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Review Article

Rotavirus infection: An unrecognised disease in Nepal

Pun SB

Everest International Clinic and Research Centre, Kathmandu, Nepal

Abstract

Rotavirus is the most common cause of acute infectious gastroenteritis in young children and is associated with substantial morbidity and mortality worldwide, mostly in developing countries. The global rotavirus disease burden has prompted study on their basic research, molecular epidemiology and vaccine development. Little is known about rotavirus infection among health professionals in Nepal. This article summarises basic and clinical features, treatment and prevention, epidemiological pattern, challenges and recommendations of human rotavirus infections in Nepal.

Key words: Rotavirus, Epidemiology, Challenges and Recommendations, Nepal

Diarrhoea remains one of the major causes of illness in children worldwide. It is the second leading cause of death, with, estimated 17% (1.8 million) among children under 5 globally each year (Fig.1)[1]. Among several microorganisms, rotavirus is the single most frequent causative agent for diarrheal episodes among infants and children in the world[2]. It is estimated that each year 702,000 deaths among children under 5 years of age from rotavirus gastroenteritis, mostly in developing countries[3]. Mortality is greatest in sub Sahara, Arica and south Asia, with about 100,000 to 150,000 (1 in 250) children die of rotavirus diarrhoea every year in India alone[4]. Rotavirus virtually infects all children by 3-5 years worldwide. Rotavirus mostly occurs between 6 to 23 months of age. Infants younger than 3 months of age are less likely to develop symptomatic illness, perhaps due to transplacental antibody, breast feeding or age dependent physiology[5,6,7], while children above 5 years of age develop less severe gastroenteritis due to previous exposure that confers greater protection against subsequent disease[8].

In the temperate countries, rotavirus infections occur in children during winter months[9]. Conversely, rotavirus infections occur throughout the year in developing countries, but disease is more commonly observed during cooler and drier months[10].

There is no difference in the rates of rotavirus illness among children between developed and developing countries, indicating that good hygiene and clean water supplies do not prevent the disease[2]. No antiviral therapies are available and treatment of rotavirus diarrhoea remains only fluids and electrolytes replacement. To reduce substantial rotavirus disease burden, safe and effective rotavirus vaccines are urgently needed. Rotavirus vaccines would have significant impact on reducing rotavirus incidence, especially in sub Sahara and south Asia, where the vaccine is in greatest need.

Virus structure and classification

Rotavirus is 70nm icosahedral, non-enveloped virus that belongs to the family *Reoviridae*. The virus is composed of three protein shells, consisting of a core, an inner and an outer capsid which make wheel-shaped structure (from the Latin *rota,* meaning "wheel") (Fig 2). It has a genome of 11 double-stranded RNA segments, which encode six structural viral proteins (VP1-VP4, VP6, VP7) and six non structural viral proteins (NSP1-NSP6)[11]. In infected cells, non structural proteins are produced and are not incorporated into the mature virions, thus known as non structural proteins. Each viral genome codes for a single protein except genome segment 11 that encodes two protein called NSP5 and NSP6. VP1, VP2 and VP3 form the core of the virion and are involved in genome replication and package[11]. The outer most capsid is made up of VP7 and VP4 proteins. They induce virus neutralization antibodies. VP4 is cleaved by an intestinal lumen protease (trypsin) into VP5* and VP8*[11]. This cleavage of VP4 enhances the infectivity of rotavirus. VP6 is the most abundant protein in the virus which forms the inner capsid and used in diagnostic assay for the detection of antigen. Group and subgroup is based on VP6 protein.

Correspondence
Dr. Sher Bahadur Pun
Everest International Clinical and Research Centre
Kathmandu, Nepal
E-mail: drsherbdr@yahoo.com

Seven distinct groups (A-G) of rotaviruses have been described [11]. Group A, B and C rotaviruses have been found in both humans and animals whereas groups D, E, F and G have been found only in animals to date. Group B rotaviruses also called adult diarrhoea rotavirus (ADRV); have been found large outbreaks of severe gastroenteritis in adults primarily in china[12]. Group B rotaviruses have been also reported from India and Bangladesh[13,14]. Group C rotaviruses have been found sporadic cases and outbreaks of diarrhoea in children. Among three human rotaviruses (A, B and C), group A rotaviruses have been established as causing several diarrheal diseases in infants and young children worldwide[11].

Group A rotaviruses are classified into serotypes on the basis of outer capsid proteins VP7 (G serotypes) and VP4 (P serotypes)[11]. The G serotype defined by glycoprotein and the P serotype defined by protease- sensitive protein. On the basis of VP7, 19 different G serotypes have been known so far[15]. P serotypes that are referred to by their numbers (eg.P1, P2), are difficult to characterise by traditional methods of virus neutralisation; therefore, molecular methods based on sequencing are widely used and are indicated by a number in square brackets (eg. P[1], P[2]). Currently 29 P genotypes are known[15]. G and P serotypes have been adopted to define rotavirus serotype. G1, G3 and G4 associated with P [8]; and G2 with P[4] represented over 88% of all rotavirus strains worldwide[16]. G and P antigens segregate independently and interspecies transmission between humans and animals are common[17]. Thus unusual combinations of P and G have been observed over the past several years[18].

Clinical features and diagnostic methods

Rotavirus infection produces in a various severity of gastroenteritis ranging from subclinical to severe life-threatening diarrhoea with dehydration. Rotavirus spreads directly via the faecal-oral route. The incubation period for rotavirus ranges from 1 to 3 days. Vomiting, Fever and dehydration are the major clinical features of rotavirus infection in children. In one study done in Eastern Nepal made a comparison between the clinical manifestations of 62 patients hospitalised with rotavirus diarrhoea and 98 patients hospitalised with non rotavirus diarrhoea[19]. Fever was seen in both groups. However, vomiting and dehydration were seen predominantly in rotavirus positive group than the rotavirus negative group. Thus more rotavirus positive group needed hospitalization as compared to rotavirus negative group. These clinical features attributable to rotavirus diarrhoea in children were comparable to findings in other studies[20]. Symptoms of acute infection can persist for 3 to 8 days. The period may be longer in immune-compromised patients[21].

The clinical features of rotavirus infections are not sufficient to identify rotavirus for diagnosis. Thus diagnosis requires viral antigens or viral nucleic acid detection. Although Electron Microscope (EM) continues to be the important in the diagnosis of rotaviral diseases, other techniques such as Enzyme-linked immunosorbent assay (ELISA), Electropherotyping (using Polyacrylamide Gel Electrophoresis, PAGE) and reverse transcription -polymerase chain reaction (RT-PCR) are widely used to detect and characterize rotavirus strains. Among these methods, ELISA has become the method of choice for screening rotavirus in many laboratories, since it is highly sensitive, provide rapid results and widely available. Electropherotype provides specific information for identifying single strain and strain diversity among circulating rotavirus strain in a given place. Thus it has been used for epidemiological studies worldwide. RT-PCR is used for identifying rotavirus genotype based on nucleotides. This method is useful for serotype-specific genotyping rapidly. PCR product further can be used for sequencing, enabling to detect genetic diversity and unusual strain among rotaviruses.

Treatment and Prevention

Intravenous fluid administration has been used for treating severe rotavirus gastroenteritis. Oral rehydration solutions (ORS) are highly effective in the treatment of dehydration caused by rotavirus. However, ORS does correct some and no dehydration and once severe dehydration is corrected and during maintenance phase. When the patient is severely dehydrated or in shock, intravenous fluids must be given. There are no antiviral agents available for the treatment of rotavirus infection.

Global burden of rotavirus disease has made development of preventive strategies as a priority by World Health Organization[22]. Vaccines were recognized as an effective intervention to prevent severe rotavirus gastroenteritis. Currently two rotavirus vaccines RotaTeq and Rotarix have been licensed in more than 100 countries[23]. The realist goal of these vaccines is to duplicate the degree of protection against diseases following natural infections that provide protection against severe rotavirus gastroenteritis leading to dehydration and hospitalisation or death.

Rotavirus Epidemiology in Nepal

Until recently, few studies were carried out on rotavirus disease in Nepal. Most of these studies were conducted for a short period of time without molecular study. Molecular characterisation of rotavirus gastroenteritis in Nepal was initiated in 2003[24]. Thus molecular knowledge on rotavirus strains in Nepal was not well known.

However, 4-year study on molecular epidemiology between 2003 and 2007 reflect rotavirus strains circulating in Nepal[24,25,26]. The studies have documented huge diversity of rotavirus strains circulating in Nepal. In addition, a significant number of unusual strains were detected among rotavirus strains. G1 and G2 have been identified as the major causes of diarrhoea in humans, whereas G11 and G12 were unusual strains emerging in Nepal.

Studies published on rotavirus infection from 1999 to 2007 showed rotavirus positivity rates ranged from 17 to 39 percent (median 31.8%) in among all hospitalised children less than 5 years[19,24,25,26,27] (Fig.3). Rotavirus infections have been found more than 85% in children by the age of 3 years, whereas 2.6% below 3 months of age group[26]. However, only 55% of rotavirus associated hospitalizations occurred among children in the first year of life. This is in contrast to other findings from low income countries, where ~80% rotavirus associated hospitalization occurred among children during the first year of life[28]. Rotavirus infections have been detected mostly in the low temperature and dry season, peaking in January, whereas lower number in the hot and rainy seasons between June and September in Nepal.

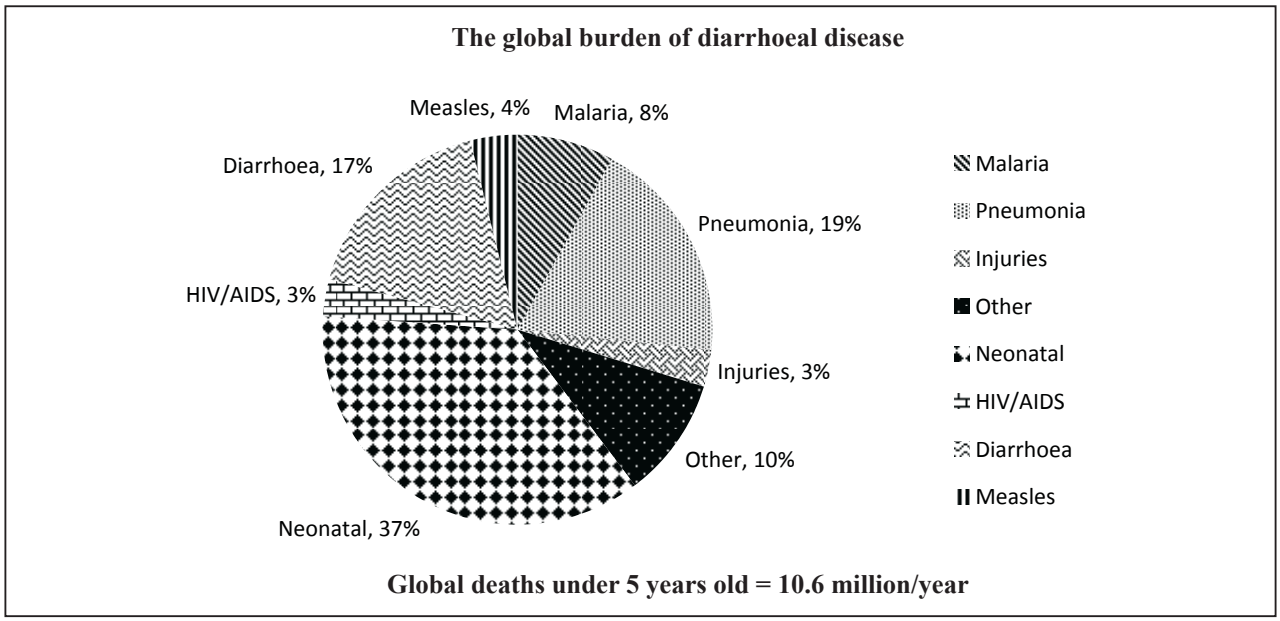

Fig 1: Global deaths of children under 5 years old and 2007

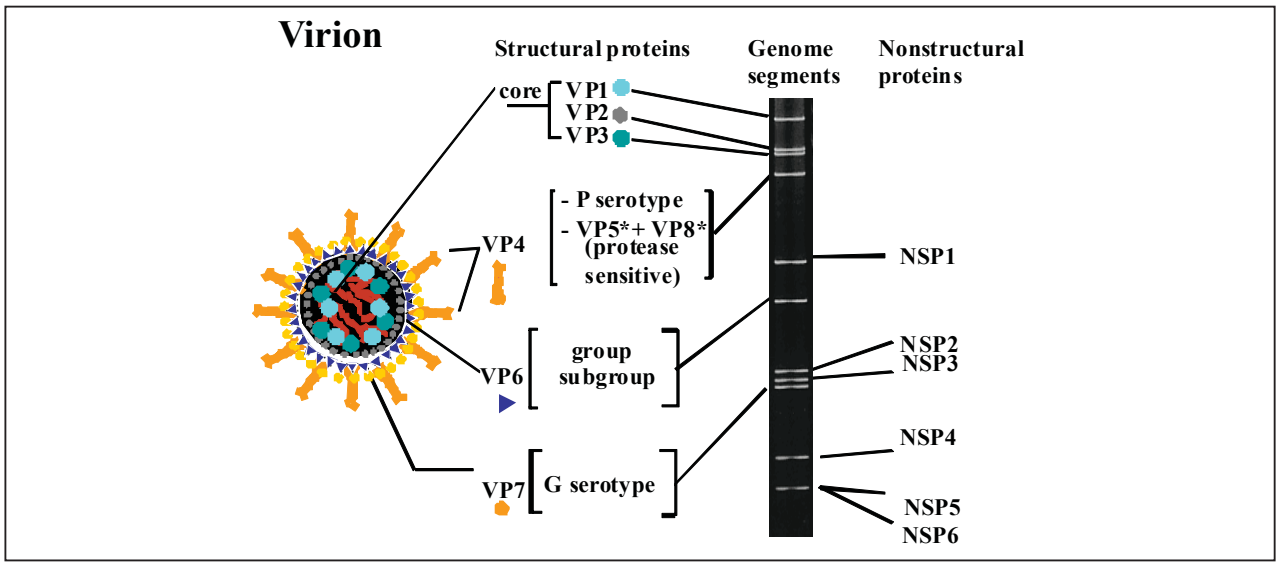

Fig 2: A Schematic diagram showing relationships among proteins (structural and non-structural) and the genomes segments which encodes these viral proteins.

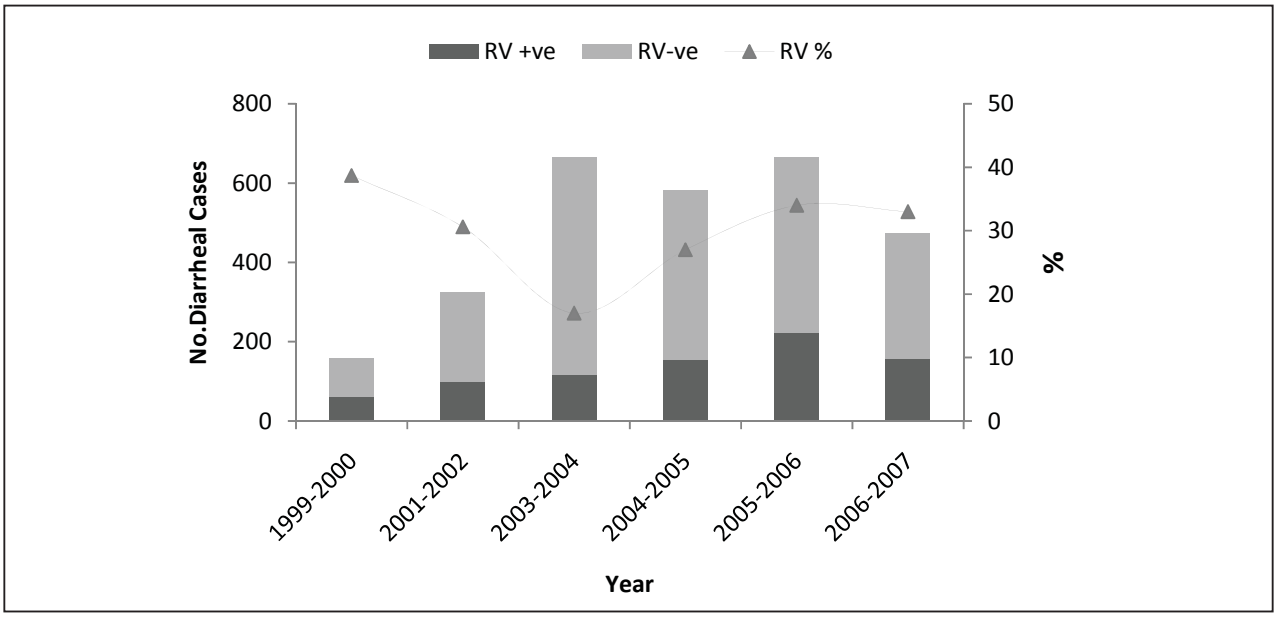

Fig 3: Yearly distribution of Rotavirus (RV) infection among hospitalized diarrhoeal children under 5 in Nepal, between 1999 and 2007

Challenges and Recommendations

Several challenges lie ahead of vaccine introduction in Nepal. Diarrhoeal diseases have long been the major public health problem, with estimated 45,000 annual deaths due to diarrhoea among children less than 5 years of age in Nepal[29]. Although rotavirus infections have been recognised as the leading cause of acute gastroenteritis among young children, only a few studies have been carried out on rotavirus diarrhoea in Nepal. Physicians do not seek rotavirus as the aetiology agent of gastroenteritis, since it does not alter treatment with rehydration therapy. Thus newly available rotavirus vaccines may not receive significant attention it deserves from decision makers and paediatricians due to the absence of knowledge about the local burden of diseases. Nationwide active rotavirus surveillance network, therefore, should be established in order to determine national rotavirus disease burden, especially beyond urban areas, where rotavirus disease burden could be greater and unusual rotavirus strains may be emerging in human populations due to close physical contact with livestock. Unusual rotavirus strains could challenge currently available vaccines, since these vaccines are primarily directed against prevalent rotavirus serotypes and protection against unusual strains have not yet fully determined.

Rotashield, the first licensed rotavirus vaccine, was withdrawal from the market in less than a year in the United States due to its association with intussusceptions among vaccine recipients[30]. Thus to ensure the risk of intussusception from future vaccines would be minimised, the two currently available vaccines (RotaTeq and Rotarix), were evaluated with samples size exceed of 60,000 that showed no association with intussusception[31,32]. However, either of the vaccine has insufficient safety baseline data with respect to intussusception in the least developed countries of sub-Saharan and south Asia, where the disease burden is greatest. Thus anticipating rotavirus vaccines in Nepal, study on intussusception among children would be crucial before and after the vaccination to compare vaccine-associated intussusception among recipients.

The question then arises as to immunogenicity and vaccine efficacy in Nepal. Currently available rotavirus vaccines have shown to be efficacious in clinical trials in the Americas and Europe, but need to be proven in poor resources countries. Although some studies have evaluated vaccine efficacy in low income countries in Africa and Asia[33,34], more studies will be required, where malnutrition, co infections and unusual rotavirus strains are prevalent. Unusual strains such as G12, which was circulating in Nepal between 2003 and 2007[24,25,26], could be a potential challenge to the currently available vaccines.

Financial sources will be the key issue in introducing rotavirus vaccine in Nepal. Although the Global Alliance for Vaccines and Immunizations (GAVI) has pledged for financial support to accelerate the introduction of rotavirus vaccine in developing countries, financial long term support will be needed to ensure a continuous vaccine supply in future.

Concluding Remarks

In 1973 Bishop and colleagues have discovered rotavirus in children with diarrhoea[35]. Since then rotavirus infection has been established as a major cause of gastroenteritis in infants and children worldwide. Rotavirus has been shown to cause 39% (range 29-45%) childhood diarrhoea worldwide[36]. Immune response that develops after primary infection is protective against severe gastroenteritis on subsequent reinfection[8]. On the basis of this simple fact, two live attenuated rotavirus vaccines (RotaTeq and Rotarix) have been developed and are now licensed more than 100 countries[23]. Although there is no significant difference in the incidence of rotavirus infection between developed and developing countries, children in developing countries have higher mortality rates than in developed countries. Thus these life saving rotavirus vaccines are urgently needed in sub Saharan and south Asia, where rotavirus disease burden is greatest.

Limited available data demonstrated that the leading cause of hospitalisation due to gastroenteritis among young children is associated with rotavirus infection in Nepal. According to the Annual Report 2006/2007(Department of Health Services, Nepal), the incidence of diarrhoea has been drastically decreased due to improved sanitation and drinking water. However, winter diarrhoea did not reduce significantly, which could be attributed to rotavirus infection[37]. The time, therefore, has come to estimate accurate rotavirus disease burden, pre-licensure clinical trials and rotavirus vaccine introduction into national immunisation schedules in Nepal. In addition poor health care facilities, insufficient health care professional and difficult geographical terrain are the major obstacles in Nepal to treat severe gastroenteritis patients on time, which often lead to severe dehydration, hospitalisations and/ death. In order to overcome with these hurdles, rotavirus vaccination is only the option likely to have a significant impact in preventing infants and young children from severe rotavirus gastroenteritis, and will be helpful to Nepal government in achieving the Millennium Development Goals (MDG) by reducing child mortality by two-third by the year 2015.

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