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Review Article

Epidemiology of Rotavirus Infection in Certain Countries

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Abstract

Acute diarrhea with severe dehydration has been a major worldwide cause of death in children younger than 5 years of age. Etiological studies of gastroenteritis have shown that rotavirus causes 40–50% of acute diarrhea among infants and children in both developing and developed *nations*. Numerous epidemiologic studies in the US and the World Health Organization have documented the clinical importance and high prevalence of severe rotavirus disease. The main *aim* of this review is to provide readers a snapshot of epidemiologic and clinical features of rotavirus diarrhea and identify epidemiologic patterns that would specifically define rotavirus disease based on studies done primarily by the CDC and Rotavirus Surveillance Network. *Every year*, rotavirus causes111million episodes of gastroenteritis in three clinical settings (mild cases requiring home care, clinic visit in moderate cases, and hospitalization for severe cases). Regarding high frequency of rotavirus infection among children aged <5 years old, development of rotavirus vaccines and prevention programs will reduce the morbidity of Rotavirus diseases that will require better-quality surveillance of *rotavirus disease burden* among children worldwide.

Keywords: Child mortality, Epidemiology, Gastroenteritis, Morbidity, Rotavirus, Vaccines

Introduction

Rotavirus is the most common cause of severe gastroenteritis and vomiting in children between six and twenty four months old, and there have been a few cases of rotavirus gastroenteritis in adults (1, 2). In 1985, information about diarrheal disease was not available for developed countries, so the Institute of Medicine, concluded that a rotavirus vaccine was not a priority for some countries such as United States. In response to this challenge, researchers began a systematic study of the epidemiology of rotavirus diarrhea, that was based on mortality and hospitalization data that were available. Data also included some from the Rotavirus Surveillance Network (an initial group of 88 North American laboratories) in order to voluntarily report rotavirus detections on a weekly basis to the Centers for Disease Control and Prevention (CDC) (3-7). These studies besides providing greater knowledge about diarrheal hospitalizations and deaths in the United States, also would help describe approaches to evaluate the disease burden of rotavirus in other countries with the probability of different investigation methods to monitor the impact of a vaccine program when was implemented (8). In the other word one of the goals is to be national measures of both morbidity and mortality to estimate the burden of rotavirus diarrhea (9). The highest burden

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has fallen for the developing countries, that account for about 600,000–800,000 deaths per year, that is >85% of deaths occurring in low-income countries of Asia and sub-Saharan Africa among children 5 years old (3, 5, 7, 10, 11). Some differences in the rotavirus epidemiology between tropical developing countries and developed countries in temperate climates could have direct consequences on future plans to administer rotavirus vaccine. First, in tropical countries, rotavirus infection occurs in all seasons, but winter peaks of infection are seen in developed countries. The seasonality could describe the age differences of illness among children 6 to 8 months in developing countries, compared with that among children 14 to 18 months in developed countries (12, 13). In the other countries around the world demonstrated that group A Rotavirus infection is responsible for 13 to 45% of all cases of diarrhea in children less than five years of age, which children between the ages of 6 and 24 months are at greatest risk for developing severe diarrhea (3). Rotavirus surveillance could identify important features in the local epidemiology, which help estimates of the burden of rotavirus diarrhea, create an awareness of rotavirus disease among pediatricians, and provide experience on the most efficient ways to monitor the impact of a rotavirus vaccine (14, 15). In June 2006, the World Health Organization Regional Office for Africa with use of WHO standardized methodology, initiated rotavirus surveillance in selected African countries. Accordingly, children <5 years of age who were hospitalized with severe diarrhea were enrolled, and stool specimens were collected for detection of rotavirus strains by a commercial enzyme immunoassay. The results indicate that rotavirus is a major cause 40% of severe diarrheal disease at 14 sites in 11 African countries. According to the similar study in Vietnam Rotavirus was identified in 56% of the 5768 patients during the period between1998 –2000 (7, 10, 11, 16, 17). Despite the effect of rotavirus infection in children morbidity and mortality worldwide, very little data on illness caused by Rotavirus has been published in Iran (18, 19). However, some studies indicate that 27 to 46% of acute diarrhea in children during the cold season is due to rotavirus infection (8, 16). A number of studies have shown that G1-G4 and G9 Rotavirus types are the most common detected, other uncommon Rotavirus G types, such as G5, G8, G10, G11 and G12 have been reported in many countries (10, 14, 20).

Rotavirus structure

Rotavirus is a 70 nm icosahedral virus that comprise the genus Rotavirus within the family Reoviridae. Mature virus particles possess a triple-layered icosahedral protein capsid. The double stranded RNA genome is enclosed in a triple capsid. In addition to mature virion incomplete rotavirus lacking the outer capsid layer are also present in infected cells in culture as well as in feces of diarrheic children or young animals (21, 22). Although convincing evidences is lacking, it is believed that the incomplete double layer particles are intermediate in the assembly pathway of rotavirus and that they represent the immediate precursor of the triple shelled mature virion. Since the immature double shelled particles are noninfectious (23, 24). It follows that the outer capsid protein must play important biological role. Two such protein VP4 and VP7 have shown to be the viral cell attachment protein, hem agglutinin and type specific antigens (25). It has been shown that divalent cations such as calcium and strontium have stabilizing effect on the integrity and infectivity of rotavirus (26) . If the virus is treated with chelating agent it will result in the detachment of the outer capsid layer and loss of infectivity (27). Therefore, calcium plays an important role in maintaining rotavirus structure. Future experiment showed VP7 was synthesized in presence and absence of calcium but did not assemble in mature viral particles. The virus grown in calcium free medium lacks VP7 as shown by polyacrylamide gel electrophoresis (Fig 1, 2) (23). Using tunicamycine it was also shown that in the absence of calcium glycosylation and the corporation of VP7 in to ER was not affected. But the assembly of the VP7 and VP4 on the virus was inhibited. It

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seemed that calcium played an important role in assembly of VP7-VP4 via NSP4 which resulted in virus budding and maturation through ER. The outer shell of complete rotavirus particle is important in pathogenicity and induction of neutralizing antibody and it is slightly changed in different strains. The Rota viral outer capsid is composed of a protease sensitive protein designated as VP4 and a glycoprotein designated as VP7 (3). The nature of two outer capsid proteins of the virus, VP4 and VP7, elicits the production of neutralizing antibodies to the virus and allows defining the P and G serotypes of the virus (3, 28). The virus genome contains 11 segments of double-stranded RNA (dsRNA). Human rotaviruses are classified into seven serogroups (A-G). Electrophoretic pattern of the genome of the group A viruses is composed of four high-molecular-weight (1 to 4), two middle-sized segments (5 and 6), a distinctive triplet of segments (7 to 9), and two smaller segments (10 and 11) (1, 29). Because various RNA patterns can arise by different mechanisms (shift, drift, rearrangements) analysis of genomic electropherotypes is a relatively easy, rapid for virus detection in order to molecular epidemiology studies (20, 30). Epidemiologic survey revealed the importance of the electrophoretic pattern because in addition to providing evidence for genetic diversity of human rotaviruses as well as heterogeneity of circulating rotaviruses, analysis of electropherotypes has also provided a method for tracing the spread of rotavirus through a population group. Rotaviruses of the same group are capable of genetic reassortment (20, 30, 31).

In recent years, development of molecular techniques such as mAb-based ELISA that

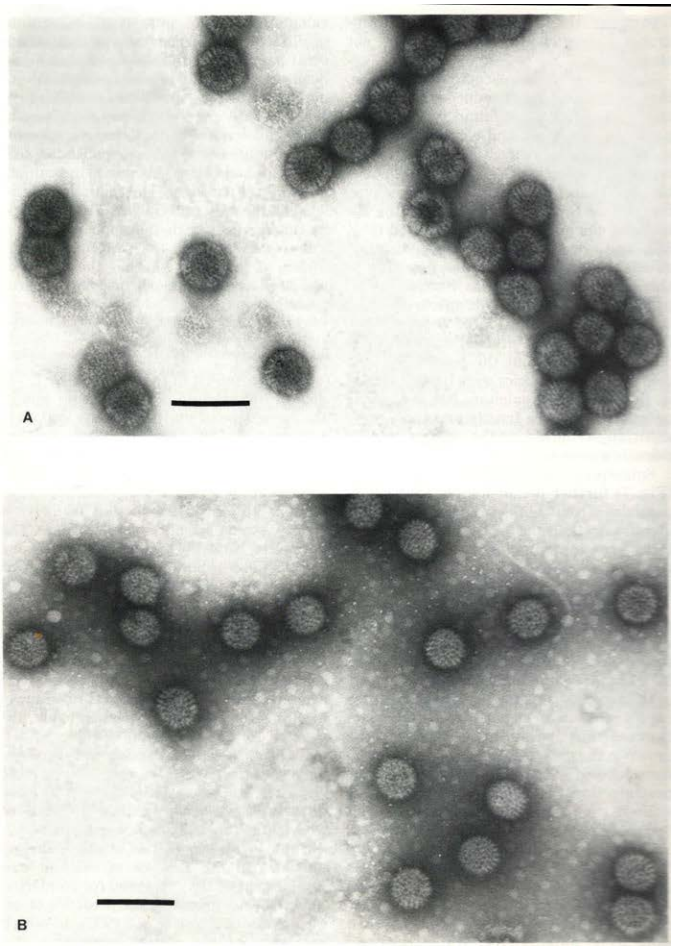

Fig. 1. (A) Electron micrograph of complete double-shelled (L) particles produced in the presence of 1.8 mM $CaCl_2$. (B) Electron micrograph of incomplete single-shelled (D) particles produced in the absence of $CaCl_2$. The bars represent 0.1µm.

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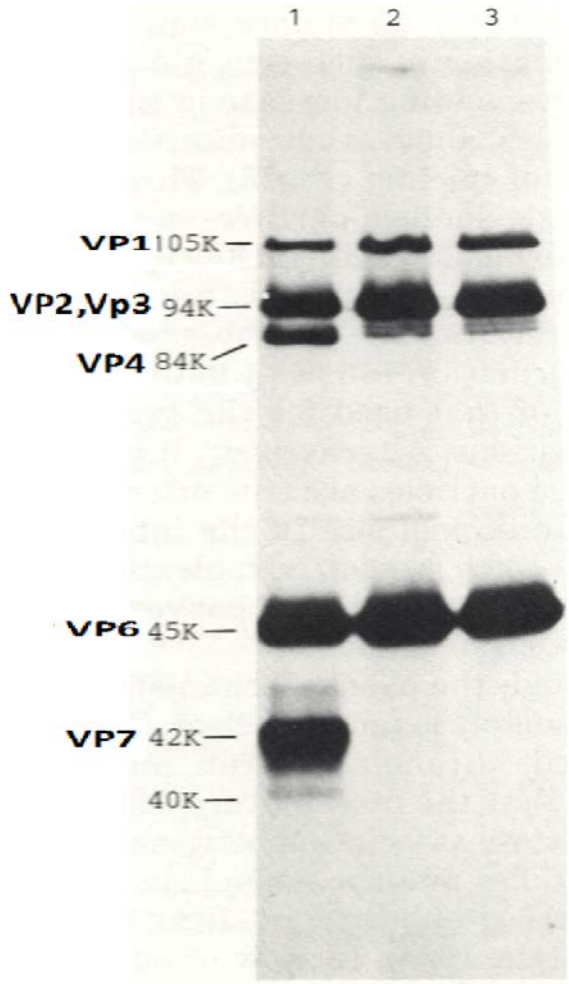

Fig. 2. SDS-polyacrylamide gel electrophoretic analysis of viral particles produced in the presence or absence of calcium. Lanes 1, complete virion grown in presence of calcium showing VP7 and VP4. Lanes 2, incomplete virus particle produced in presence of calcium. Lanes 3 total virus grown in the absence of calcium lacking both VP7 and VP4.

identify the VP7 of most clinical isolate, RT-PCR genotyping and nucleotide sequencing, have extended our information about rotavirus epidemiology (3, 11, 21, 31). The global distribution of rotavirus serotypes has been consistent of G1 strains comprised the most frequently detected serotype and G1 to G4 strains accounted for 97.5% of all rotavirus infections in Asia, North America, and Europe; 83.5% to 90.4% in South America, Africa, and Australia; whereas G9 strains in Australia, Ghana, India, and Brazil and G8 strains in Africa have appeared as important strains (1, 3, 7, 17, 18) .

Burden of rotavirus gastroenteritis

Rotavirus gastroenteritis is sufficiently severe to require hospitalization characteristically occurs most frequently in infants and young children from approximately 6 months to 2 years of age. Adults appear to undergo rotavirus reinfections commonly, but usually with minimal or no clinical manifestations (2, 32). Epidemiologic studies have shown that rotaviruses are the major etiologic agents of diarrheal illness among children in both developed and developing countries. Although rotavirus diarrhea occurs with high frequency in the developed countries mortality is low, but diarrhea-related mortality responsible for half a million deaths per year among children particularly in developing countries (17, 32).

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Studies of hospitalized infants and young children with diarrheal illnesses estimates a total of 223,000 hospitalizations in industrialized countries, results in more than $400 million medical costs and more than $1 billion social costs (33). In developing countries Rotaviruses has been documented as the leading cause of life-threatening diarrhea, that is estimated to be more than a 100 million episodes of diarrhea and 600,000 deaths(17). Hospital-based studies in Asia, Africa, and Latin America show that 25% to 55% of hospitalizations for diarrheal illnesses in children less than 5 years of age are linked to rotavirus infection, with more than 80% of all rotavirus deaths occurring in low income countries of South Asia and sub-Saharan Africa (1, 5, 34, 35). For example, recent estimates indicate that Asian countries have more than 230,000 deaths, African countries approximately 183,000 deaths, and Latin American countries approximately 15,000 deaths. Individual countries with the highest number of deaths include India (>100,000), China (>30,000), and Pakistan (>25000) (5, 35-37). By adding the total prevalence of rotaviral infection in developing and industrialized countries, it was assessed that each year rotavirus causes approximately 111 million episodes of gastroenteritis that require home care only, 25 million clinic visits, and 2 million hospitalizations in children <5 years of age worldwide (1, 2, 11, 15). Based on these age-specific incidence data with the population of children in each age group during the first 5 years of life globally in both developed and developing countries, virtually every child will experience an episode of rotavirus diarrhea, but the consequences of the rotavirus infection are quite different (Table 1) (15, 16, 38).

Geographic and seasonal patterns

Rotaviruses have been detected throughout the world, it was still major etiologic agents of severe infantile diarrhea during the second year. Epidemiological studies have indicated that rotavirus infection has a seasonal pattern with epidemic peaks in the cooler months (39).The winter admission peak was attributed to the increase in total incidence of rotavirus gastroenteritis during this season. A correlation of relative humidity with the temporal pattern of infection has not been observed, however, but the impact of low relative humidity in the home has been suggested as a assisting factor for the survival of rotaviruses on surfaces (3, 39). Rotavirus was more severe in younger children and was more common in boys than in girls, other studies where no differences by gender were found. Other factors related to

Table 1: Total number of patient aged <5 years who were tested for acute gastroenteritis and median detection rate of rotavirus by WHO, 2001-2008

WHO region	No .of countries	Total no. of patent tested (range by country) No		Median detection rate for all countries (range by country) Rate (%)	
		Range		Range	
African	4	4356	(642-1702)	41	(39-52)
Americas	11	26065	(192-6062)	34	(10-51)
European	3	3374	(702-1969)	40	(38-45)
Eastern Mediterranean	9	17291	(316-6553)	40	(29-55)
South-East Asian and Western Pacific	8	11498	(388-2986)	45	(28-59)
Total	35	62584	(192-6553)	40	(10-59)

*This table was reported in the journal Vaccine by Nelson and et all (38).

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host and population with poor living conditions may increase the risk for maintaining virus transmission (13, 17, 40).

Clinical signs and disease development

Rotaviruses are transmitted by the fecal-oral route. There has been theory on the role of animal's source of rotavirus infection. Rotavirus infections produce a range of effects from mild, watery diarrhea for a limited period to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death (32).The illness often begins following an incubation period of 1 to 3 days, and vomiting often precedes the onset of diarrhea. Gastrointestinal symptoms usually resolve in 3–7 days. Up to one-third of patients have a temperature of higher than 39°C. Rotaviruses can produce a chronic symptomatic infection or serious illness in children who are immunodeficient. For example, chronic diarrhea associated with continued shedding of rotavirus was described in children with primary immunodeficiency, T-cell immunodeficiency (12).

Diagnosis and Treatment

The clinical manifestations of rotavirus requires laboratory confirmation for virus or viral antigen detection. Specimens from the first to the fourth day of illness are optimal for virus detection using conventional assays (e.g., EM or ELISA); however, shedding can continue for up to 3 weeks depending on the duration of symptoms, and may be detected by highly sensitive assays (e.g., RT-PCR). Electron microscopy is the gold standard but it is expensive and requires specialized skill personnel. ELISA is also a sensitive reliable test and can be used in most diagnostic laboratories. Latex agglutination is a rapid inexpensive test and usable even in physician's office. RT-PCR is not desirable since it is expensive and very sensitive which can detect even a few particles which may not be the causative agent (41).

The primary aim of treatment of rotaviral gastroenteritis is to replace fluids and electrolytes lost by vomiting and diarrhea. Intravenous fluid administration has been used for many years in treating dehydration from diarrhea. Because facilities for parenteral administration of fluids and electrolytes are not readily available in many parts of the world, intensive efforts have been made to evaluate the efficacy of oral fluid replacement therapy (2, 4, 16, 42).

Rotavirus Vaccines

Rotaviruses as a cause of significant morbidity and mortality among infants and young children cannot be prevented basically, but the burden of rotavirus disease may be able to reduce through the implementation of an effective vaccine and continual surveillance for the detection of rotavirus genotypes circulating in other regions (43, 44). Introduction of new rotavirus vaccines need to epidemiologic data of rotavirus disease. WHO recommended that broad protocols be used and that regional surveillance networks be established to collect these data, thereby helping to fast-track the introduction of these new vaccines into developing countries (14, 15, 45). The Asian Rotavirus Surveillance Network (ARSN) data collection of rotavirus strain diversity commenced in 2004 and included a larger percentage of poorer countries for future rotavirus immunization support. In Asia economic evaluations have demonstrated the potential for new rotavirus vaccines to be cost-effective but more local analyses are required (2, 46, 47). Nine countries participated in the first phase of the ARSN, which collected data during a 2-year period (2001–2003) (38, 47). Overall 45% of hospital admissions were positive for rotavirus diarrhea in the region, which was higher than had been anticipated. The regional surveillance networks includes Ghana, Kenya, Uganda, and Zambia in the African Region; Guyana, Nicaragua, Suriname, St. Vincent and Grenadine, Chile, Venezuela, Paraguay, Bolivia, El Salvador, Honduras, and Guatemala in the Region of the Americas; Georgia, Tajikistan, and Ukraine in the

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European Region; Egypt, Iran, Jordan, Libya, Morocco, Oman, Pakistan, Sudan, and Yemen in the Eastern Mediterranean Region; and China, Hong Kong, Malaysia, Myanmar, South Korea, Taiwan, Thailand, and Vietnam in the South-East Asian and Western Pacific regions(38). Despite the broad data from developed and developing countries, Asia has wrapped the Americas in terms of the introduction of rotavirus vaccines (38, 44). RotaShield a live rotavirus vaccine composed of 3 human-rhesus reassortant rotavirus strains and 1 rhesus rotavirus strain, was introduced in 1998 as a first rotavirus vaccine. This vaccine 9 months after it became available was withdrawn in July 1999, because some infants developed intussusception. Two Newer live attenuated oral rotavirus vaccines, pentavalent, human-bovine reassortant rotavirus vaccine RotaTeq® (RV 5; Merck) and Rotarix® (RV 1; GlaxoSmithKline) with good efficacy and safety profile against severe rotavirus gastroenteritis could significantly impact the burden of this disease (3, 9, 45, 48, 49).

Discussion

Rotavirus is a widespread endemic virus in all areas of the world. This virus is the etiological agent that causes severe diarrhea. Different studies have reported that children with rotavirus diarrhea were more likely to develop dehydration, fever and vomiting or hospitalization than the children with other causes of diarrhea (50). Globally, every year, rotavirus causes an estimated 111 million episodes of diarrhea requiring home care, 25 million clinic visits, 2 million hospitalizations, and 352,000–592,000 deaths in children less than 5 years of age (10, 16, 18). The incidence of rotavirus gastroenteritis was observed to be similar in children in both developed and developing countries. However, developing nations have higher mortality rates, due to many factors, such as, lesser access to hydration therapy and a greater prevalence of malnutrition. An estimated 82% of rotavirus deaths occur in the poorest countries (6). However, several findings demonstrated that the generation of rotavirus vaccines will have highest effect in developing countries. The establishment of regional networks for rotavirus surveillance in sentinel hospitals will facilitate more accurate estimates of the disease and death (16). These data, along with information on illness and costs of infections, will help strategy makers in assessing the degree of the problem of rotavirus for the development of the next generation of rotavirus vaccines (16). The results from studies published from 1986 to 1999 indicated that rotavirus causes 22% diarrhea hospitalizations, this proportion have increased between 2000 and 2004 to 39%. This occurrence likely reflects a slower rate of decrease in rotavirus hospitalizations compared with other causes of childhood diarrhea (8). Due to the diverse nature of rotavirus, the genomic study and continuous surveillance of changes in rotavirus strains are crucial (1). The global burden of rotavirus disease can be reduced significantly if the focus is to improve a vaccine which will not only protect against all types of heterologous strains, but will also be available to the poorest countries with the greatest burden of rotavirus infection (1). In this review the degree of rotavirus infection and its worldwide occurrence was presented in combination with the importance of its control in causing morbidity and mortality among children. Using national data for surveillance and to obtain information, it has been possible to describe trends in rotavirus activity and obtaining better estimates of the burden of rotavirus disease.

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