distributions were consequences of a rotavirus vaccination program in a developed country and were unrelated to waning immunity or falling vaccine coverage. Pitzer et al., calculated that the mean age of severe rotavirus cases would increase with higher vaccine coverage due to delays in primary rotavirus infection, that the spatiotemporal characteristics of rotavirus epidemics are largely related to accumulations of fully susceptible individuals by geographic location, and that the reduction in rotavirus prevalence would be greater than that predicted by the direct effect of vaccination alone. These modeling predictions have matched published empirical observations.

Vaccine safety:
A modestly elevated risk of intussusception (~1-2 cases per 100,000 vaccine recipients) among rotavirus vaccine recipients has been noted in some international settings, a level that would be 5-10 fold lower than the risk observed in 1999 with the Rotashield vaccine (no longer on the market). It is not known whether any association is also present in the United States. US studies so far have found no increase in risk of intussusception after vaccination. However, while the US studies have been powerful enough to exclude a risk of the size observed in 1999 with the earlier generation Rotashield vaccine, they do not yet have the power to exclude the lower risk observed overseas.

IV. Importance of Surveillance
With the introduction of a new rotavirus vaccine into the US childhood immunization program, it is important to conduct surveillance to: 1) monitor the impact of vaccination in reducing the morbidity and mortality from rotavirus disease; 2) evaluate vaccine effectiveness in field use and identify and determine the causes of possible vaccine failure; 3) monitor the possible emergence of rotavirus strains that might escape vaccination; 4) identify population groups that might not be adequately covered by vaccination; and 5) continue to monitor the safety of rotavirus vaccines. Since nearly every child suffers from rotavirus gastroenteritis by age 5 and confirming a diagnosis of rotavirus requires laboratory testing of fecal specimens, identification of every case of rotavirus is not practical or necessary at this stage of the vaccination program. Instead, surveillance efforts should focus on monitoring trends of severe rotavirus disease, such as rotavirus hospitalizations or emergency room visits, at the national level and through more intensive efforts at some sentinel sites. In addition to severe and medically-attended disease surveillance, viral strain surveillance is also important to evaluate whether strain variability is a secular phenomenon or whether it is the result of a potential selection of rotavirus serotypes through vaccine pressures.

V. Disease Reduction Goals
Healthy People 2020 does not state a goal for overall rotavirus disease reduction or target for vaccination coverage at this time.

VI. Case Definitions
Definitive diagnosis of rotavirus gastroenteritis requires laboratory confirmation of infection. Currently, no case definition for rotavirus gastroenteritis is approved by the Council of State and Territorial Epidemiologists (CSTE). Active surveillance being conducted at sentinel sites by CDC defines a confirmed case of rotavirus gastroenteritis as a child with diarrhea (≥3 loose stools in 24 hrs) OR vomiting (≥1 episodes in 24 hrs) and with detection of rotavirus in a fecal specimen by a standard assay (e.g., commercially available enzyme immunoassays).
VII. Laboratory Testing

It is not possible to diagnose rotavirus infection by clinical presentation because the clinical features of rotavirus gastroenteritis do not differ from those of gastroenteritis caused by other pathogens. Confirmation of rotavirus infection by laboratory testing is necessary for reliable rotavirus surveillance and can be useful in clinical settings to avoid inappropriate use of antimicrobial therapy.

Rotavirus is shed in high concentration in the stool of children with gastroenteritis and a fecal specimen is the preferred specimen for diagnosis. The most widely available method for detection of rotavirus antigen in stool is an enzyme immunoassay (EIA) directed at an antigen common to all group A rotaviruses. Several commercial EIA kits are available that are inexpensive, easy to use, rapid, and highly sensitive (approximately 90-100%), making them suitable for rotavirus surveillance and clinical diagnosis. Polyacrylamide gel electrophoresis and silver staining is about as sensitive as EIA but is very labor intensive. Latex agglutination is less sensitive and specific than EIA but is still used in some settings. Other techniques, including electron microscopy, reverse transcription-polymerase chain reaction, nucleic acid hybridization, sequence analysis, and culture are used primarily in research settings.

Rotavirus serotypes can be determined directly from rotavirus positive stool specimens using both EIA and reverse transcriptase polymerase chain reaction (RT-PCR) methods. Monoclonal antibody-based EIA techniques have been invaluable in defining four globally common serotypes (G1-G4) that represent >90% of the circulating strains and make up 4/5 serotypes in the RotaTeq® vaccine. More recently, molecular methods, predominantly multiplexed, semi-nested RT-PCR genotyping and nucleotide sequencing have been developed as a surrogate for serotypes and have become widely used to identify the most common and several uncommon rotavirus G and P genotypes. Nucleotide sequencing has been extensively used to identify uncommon strains and genetic variants that cannot be identified by RT-PCR genotyping and to confirm the results of genotyping methods.

VIII. Reporting

Rotavirus gastroenteritis is not a nationally reportable disease and notification is not required by CDC. Contact the state health department for reporting requirements in your state.

Current national rotavirus surveillance includes the following:

1. **New Vaccine Surveillance Network (NVSN):** Active rotavirus surveillance activities through NVSN commenced in the 2005-2006 rotavirus season with 3 original sites and have continued prospectively with 7 sites in 2011. These participating medical centers are in Tennessee, New York, Ohio, Texas, Kansas, Washington, and California that conduct active, population-based surveillance for rotavirus-associated hospitalizations and emergency room visits among children <5 years of age. Acute gastroenteritis cases are identified and additional epidemiological and clinical information is collected from parental interviews and medical chart reviews. Stool specimens are tested for rotavirus antigen at each study site, and CDC laboratories type all positive specimens. Analyses are conducted to estimate disease burden and to assess rotavirus vaccine effectiveness in field use.

2. **National Respiratory and Enteric Virus Surveillance System (NREVSS) and the National Rotavirus Strain Surveillance System (NRSSS):** NREVSS is a laboratory-based sentinel surveillance system that monitors temporal and geographic patterns associated with the detection of several viruses, including rotavirus. Approximately 90 laboratories located in state and local health departments, universities, and hospitals have participated in the NREVSS since 2001. Participating laboratories report on a weekly basis to the CDC the total number of fecal specimens submitted for rotavirus testing and the number that tested positive for rotavirus. A subset of 10-12 NREVSS laboratories participate in NRSSS. These NRSSS laboratories submit a representative sample of rotavirus-positive fecal specimens to CDC for strain characterization by molecular methods.
3. **Secondary Analysis of National Health Utilization Datasets:** National estimates of the burden of rotavirus disease have been derived primarily through review of passive surveillance data on diarrhea mortality, hospitalizations, and ambulatory visits collected by the National Center for Health Statistics (e.g., National Hospital Discharge Survey, National Ambulatory Care Survey). In this approach, a set of International Classification of Diseases, 9th Volume, Clinical Module (ICD–9–CM) codes have been first used to identify events attributable to acute gastroenteritis. Then, the unique epidemiologic characteristics of rotavirus gastroenteritis (i.e., predilection for children 4-35 months of age, marked winter seasonality) have been used to estimate the proportion of diarrhea events attributable to rotavirus. A rotavirus-specific ICD-9-CM code was introduced in 1992. One validation study found that this code had a high positive predictive value (i.e., coded events were highly likely to be true cases) but had a sensitivity of <50%. Nonetheless, applying a variety of ICD-9-CM codes related to acute gastroenteritis to these large databases and accounting for the seasonal and age-specific distributions of rotavirus incidence, it is possible to deduce large-scale rotavirus disease patterns and impacts using these methods.

IX. **Case Investigation**

Case investigations are usually not warranted, except perhaps during outbreaks or in the case of deaths or other serious manifestations of rotavirus infections. Because diarrheal outbreaks can be caused by many pathogens, a laboratory investigation for the causative agent that includes viral, bacterial and parasitic agents should be considered for gastroenteritis cases seeking medical attention.

X. **Control**

Routine immunization of infants is anticipated to be the most effective public health intervention for population-wide rotavirus infection control. Post-exposure vaccine prophylaxis is not a recommended strategy in response to an outbreak of rotavirus gastroenteritis.

**References**


