# 101 - 209 Viral Gastroenteritis

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virus; (2) the fact that the infection can be transmitted by cell-free or cell-associated virus; (3) the fact that the HIV provirus integrates itself into the genome of the target cell and may remain in a latent form unex posed to the immune system; (4) the likely need for the development of effective mucosal immunity; and, importantly, (5) the difficulty that the immune system has in readily mounting broadly neutralizing antibodies in response to natural infection with HIV (see below). Early attempts to develop a vaccine with the envelope protein gp120 aimed at inducing neutralizing antibodies in humans were unsuccess ful; the elicited antisera failed to neutralize primary isolates of HIV. In this regard, two phase 3 trials were undertaken in the United States and Thailand using soluble gp120, and the vaccines failed to protect human volunteers from HIV infection. In addition, two separate vaccine trials aimed at eliciting CD8+ T cell responses to prevent infection and, if unsuccessful in preventing infection, to control postinfection viremia, also failed at both goals. In 2009, a vaccine using a poxvirus vector prime expressing various viral proteins followed by an envelope protein boost was assessed in a 16,000-person clinical trial (RV144) conducted in Thailand among predominantly low-HIV-prevalence heterosexu als. The vaccine provided the first positive, albeit very modest, signal ever reported in an HIV vaccine trial, showing 31% protection against acquisition of infection. Such a result is certainly not sufficient justifi cation for clinical use of the vaccine; however, it served as an important first step in the direction of the development of a safe and effective vaccine against HIV infection. Follow-up studies of RV144 indicate that nonneutralizing or weakly neutralizing antibody responses against certain constant epitopes in the otherwise highly variable V1–V2 region of the HIV envelope may be associated with the modest degree of protection observed in that clinical trial. Three additional similar studies were undertaken in high-HIV-prevalence countries in sub-Saharan Africa as well as in the Americas and certain European countries in attempts to improve on the results of RV144 by a variety of approaches, including increasing the number of vaccine boosts with envelope protein, the use of mosaic antigens, and the addition of adjuvant. Unfortunately, all three of these phase 3 studies of candidate vaccines failed to show efficacy. Another study was terminated early due to lack of efficacy. An area of HIV vaccine research that is currently being actively pursued is the attempt to induce broadly neutralizing antibodies by developing as immunogens for vaccination certain epitopes on the HIV envelope that are the targets of naturally occurring broadly neutralizing antibodies during HIV infection (Fig. 208-30). It is curious that only about 20% of people with HIV develop broadly neutralizing antibod ies in response to natural infection and they do so only after 2–3 years of ongoing infection. By the time these antibodies appear, they can neutralize a broad

range of primary HIV isolates, but they appear to be ineffective against the autologous virus in the infected subject. Upon close examination, these broadly neutralizing antibodies manifest a high degree of somatic mutations that accumulated over time and are responsible for their affinity maturation and broadly neutralizing capacity. The goal of current efforts is to develop the conformationally correct HIV envelope epitopes that, when used as immunogens, would direct the immune response of an uninfected individual to the produc tion of broadly neutralizing antibodies over a reasonable time frame by sequential immunizations. It remains to be seen whether this approach will be feasible. ■ ■FURTHER READING Bekker LG et al: HIV infection. Nat Rev Dis Primers 9:42, 2023. Beyrer C et al: Is HIV epidemic control by 2030 realistic? Lancet HIV 7:e489, 2024. Centers for Disease Control and Prevention (CDC): Clinical Guidance for PrEP. Available at www.cdc.gov/hivnexus/hcp/prep/. Centers for Disease Control and Prevention (CDC): Clinical Guidance for PEP. Available at www.cdc.gov/hivnexus/hcp/pep/. Centers for Disease Control and Prevention (CDC): Clinical Care of HIV. Available at www.cdc.gov/hivnexus/hcp/clinical-care/. Cohn LB et al: Biology of the HIV-1 latent reservoir and implications for cure strategies. Cell Host Microbe 27:519, 2020.

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.unaids.org/en/resources/documents/2024/global-aids-update-2024. U.S. Department of Health and Human Services Panel on Viral Gastroenteritis Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adoles cents living with HIV. Available at clinicalinfo.hiv.gov/en/guidelines/ hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new. Venter WDF et al: The long wait for long-acting HIV prevention and treatment formulations. Lancet HIV 11:e711, 2024. Section 15 Infections Due to RNA Viruses Umesh D. Parashar, Roger I. Glass

Viral Gastroenteritis Acute infectious gastroenteritis is a common illness that affects persons of all ages worldwide. It is a leading cause of death among children in developing countries, accounting for an estimated 0.5 million deaths each year, and is responsible for up to 6–8% of all hospitalizations among children in industrialized countries, including the United States. Elderly persons, especially those with debilitating health conditions, also are at risk of severe complications and death from acute gastroen teritis. Among healthy young adults, acute gastroenteritis is rarely fatal but incurs substantial medical and social costs, including those of time lost from work. Several enteric viruses have been recognized as important etiologic agents of acute infectious gastroenteritis (Table 209-1, Fig. 209-1).

TABLE 209-1 Viral Causes of Gastroenteritis among Humans VIRUS FAMILY GENOME PRIMARY AGE GROUP AT RISK Group A rotavirus Reoviridae Double-strand segmented RNA Children <5 years

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EIA (commercial), RT-PCR, EM, PAGE Norovirus Caliciviridae Positive-sense single-strand RNA All ages

- ○

RT-PCR, EM, EIA (commercial) Sapovirus Caliciviridae Positive-sense single-strand RNA Children <5 years + RT-PCR, EM Astrovirus Astroviridae Positive-sense single-strand RNA Children <5 years + EIA, RT-PCR, EM Adenovirus (mainly types 40 and 41) Adenoviridae Double-strand DNA Children <5 years +/+ + EIA (commercial), PCR, EM Abbreviations: EIA, enzyme immunoassay; EM, electron microscopy; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction; RT-PCR, reversetranscription PCR. Although most viral gastroenteritis is caused by RNA viruses, the DNA viruses that are occasionally involved (e.g., adenovirus types 40 and 41) are included in this chapter. Illness caused by these viruses is characterized by the acute onset of vomiting and/or diarrhea, which may be accompanied by fever, nausea, abdominal cramps, anorexia, and malaise. As shown in Table 209-2, several features can help dis tinguish gastroenteritis caused by viruses from that caused by bacterial agents. However, the distinction based on clinical and epidemiologic parameters alone is often difficult, and laboratory tests are required to confirm the diagnosis. ■ ■HUMAN CALICIVIRUSES Etiologic Agent The Norwalk virus is the prototype strain of a group of small (27–40 nm), nonenveloped, round, icosahedral viruses with relatively amorphous surface features on visualization by electron microscopy. Molecular cloning and characterization have demonstrated that the viruses have a single, positive-strand RNA genome ~7.5 kb in length and possess a single virion-associated protein—similar to that of typical caliciviruses—with a molecular mass of 60 kDa. On the basis of these molecular characteristics, these viruses are presently classified into two genera belonging to the fam ily Caliciviridae, the noroviruses and the sapoviruses, which are fur ther classified into genogroups and genotypes. Of the 10 recognized norovirus genogroups in humans and animals, 35 different genotypes belonging to 5 genogroups (GI, GII, GIV, GVIII, and GIX) are known to infect humans. PART 5 Infectious Diseases Epidemiology Infections with human caliciviruses are common worldwide, and most adults have antibodies to these viruses. Antibody is acquired at an earlier age in developing countries—a pattern con sistent with the presumed fecal–oral mode of transmission. Infections occur year-round, although, in temperate climates, a distinct increase has been noted in cold-weather months. Noroviruses may be the most common infectious agents of mild gastroenteritis in the community Rotavirus Adenovirus Astrovirus Calicivirus—NV Calicivirus—SV Torovirus Picobirnavirus Enterovirus 22

FIGURE 209-1 Viral agents of gastroenteritis. NV, norovirus; SV, sapovirus.

CLINICAL SEVERITY DETECTION ASSAYS and affect all age groups, whereas sapoviruses primarily cause gastro enteritis in children. Noroviruses also cause traveler’s diarrhea, and outbreaks have occurred among military personnel deployed to various parts of the world. The limited data available indicate that norovirus may be the second most common viral agent (after rotavirus) among young children and the most common agent among older children and adults. In the United States and some other developed countries, with the decline in severe rotavirus disease following implementation of a rotavirus vaccination program, norovirus has become the leading cause of medically attended gastroenteritis in young children. Noroviruses are also recognized as the major cause of epidemics of gastroenteritis worldwide. In the United States, ~50% of all reported outbreaks of gastroenteritis are caused by noroviruses. Norovirus is transmitted predominantly by the fecal–oral route but is also present in vomitus. Because an inoculum with very few viruses can be infectious, transmission can occur by aerosolization, by contact with contaminated fomites, and by person-to-person contact. Viral shedding and infectivity are greatest during the acute illness, but challenge studies with Norwalk virus in volunteers indicate that viral antigen may be shed by asymptomatically infected persons and also by symptomatic persons before the onset of symptoms and for several weeks after the resolution of illness. Viral shedding can be prolonged in immunocompromised individuals. Pathogenesis The exact sites and cellular receptors for attachment of viral particles have not been determined. Data suggest that carbohy drates that are similar to human histo-blood group antigens (HBGA) and are present on the gastroduodenal epithelium of individuals with the secretor phenotype may serve as ligands for the attachment of norovirus. Additional studies must more fully elucidate norovirus– carbohydrate interactions, including strain-specific variations. After the infection of volunteers, reversible lesions are noted in the upper jejunum, with broadening and blunting of the villi, shortening of the microvilli, vacuolization of the lining epithelium, crypt hyperplasia,

TABLE 209-2 Characteristics of Gastroenteritis Caused by Viral and Bacterial Agents FEATURE VIRAL GASTROENTERITIS BACTERIAL GASTROENTERITIS Setting Incidence similar in developing and developed countries More common in settings with poor hygiene and sanitation Infectious dose Low (10–100 viral particles) for most agents High (>105 bacteria) for Escherichia coli, Salmonella, Vibrio; medium (102–105 bacteria) for Campylobacter jejuni; low (10–100 bacteria) for Shigella Seasonality In temperate climates, winter seasonality for most agents; year-round occurrence in tropical areas Incubation period 1–3 days for most agents; can be shorter for norovirus 1–7 days for common agents (e.g., Campylobacter, E. coli, Shigella, Salmonella); a few hours for bacteria producing preformed toxins (e.g., Staphylococcus aureus, Bacillus cereus) Reservoir Primarily humans Depending on bacterial species, human (e.g., Shigella, Salmonella), animal (e.g., Campylobacter, Salmonella, E. coli), and water (e.g., Vibrio) reservoirs exist Fever Common with rotavirus and norovirus; uncommon with other agents Vomiting Prominent and can be the only presenting feature, especially in children Diarrhea Common; nonbloody in almost all cases Prominent and occasionally bloody with agents causing inflammatory diarrhea Duration 1–3 days for norovirus and sapovirus; 2–8 days for other viruses Diagnosis This is often a diagnosis of exclusion in clinical practice. Commercial enzyme immunoassays are available for detection of rotavirus and adenovirus, but identification of other agents is limited to research and public health laboratories. Treatment Supportive therapy to maintain adequate hydration and nutrition should be given. Antibiotics and antimotility agents are contraindicated. and infiltration of the lamina propria

by polymorphonuclear neu trophils and lymphocytes. The lesions persist for at least 4 days after the resolution of symptoms and are associated with malabsorption of carbohydrates and fats and a decreased level of brush-border enzymes. Adenylate cyclase activity is not altered. No histopathologic changes are seen in the stomach or colon, but gastric motor function is delayed, and this alteration is believed to contribute to the nausea and vomiting that are typical of this illness. Clinical Manifestations Gastroenteritis caused by human cali civiruses has a sudden onset following an average incubation period of 24 h (range, 12–72 h). The illness generally lasts 12–60 h and is characterized by one or more of the following symptoms: nausea, vomiting, abdominal cramps, and diarrhea. Vomiting is more preva lent among children, whereas a greater proportion of adults develop diarrhea. Constitutional symptoms are common, including headache, fever, chills, and myalgias. The stools are characteristically loose and watery, without blood, mucus, or leukocytes. White cell counts are generally normal; rarely, leukocytosis with relative lymphopenia may be observed. Death is a rare outcome and usually results from severe dehydration in vulnerable persons (e.g., elderly patients with debilitat ing health conditions). Immunity Approximately 50% of persons challenged with Norwalk virus become ill and acquire short-term immunity against the infecting strain. In early human volunteer studies, immunity to Norwalk virus appeared to correlate inversely with level of antibody; i.e., persons with higher levels of preexisting antibody to Norwalk virus were more sus ceptible to illness on rechallenge. This paradoxical observation was later explained by data indicating that some individuals have a genetic predis position to illness, with specific HBGA phenotypes influencing suscep tibility to norovirus infection. Contemporary data show that functional antibodies that block norovirus binding to HBGAs correlate with protec tive immunity in human volunteer challenge and vaccination studies. Furthermore, initial studies have demonstrated that norovirus grown in vitro in the newly developed human intestinal enteroid (HIE) cell-based system can be neutralized by sera containing blocking antibodies. Diagnosis Cloning and sequencing of the genomes of Norwalk and several other human caliciviruses have allowed the development

More common in summer or rainy months, particularly in developing countries with a high disease burden Common with agents causing inflammatory diarrhea (e.g., Salmonella, Shigella) Common with bacteria producing preformed toxins; less prominent in diarrhea due to other agents 1–2 days for bacteria producing preformed toxins; 2–8 days for most other bacteria Fecal examination for leukocytes and blood is helpful in differential diagnosis. Culture of stool specimens, sometimes on special media, can identify several pathogens. Molecular techniques are useful epidemiologic tools but are not routinely used in most laboratories. Supportive hydration therapy is adequate for most patients. Antibiotics are recommended for patients with dysentery caused by Shigella or diarrhea caused by Vibrio cholerae and for some patients with Clostridium difficile colitis. CHAPTER 209 of assays based on polymerase chain reaction (PCR) for detection of virus in stool and vomitus. PCR-based detection assays for norovirus combined with those for multiple enteric pathogens are commercially available and are increasingly used in clinical settings. Virus-like parti cles (VLPs) produced by expression of capsid proteins in a recombinant baculovirus vector have been used to develop enzyme immunoassays (EIAs) for detection of virus in stool or a serologic response to a spe cific viral antigen. Commercial EIA kits for detection in stool have limited sensitivity and usefulness in clinical practice and are of greatest utility in outbreaks, in which many specimens are tested and only a few need be positive to identify norovirus as the cause. Viral Gastroenteritis TREATMENT Infections with Norwalk and Related Human Caliciviruses The disease is self-limited, and oral rehydration therapy is generally adequate. If severe dehydration develops, IV fluid therapy

is indi cated. No specific antiviral therapy is available. Prevention Epidemic prevention relies on situation-specific mea sures, such as control of contamination of food and water, exclusion of ill food handlers, and reduction of person-to-person spread through good personal hygiene and disinfection of contaminated fomites. The role of immunoprophylaxis is not clear, given the lack of long-term immunity from natural disease, but efforts to develop norovirus vaccines are ongo ing. Vaccines based on VLPs are being tested in human volunteers. In a proof-of-concept trial, the efficacy of a monovalent GI.1 VLP vaccine was 47% among volunteers who received the vaccine intranasally and were then challenged with a homologous strain. In a second trial, noro virus disease severity was reduced in volunteers who received a bivalent G1.1/GII.4 VLP vaccine intramuscularly (with the GII.4 component including a consensus sequence from three different GII.4 strains) and were subsequently challenged with a GII.4 norovirus strain. Data from the first field efficacy study of this bivalent vaccine conducted in ~4700 healthy U.S. Navy recruits given 1 intramuscular injection of the bivalent vaccine were recently reported. While the primary endpoint of

protection against homotypic infection could not be evaluated because only 6 total moderate/severe cases due to GI.1 or GII.4 norovirus strains occurred during the trial, the vaccine efficacy was 61.8% (95.01% con fidence interval, 20.8–81.6%) for moderate/severe norovirus acute gas troenteritis due to any type. These initial data are encouraging; however, key issues to be further studied include the duration of protection and the level of heterotypic protection against antigenically distinct strains, particularly given the continuing and rapid natural evolution leading to the emergence of novel norovirus strains.

■ ■ROTAVIRUS Etiologic Agent Rotaviruses are members of the family Reoviri dae. The viral genome consists of 11 segments of double-strand RNA enclosed in a triple-layered, nonenveloped, icosahedral capsid 75 nm in diameter. Viral protein 6 (VP6), the major structural protein, is the target of commercial immunoassays and determines the group specific ity of rotaviruses. Seven major groups of rotavirus (A through G) exist; human illness is caused primarily by group A and, to a much lesser extent, by groups B and C. Two outer-capsid proteins, VP7 (G-protein) and VP4 (P-protein), determine serotype specificity, induce neutral izing antibodies, and form the basis for binary classification of rota viruses (G and P types). The segmented genome of rotavirus allows genetic reassortment (i.e., exchange of genome segments between viruses) during co-infection—a property that plays a role in viral evolution and that has been utilized in the development of reassortant animal/human rotavirus–based vaccines. Epidemiology Worldwide, nearly all children are infected with rotavirus by 3–5 years of age. Neonatal infections are common but are often asymptomatic or mild, presumably because of protection by maternal antibody or breast milk. Compared with rotavirus disease in industrialized countries, disease in developing countries occurs at a younger age, is less seasonal, is more frequently caused by uncommon or multiple rotavirus strains, and is more often fatal. Moreover, because of suboptimal access to hydration therapy, rotavirus is a leading cause of diarrheal death among children in the developing world, with the PART 5 Infectious Diseases Rates per 100,000 PY: 0 to <10 10 to <50 FIGURE 209-2 Rotavirus mortality rates by country, per 100,000 children <5 years of age. (From JE Tate et al: Global, regional, and national estimates of rotavirus mortality in children <5 years of age, 2000–2013. Clin Infect Dis 62:S96, 2016.)

highest mortality rates among children in sub-Saharan Africa and southern Asia (Fig. 209-2). First infections after 3 months of age are likely to be symptomatic, and the incidence of disease peaks among children 4–23 months of age. Reinfections are common, but the severity of disease decreases with each repeat infection. Therefore, severe rotavirus infections are less common among older children and adults than among younger individuals. Nevertheless, rotavirus can cause illness in parents and caretakers of children with rotavirus diarrhea, immunocompromised persons, travelers, and elderly individuals and should be considered in the differential diagnosis of gastroenteritis among adults. In tropical settings, rotavirus disease occurs year-round, with less pronounced seasonal peaks than in temperate settings, where rotavirus disease occurs predominantly during the cooler fall and winter months. Before the introduction of rotavirus vaccine in the United States, the rotavirus season each year began in the Southwest during the autumn and early winter (October through December) and migrated across the continent, peaking in the Northeast during late winter and spring (March through May). The reasons for this characteristic pattern are not clear but may be correlated with statespecific differences in birth rates, which could influence the rate of accumulation of susceptible infants after each rotavirus season. After the implementation of routine vaccination of U.S. infants against rotavirus in 2006, the characteristic prevaccine geotemporal pattern of U.S. rotavirus was dramatically altered, and these changes were accompanied by substantial declines in rotavirus detections by a national network of sentinel laboratories. During episodes of rotavirus-associated diarrhea, virus is shed in large quantities in stool (107–1012/g). Viral shedding detectable by EIA usually subsides within 1 week but may persist for >30 days in immu nocompromised individuals; it may be detected for longer periods by sensitive molecular assays, such as PCR. The virus is transmitted pre dominantly through the fecal–oral route. Spread through respiratory secretions, person-to-person contact, or contaminated environmental surfaces has been postulated to explain the rapid acquisition of anti body in the first 3 years of life, regardless of sanitary conditions. 50 to <100 ≥100

At least 10 different G serotypes of group A rotavirus have been identified in humans, but only 5 types (G1 through G4 and G9) are common. While human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified, animal-tohuman transmission appears to be uncommon. Group B rotaviruses have been associated with several large epidem ics of severe gastroenteritis among adults in China since 1982 and have also been identified in India. Group C rotaviruses have been associated with a small proportion of pediatric gastroenteritis cases in several countries worldwide. Pathogenesis Rotaviruses infect and ultimately destroy mature enterocytes in the villous epithelium of the proximal small intestine. The loss of absorptive villous epithelium, coupled with the prolifera tion of secretory crypt cells, results in secretory diarrhea. Brush-border enzymes characteristic of differentiated cells are reduced, and this change leads to the accumulation of unmetabolized disaccharides and consequent osmotic diarrhea. Studies in mice indicate that a non structural rotavirus protein, NSP4, functions as an enterotoxin and contributes to secretory diarrhea by altering epithelial cell function and permeability. In addition, rotavirus may evoke fluid secretion through activation of the enteric nervous system in the intestinal wall. Rotavirus antigenemia and viremia are common among children with acute rotavirus infection, although the antigen and RNA levels in serum are substantially lower than those in stool. Clinical Manifestations The clinical spectrum of rotavirus infec tion ranges from subclinical infection to severe gastroenteritis leading to life-threatening dehydration. After an incubation period of 1–3 days, the illness has an abrupt onset, with vomiting frequently preceding the onset of diarrhea. Up to one-third of patients may have a temperature of >39°C. The stools are

characteristically loose and watery and only infrequently contain red or white cells. Gastrointestinal symptoms generally resolve in 3–7 days. Respiratory and neurologic features in children with rotavirus infection have been reported, but causal associations have not been proven. Moreover, rotavirus infection has been associated with a vari ety of other clinical conditions (e.g., sudden infant death syndrome, necrotizing enterocolitis, intussusception, Kawasaki disease, and type 1 diabetes), but no causal relationship has been confirmed with any of these syndromes. Rotavirus does not appear to be a major opportunistic pathogen in children with HIV infection. In severely immunodeficient children, rotavirus can cause protracted diarrhea with prolonged viral excretion and, in rare instances, can disseminate systemically. Persons who are immunosuppressed for bone marrow transplantation also are at risk for severe or even fatal rotavirus disease. Immunity Protection against rotavirus disease is correlated with the presence of virus-specific secretory IgA antibodies in the intestine and, to some extent, the serum. Because virus-specific IgA production at the intestinal surface is short-lived, complete protection against disease is only temporary. However, each infection and subsequent reinfection confers progressively greater immunity; thus, severe disease is most common among young children with first or second infections. Immunologic memory is believed to be important in the attenuation of disease severity upon reinfection. Diagnosis Illness caused by rotavirus is difficult to distinguish clini cally from that caused by other enteric viruses. Because large quantities of virus are shed in feces, the diagnosis can usually be confirmed by a wide variety of commercially available EIAs or by techniques for detect ing viral RNA, such as gel electrophoresis, probe hybridization, or PCR. TREATMENT Rotavirus Infections Rotavirus gastroenteritis can lead to severe dehydration; appropri ate treatment should be instituted early. Standard oral rehydra tion therapy is successful for most children who can take fluids

by mouth, but IV fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting. The therapeutic roles of probiotics, bismuth subsalicylate, enkephalinase inhibitors, and nitazoxanide have been evaluated in clinical studies but are not clearly defined. Antibiotics and antimotility agents should be avoided. In immuno compromised children with chronic symptomatic rotavirus disease, orally administered immunoglobulins or colostrum may result in the resolution of symptoms, but the best choices regarding agents and their doses have not been well studied, and treatment decisions are often empirical.

Prevention Efforts to develop rotavirus vaccines were pursued because it was apparent—given the similar rates in less developed and industrialized nations—that improvements in hygiene and sanitation were unlikely to reduce disease incidence. The first rotavirus vaccine licensed in the United States in 1998 was withdrawn from the market within 1 year because it was linked with a low incidence of intussuscep tion, a form of bowel obstruction. In 2006, promising safety and efficacy (85−98% against severe rota virus disease) data for two new rotavirus vaccines—RotaTeq (Merck, United States) and Rotarix (GlaxoSmithKline, Belgium)—were reported from large clinical trials conducted in North America, Europe, and Latin America. Both vaccines are now recommended for routine immuniza tion of all U.S. infants, and their use has led to a >70–80% decline in rotavirus hospitalizations and emergency department visits at hospitals across the United States. Somewhat unexpectedly, rotavirus vaccination of young infants has also resulted in the added benefit of declines in rotavirus disease among children who miss vaccination and even among older children and adults who are not eligible for vaccination in some settings. The reason is

likely to be a reduction in community transmis sion of rotavirus because of vaccination—i.e., herd protection. In April 2009, the World Health Organization (WHO) recommended the use of rotavirus vaccines in all countries worldwide. As of December 2003, over 120 countries, including several low-income countries in Africa and Asia, have incorporated rotavirus vaccine into their national childhood immunization programs (Fig. 209-3). Large declines in severe morbid ity and mortality from childhood diarrhea have been documented in many countries. Postmarketing surveillance has identified a low risk of intussusception in some high- and middle-income countries; however, the benefits of vaccination exceed the risks, and no changes in vaccine administration policy have been implemented. An intussusception risk has not been identified in several postmarketing evaluations in develop ing countries to date. CHAPTER 209 Viral Gastroenteritis The different epidemiology of rotavirus disease and the greater prevalence of co-infection with other enteric pathogens, of comorbidi ties, and of malnutrition in developing countries may adversely affect the performance of oral rotavirus vaccines, as is the case with oral vaccines against poliomyelitis, cholera, and typhoid in these regions. Therefore, evaluation of the efficacy of rotavirus vaccines in resourcepoor settings of Africa and Asia was specifically recommended, and these trials have now been completed. As anticipated, the efficacy of rotavirus vaccines was moderate (50–65%) in these settings when com pared with that in industrialized countries. Despite modest efficacy, routine use of rotavirus vaccines in low-income African countries with a heavy disease burden has yielded substantial public health benefits. Several manufacturers in emerging markets, including India, China, Vietnam, Indonesia, and Brazil, are developing candidate rotavirus

vaccines. Beginning in 2016, two Indian-made rotavirus vaccines— Rotavac (Bharat Biotech, India) and Rotasiil (Serum Institute, India)— were implemented in India’s routine childhood immunization program, which has since expanded to all Indian states with a birth cohort of

> 25 million. In trials conducted in low-income countries, the efficacy of Rotavac and Rotasiil ranged from 36 to 66%, similar to the efficacy of multinational vaccines in these settings. In 2018, these two vaccines were prequalified by WHO, allowing their procurement with funding support from Gavi, the Vaccine Alliance, in low-income countries outside India.

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