Chapter 13: Rotavirus

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I. Disease Description

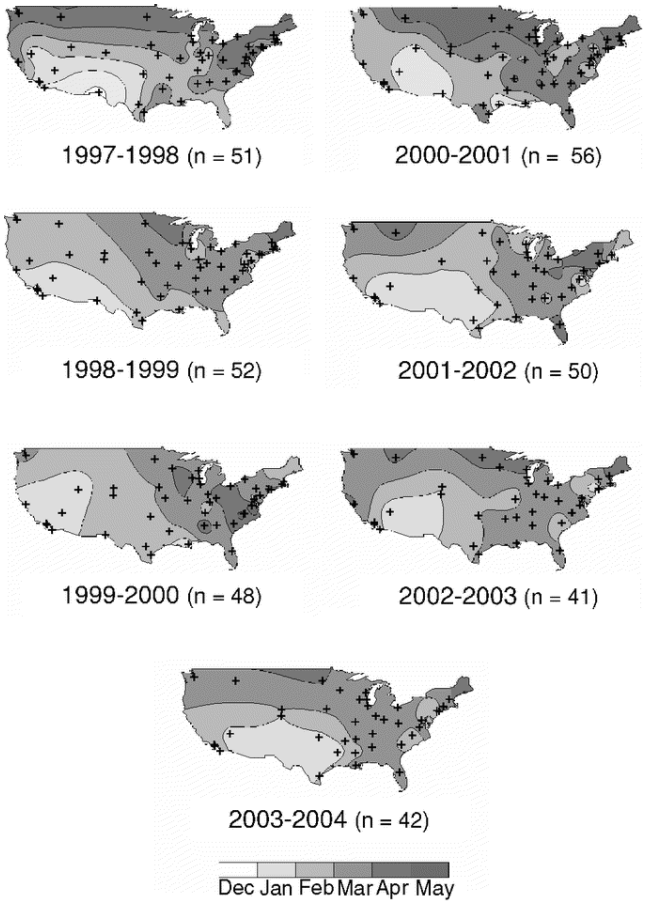
Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Nearly every child in the United States is infected with rotavirus by age 5 years, and the majority will have symptomatic gastroenteritis. The clinical spectrum of rotavirus illness ranges from mild, 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. As many as one-third of patients have a temperature of greater than 102°F (39°C). Severe, dehydrating rotavirus infection occurs primarily among children aged 3–35 months.[1–6]

The risk for rotavirus gastroenteritis and its outcomes does not appear to vary by geographic region.

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 fewer than 100 virus particles.[9]

In the United States, rotavirus causes marked winter seasonal peaks of gastroenteritis. Of note, peak activity usually begins in the Southwest during November–December and spreads to the Northeast by April–May (Figure 1).[10–12] The risk for rotavirus gastroenteritis and its outcomes does not appear to vary by geographic region. Some studies suggest that premature infants and children from disadvantaged socioeconomic backgrounds have an increased risk for hospitalization from gastroenteritis, including rotavirus.[13, 14] At least one study has observed that breastfeeding might have a protective effect against hospitalization for rotavirus patients under 6 months of age.[14] Children who are immunocompromised sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis.[15–18] Repeated infections occur from birth to old age, but natural immunity renders the majority of infections asymptomatic after the first years of life.[19] Rotavirus also is an important cause of nosocomial gastroenteritis.[3, 20–25]

Figure 1. Maps reflecting the peak month of rotavirus activity reported by National Respiratory and Enteric Virus Surveillance System laboratories.[12]



Crosses indicate the location of reporting laboratories whose data were included for analysis each season. The total number of laboratories included for analysis is noted in parentheses.

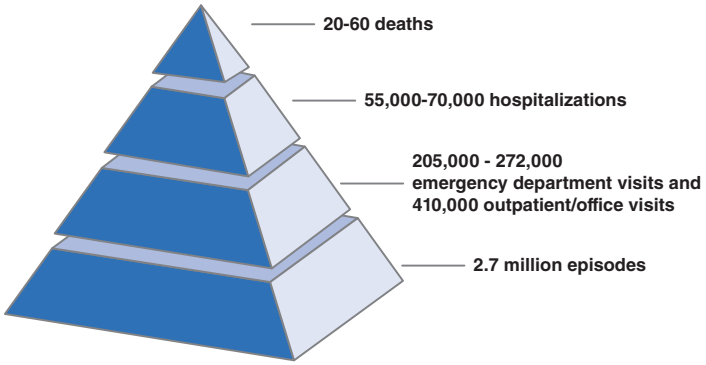
Among U.S. adults, rotavirus infection can cause gastroenteritis, primarily in travelers returning from developing countries, persons caring for children with rotavirus gastroenteritis, immunocompromised persons, and older adults.[26]

II. Background

Burden of disease

In the first 5 years of life, four of five children in the United States will have symptomatic rotavirus gastroenteritis,[4, 27, 28] one in seven will require a clinic or emergency department (ED) visit, one in 70 will be hospitalized, and one in 200,000 will die from this disease.[5, 29] The direct and indirect costs of these 410,000 physician visits, 205,000–272,000 ED visits, and 55,000–70,000 hospitalizations is approximately $1 billion (Figure 2). Relatively few childhood deaths are attributed to rotavirus in the United States (approximately 20–60 deaths per year among children younger than 5 years of age).[30] However, in developing countries, rotavirus gastroenteritis is a major cause of severe childhood morbidity and is responsible for approximately half a million deaths per year among children aged younger than 5 years.[31]

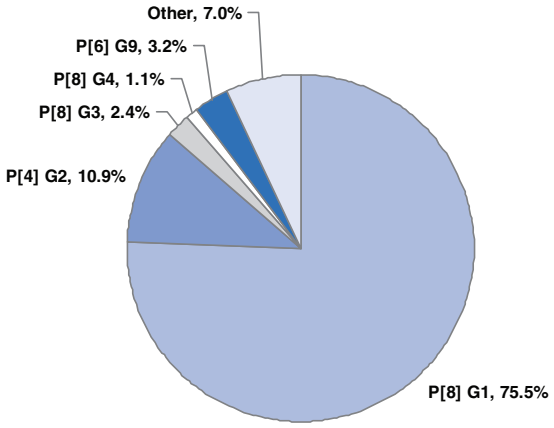
Figure 2. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among United States children aged <5 years. [1]



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. In the United States, viruses containing six distinct P and G combinations are most prevalent: P[8]G1, P[4] G2, P[8] G3, P[8] G4, P[8] G9, and P[6] G9 (Figure 3), although more than 40 rare or regional strains have been identified in the United States and globally.[32] 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 to have been formed by reassortment of one or more animal rotavirus genes into a human rotavirus during a mixed infection in vivo.

Figure 3. Prevalent strains of rotavirus among children aged <5 years in the United States, 1996–1999[33]



III. Vaccination

In 2006, a live, oral, human–bovine reassortant rotavirus vaccine (RotaTeq®, produced by Merck and Company, Whitehouse Station, New Jersey) was licensed in the United States. The Advisory Committee on Immunization Practices has recommended routine vaccination of U.S. infants with three doses of this vaccine administered at ages 2, 4, and 6 months, concurrently with other vaccines given at this age.[1] 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 three phase III trials, including a large-scale clinical trial of more than 70,000 infants. The efficacy of three doses of RotaTeq against rotavirus gastroenteritis of any severity was 74% (95% confidence interval [CI] = 67%–79%) and against severe rotavirus gastroenteritis was 98% (CI = 90%–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 cause was 59% (CI = 56%–65%).[1]

Surveillance efforts should focus on monitoring trends of severe rotavirus disease.

IV. Importance of Surveillance

With the introduction of a new rotavirus vaccine into the U.S. childhood immunization schedule, surveillance is important to 1) monitor the impact of vaccination in reducing 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; and 4) identify population groups that might not be adequately covered by vaccination. Since nearly every child experiences 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 ED visits, at the national level and through more intensive efforts at some sentinel sites. In addition to surveillance of severe and medically attended disease, viral strain surveillance is also essential.

V. Disease Reduction Goals

Because the current rotavirus vaccine was licensed in 2006, *Healthy People 2010* does not state a goal for overall rotavirus disease reduction or target for vaccination coverage at this time.

VI. Case Definition

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

VII. Laboratory Testing

Rotavirus infection cannot be diagnosed 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.[34] Polyacrylamide gel electrophoresis and silver staining is about as sensitive as EIA but is very labor intensive.[35] Latex agglutination is less sensitive than EIA but is still used in some settings.[1] Other techniques, including electron microscopy, reverse transcription polymerase chain reaction (RT-PCR), nucleic acid hybridization, sequence analysis, and culture are used primarily in research settings.

Rotavirus serotypes can be determined directly from rotavirus-positive stool specimens by using both EIA and RT-PCR methods. Monoclonal antibody–based EIA techniques have been invaluable in defining four globally common serotypes (G1–G4) that represent more than 90% of the circulating strains and make up four of the five serotypes in the Rotateq vaccine.[36, 37] 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.[38–41] 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. Persons reporting should contact the state health department for state-specific reporting requirements.

National rotavirus surveillance is currently being done by the following methods:

New Vaccine Surveillance Network (NVSN)

The NVSN consists of three participating medical centers in Tennessee, New York, and Ohio that conduct active, population-based surveillance for rotavirus-associated hospitalizations, ED visits, and outpatient visits among children younger than 3 years of age. Rotavirus surveillance activities through NVSN began in the 2005–2006 rotavirus season. Acute gastroenteritis cases are identified during the rotavirus season, and additional epidemiologic 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. Future efforts will include observational studies to assess rotavirus vaccine effectiveness in field use.

National Respiratory and Enteric Virus Surveillance System (NREVSS) and 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 participate in NREVSS. Participating laboratories submit weekly reports to CDC on 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.

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 Edition, 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 less than 50%.

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 that warrant medical attention.

X. Control

Routine immunization of infants is anticipated to be the most effective public health intervention for population-wide rotavirus infection control.

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

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