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Is Rotavirus Gastroenteritis a Global Emerging/Re-Emerging Problem?

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Introduction

Group A rotaviruses are the most important etiological agents of acute, dehydrating gastroenteritis in infants and young children. The rotavirus gastroenteritis (RVGE), among infants and children <5 years, causes global hospitalization of approximately 2 million cases, and 453,000 deaths [1], representing 37% of all deaths due to diarrheal diseases that constitute one of the top two killers of patients in this age group [2]. According to the WHO [3], the number of reporting countries has grown from 44 (in 2008) to 64 (in 2011), and the median global rotavirus detection rates in stool specimens varied from 36–41% during 2008–2011. Rotavirus causes approximately 111 million episodes of AGE requiring home care, 25 million clinic visits and 2 million hospitalizations in the U.S. and Europe [4]. The rotavirus diarrhea causes an estimated 122,000-153,000 deaths, 457,000-884,000 hospitalizations, and 2 million outpatient visits in children <5 years of age, in India, who spends Rs 2.0-3.4 billion (US$ 41-72 million) annually in medical costs to treat rotavirus diarrhea [5]. The RVGE is though a global problem, it kills a few children in developed countries, where hospitalization and intravenous rehydration facilities are readily available and vaccination is becoming more common [6].

Rotavirus-associated diarrhea occurred year-round but predominantly in winter. Transmission of rotavirus occurs mainly through the fecal-oral route directly from person to person, and the clinical spectrum of rotavirus infection ranges from loose stool to severe diarrhea and vomiting that cause dehydration, electrolyte disturbances, and shock and death without proper management [7]. Increase in diarrhea cases during the cold dry season with severe dehydration, vomiting and fever has been reported [8]. Pandey and Pun observed a remarkable increase in rotavirus-positive cases in between December and February, with a peak in January, demonstrating a marked seasonality of rotavirus [9]. Although, in rainy monsoon and summer season (June to September), detection of rotavirus infection is rare, the incidence in Bangladesh peaked during the monsoon [10]. The group A rotavirus affects individuals in all age groups, but predominantly the infants and young children. Salim et al. [9]. Showed the rotavirus susceptibility less in children aged <3 months, and high in the age group of 6 - 24 months (Figure 1). Fluid replacement with solutions of low osmolarity oral rehydration salts is the effective treatment regimen for RVGE/rotavirus infection.

As determined by the proteins of the viral capsid, rotaviruses have 3 important antigenic characteristics based on group, subgroup and serotype. Based on the antigenic specificity of the VP6 capsid proteins, 7 rotavirus groups (A to G) have been described, of which A, B and C groups infect humans; group A is the prime cause of the acute gastroenteritis in infants and young children. The B and C groups are occasionally associated with human illness. On the basis of VP6 diversity, there are 2 subgroups (I and II) within group A, and the serotypes described include P serotypes (depending on the VP4 protein) and G serotypes (depending on the VP7 protein). In human rotaviruses, 12 different VP7 antigens (G-types) and 15 different VP4 antigen (P-types) have been identified, and currently, 5 G-P combinations (G1P[8], G2P[4], G3P[8], G4P[8]and G9P[8]account for approximately 90% of all human rotavirus infections in the globe; type G1P being the most prevalent one, and the regional and temporal differences in strain genotypes exist [7,8]. The studies conducted by Sharma et al. during 2004-2007, revealed the increased frequency of G12 and G9 strains, while the G1 strain was decreased and the G3 and G4 were rarely isolated [9]. The unusual rotavirus P-G combinations may result from mixed rotavirus infections, and the strain variations have also been known to occur, wherein the rotavirus strain predominance patterns undergo variations [10,11]. Also, together with the re-assortments that occur from animal strains, there could be a wide variability in the rotavirus types that cause infections in children in the globe [12-16].

Different studies reported the emergence of unusual and uncommon G-P combinations (G3P[10] from India and Thailand, G3P[4] and G2P[8] from Japan, G2P[6], G3P[6], G12P[8], G12P[6], G9P[6] from African and South-East Asian regions) contributing rotavirus associated disease burden [17]; some such combinations along with the predominant ones emerged from time to time in different parts of the globe has been represented in (Table 1). The unusual G-P combination G9P[6] and G-mixed type G3/G4 combined with P[8] along with the predominant single G-P combination G1P[8] have been reported from Tunisia [18]. The G9 and G12 (common current prevalent) serotypes were predominant during pre-vaccine introduction years (1996-1998), and there was sudden emergence of G2 and G3 types during post-vaccine introduction years (2006-2008), respectively in Brazil and United States. The G9 in conjunction with P[4] and P[8], was most prevalent, followed by G2P[4]; G1P[8], and G12 combined with P[8]/P[4]/P[6] were emerged in Kolkata, India [19]. The variation of serotypes was observed in China; before the year 2000, G1 was the predominant strain and since the year 2000, G3 has been found as the predominant serotype [20]. Beside, G2P[4] strains were emerged after the introduction of RV1 in states of Australia, and at later sage were replaced by G1P[8], but in states using *RotaTeq* vaccine, G1P[8]was predominant in the early years after its introduction and at the later G2P[4] was increased in prevalence, while in Nicaragua, the prevalent strain was G2P for the first 2 years after *RotaTeq* vaccine introduction, and G1P[8] re-emerged the next year [21]. The G1P[8] associated RVGE outbreak in Australia occurred following the introduction of the homotypic (*Rotarix*: G1P[8]) vaccine [22]. The RVGE is thus a great global concern, and is emerging (spatially) as well as re-emerging (both spatially and temporally) problem too.

For etiological diagnosis of rotavirus gastroenteritis, different tests are available: serological (latex agglutination and strip tests, ELISA) and molecular (RNA-PAGE and RT-PCR); RT-PCR being the highly sensitive one in detecting rotavirus in stool specimens, as well as in

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Geographical region (Year)	G-P Combination		Reference
	Predominant	Unusual	
São Paulo, Brazil, (1996-2003)	G1P[8], G4 P[8], G2 P[4], G3P[8]	G9 P[8], G9P[4], G9P[6], G1P[4], G1P[6], G2P[6], G4P[4]	Carmona et al. [45]
Dhaka, Bangladesh (2001–2005)	G1P[8], G9P[8]	G2[4], G12P[6]	Rahman et al. [10]
Dhaka, Bangladesh (2005–2006)	G2[4], G12P[6]	–	
New Delhi, India (2005–2007)	G1P[8], G1P[4], G1P[6]	G12P[4]	Chakravarti et al. [46]
Salento, Italy (2006–2007)	G2P[8], G1P[8], G2P[4], G9P[8]	G2P[10], G4P[10], G8P[4], G9P[11], G10P[8]	Donno et al. [47]
Matlab, Bangladesh (2006–2012)	G1P[8], G9P[8], G2P[4], G12P[8]	G9P[4]	Afrad et al. [42]
Abidjan, the Republic of Ivory Coast (2007-2009)	G1P[8], G8P[6]	G4P[6]	Akoua-Koffi et al. [48]

Table 1: The predominant and uncommon rotavirus G-P serotypes causing acute gastroenteritis among children in different parts of the globe.

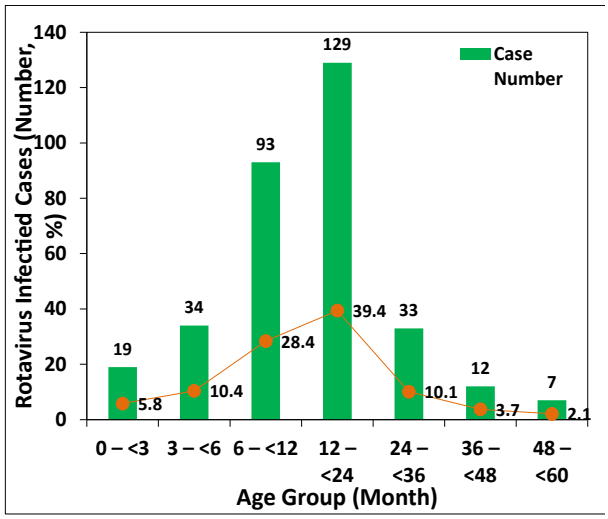

Figure 1: Age distribution of children with rotaviral diarrhea (n=327) in Sanglah Hospital, Denpasar

strain identifying and typing. The pattern of electrophoretic mobility of the 11 dsRNA segments of the viral genome determines rotavirus groups; group A rotavirus shows a characteristic 4-2-3-2 pattern of migration. Two prominent rotavirus electrophore types have been identified: long (L) and short (S) strains, respectively in 78% and 20.3% cases, and only one strain had more than 11 RNA segments, a typical feature of mixed infections [23]; similar to this many studies showed isolates with long RNA electropherotype more than strains with short pattern [24,25]. The migration patterns are classified as 'L' with faster migration of gene segments 10 and 11, and 'S' with slower migration of gene segments 10 and 11. There were 35 'L' electrophoretypes and 15 'S' electrophoretype, as has been observed by Venkatesh et al., among 50 PAGE positive stool samples from children <5 years of age (Karnataka, India) [26]. In a hospital based study, conducted by Ayolabi et al. in Nigeria, 12 different electropherotypes (7 long E-types and 5 short E-types) were found; the predominance of 'L' pattern over 'S' one, irrespective of the zone of the country, was in accordance with findings of many researchers and it seems to be a norm [27]. Different G-types (G1, G2, G3, G4, G9, and G12) have been detected by Ayolabi et al. [27] among the rotavirus having distinct group A rotavirus RNA migration pattern, of which serotypes G1 and G12 showed 'L' lectropherotypic pattern, and G2, G3 and G9 exhibited either 'S' or 'L' electropherotype; the G4 serotype detected had 'S' electropherotypic pattern (Figure 2). Thus, reports from different parts of the world including India have indicated electrotyping as a potential tool for studying the molecular epidemiology of human rotavirus infections [28].

Since specific therapy is not available against RVGE, vaccination has been suggested as a public health strategy in combating rotavirus infection as well as reducing the disease burden. The World Health Organization currently has recommended two live, oral, attenuated rotavirus vaccines: pentavalent *RotaTeq* (RV5; Merck) and monovalent *Rotarix* (RV1; GlaxoSmith-Kline), demonstrating the safety and efficacy in clinical trials. The RV1 and RV5 rotavirus vaccines provide a comparable level of protection against severe infections with homotypic, partly- and fully heterotypic rotavirus strains [28]. A significant decrease in the prevalence of rotavirus in Brazil, mainly in children aged 0 – 36 months, during 2007-2011, as well as a reduction in G1 genotype circulation have been noticed after the vaccine introduction [29]. *Rotarix* demonstrated efficacy against severe GE caused by diverse circulating rotavirus types, including rotaviruses sharing neither G nor P type with the vaccine strain [30]. The occurrence of severe RVGE in the season after the introduction of rotavirus vaccines was found to be reduced compared with that in the season before rotavirus vaccination [31,32]. The studies showed safety and efficacy of the human-bovine 116E rotavirus vaccine (ROTAVAC, Bharat Biotech International, India) against severe RVGE in Indian infants; the vaccine had an efficacy similar to that of the licensed oral rotavirus vaccines- *RotaTeq* and *Rotarix*- when tested in low-income settings [33]. The human-bovine 116E rotavirus vaccine is a monovalent vaccine that contains 116E rotavirus strain, a naturally occurring reassortant G9P with one bovine rotavirus gene P and ten human rotavirus genes [34].

However, an important concern about rotavirus vaccine is its possible association with intussusceptions [35], which is an intestinal invagination causing obstruction, and is characterized by severe abdominal pain, blood in the stools, a palpable lump in the abdomen, and vomiting. Currently, as per the WHO, the risk of intussusception is 1-2 per 100,000 rotavirus immunizations [36]. Thus, both the new vaccines are able to exclude the level of risk associated with the first-generation vaccine *Rotashield*, but are not powered to exclude a lower level of risk [37]. The associated risk of intussusception with *Rotashield* vaccine had been recorded as 1–2 cases for every 10,000 vaccinated children. Moreover, the emerging risk of side effects of rotavirus vaccination with *RotaTeq* and/or *Rotarix* is substantially lower than the number of diarrhea hospitalizations prevented annually. Thus, the benefits are considered to greatly outweigh such risk, and the WHO appropriately has recommended the global use of the RV1 and RV5 in order to involve more children to receive the benefits of the vaccine

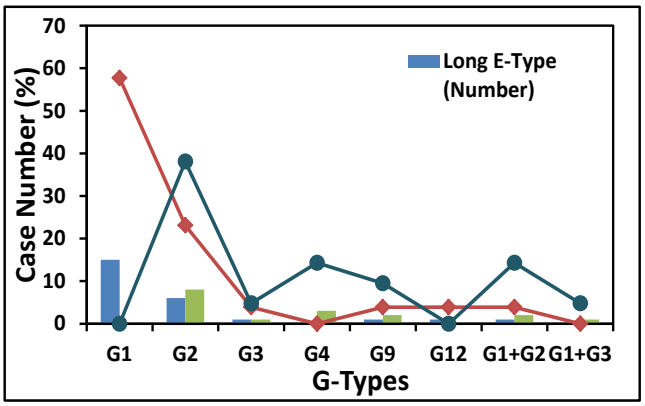

Figure 2: Electropherotypes and G-types of Group A rotaviruses

[38]. Therefore, national level assessment for risk of intussusceptions, potentially attributable to RV1 and RV5, in balance with the benefit of the vaccines in preventing deaths and hospitalization is important [39,40]. Although the RV1 and RV5 cannot entirely exclude the possibility of a low-level risk, the available reports of current scientific studies strengthen the evidence in favor of vaccination for effective control of severe childhood RVGE [41]. Also, appropriate rotavirus genotypes are required to employ for the selection of vaccine strains, development of alternative vaccines, and rotavirus vaccine introduction in national immunization programs in countries, like Bangladesh, where the licensed rotavirus vaccines did not show desirable efficacy [42]. Finally, it is interesting to note that the probiotic *Lactobacillus acidophilus* and *L. rhamnosus* has been found effective in treating rotavirus diarrhea; however, the appropriate bacterial dose should be determined for their safe and effective use [43].

Conclusion

In conclusion, group A rotavirus remain the major etiological agent of acute GE in infants and younger children of <5 years of age in both developing and developed countries of the globe, in spite vaccination, and thus RVGE remains a public health concern. The diversity of rotavirus group A [P] and G genotypes/serotypes (of which some are re-emerged in new areas or in the same areas in later periods of their original emergence, while others include emergence of uncommon and new causing the similar disease burden) [44] underlines the need for continuous characterization of circulating strains of rotaviruses among populations in different epidemiological settings (high-, middle- and low-income countries) to assess and supply strain specific as well as effective vaccine against RVGE in order to reduce the rotavirus associated disease burden, but is an onerous task.

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