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ROTAVIRUS AND THE EMERGENCE OF NEW GENOTYPES: A NARRATIVE REVIEW

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Resumo

A infecção por rotavírus, diretamente relacionada à qualidade de vida da população, pode culminar na morte, principalmente de crianças. Esta revisão discute a prevalência e distribuição de genótipos de rotavírus, com foco na variação genotípica do vírus após a implementação de vacinas e a infecção cruzada entre espécies animais e humanas. Foi pesquisada a literatura publicada de janeiro de 2006 a julho de 2017, utilizando o banco de dados Web of Knowledge e os termos de pesquisa "rotavirus", "genotype", "prevalence post vaccine", e "emerging genotypes". Observou-se que os genótipos predominantes mudaram em todos os continentes e que alguns genótipos ainda estão emergindo. Duas hipóteses para essa mudança global são a variabilidade genética do vírus e o surgimento de genótipos resistentes a vacinas. Além disso, o vírus pode facilmente infectar várias espécies de animais que não o ser humano, como evidenciado por relatos de infecção cruzada de cepas, que serviram de alerta para a geração de novos genótipos de vírus. As ações intersetoriais que abrangem não apenas o setor da saúde, mas também todo o setor socioeconômico, incluindo o governo, pesquisadores, professores, agentes de saúde e comunidades, contribuem para diminuir os gastos relacionados à saúde e reduzir a mortalidade causada pelo rotavírus, melhorando assim indicadores de saúde e promoção da saúde em todo o mundo.

Rotavirus and the emergence of new genotypes: a narrative review

Rotavirus infection, which is directly related to the population's quality of life, can culminate in death, mainly of children. This review discusses the prevalence and distribution of rotavirus genotypes, focusing on the genotypic variation of the virus after vaccines were implemented and cross-infection between animal and human species took place. We conducted a search of the literature from January 2006 to July 2017 by using the Web of Knowledge database and the search terms "rotavirus", "genotype", "prevalence post vaccine", and "emerging genotypes". The predominant genotypes changed in all the continents, and some genotypes are still emerging. There are two hypotheses for this global change: the genetics of the virus is variable, and vaccine-resistant genotypes have emerged. In addition, the virus can easily infect several animal species other than humans, as evidenced by reports of cross-infection of strains, which have served as a warning that new virus genotypes have been generated. Inter-sectoral actions that encompass not only the health sector, but also all the socio-economic sector including the government, researchers, teachers, health agents, and communities have contributed to reduce the health-related costs and mortality due to rotavirus infection, thereby improving health indicators and promoting health worldwide.

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Introduction

Globally, diarrhea is still the second leading cause of death among children aged less than five years (preceded only by respiratory infections). In 2015, diarrhea accounted for approximately 800,000 (~10.5%) global deaths (HUNGERFORD et al., 2016). Rotavirus infection does not occur in economically disadvantaged countries only. Cases of this infection have also been recorded in developed countries despite significant improvements in hygienic conditions and water quality (GRAY, 2011).

Vaccination against the human rotavirus has helped to immunize much of the world population, but prevalence and emergence of new serotypes have been verified over the last decades (Dóró et al., 2014).

In Brazil, the rotavirus vaccine was introduced in 2006, but 2,475 cases were still registered in 2007. Before the vaccine was introduced, the most common rotavirus serotypes were G9P[4] and G1P[8]. In the years 2007, 2008, and 2009, after the vaccine had been implemented, genotype G2 prevailed. Therefore, the introduction of the rotavirus vaccine has clearly contributed to modifying the circulating genotypes, which has also been verified in other countries Dóró et al., 2014.

Rotavirus infection can culminate in death and lead to significant hospitalization, treatment, and prevention expenses. According to Ayres (2002), conditions that affect the frequency of contact between a specific microorganism and the host population are subject to multiple variations related to changes in habits or the environment combined with the production of knowledge in the field of infectious diseases.

In light of the fact that health surveillance should assess the vulnerability of different populations and populations at risk so that the relevant technologies for protection and health promotion can be combined, this review aims to provide a narrative overview of rotavirus infection, focusing on the genotypic variation of the virus after vaccines were implemented. Additionally, we report cross-infection between animal and human species.

The virus

It was in 1973 that the rotavirus was first described as a gastrointestinal agent in humans. This wheel--shaped virus was detected in biopsies of duodenal mucosa obtained from children with acute gastroenteritis (DAVIDSON; BARNES, 1979). Its shape is the reason for its name, rotavirus, derived from the Latin word ‘’route”, which means wheel.

The rotavirus is a double-stranded RNA virus belonging to the *Reoviridae* family. The complete particle consists of a triple-layered capsid protein that involves 11 RNA segments of different sizes, ranging from 667 (segment 11) to 3,302 base pairs (Segment 1), amounting to RNA with 18,680 base pairs (RIXON, TAYLO, DESSELBERGER, 1984). The rotavirus RNA encodes six capsid proteins (VP1–VP4, VP6, and VP7) and six non-structural proteins (NSP1-NSP6), which account for functions that are essential to the replication, pathogenesis, and determination of the specificity of the species (SALGADO; UPADHYAYULA; HARRISON, 2017). The virus also produces particles with double layer protein or just a protein layer (“core”) involving the genome (PRASAD et al., 1988).

Development

Rotavirus classification

The rotavirus was initially classified into six serogroups: Rotavirus A (RVA), Rotavirus B (RVB), Rotavirus C (RVC), Rotavirus D (RVD), Rotavirus E (RVE), and Rotavirus F (RVF), on the basis of virus capsular antigens detected by serological reactions (EESTES; KAPIKIAN, 2007). Groups A–C can be identified in both humans and animals, whereas groups D-F occur exclusively in animals. The rotavirus belonging to Group A causes over 95% of human infections around the world, whereas the rotavirus belonging to Group B underlies large outbreaks of gastroenteritis in children and adults in China. Despite

its worldwide distribution, the rotavirus belonging to Group C has low prevalence Costa et al., 2004.

Antibody neutralization reactions that use antisera obtained from animals previously immunized with proteins VP4 or VP7, located on the outer side of the rotavirus capsid, have also helped to classify the virus into serotypes G, defined by epitopes on glycoprotein VP7, and serotypes P, related to the protease-sensitive protein VP4 (KAPIKIAN, 2007; COSTA et al., 2004). Nine antigenic types of VP7 (protein with greater expression in the external capsid of the virus and with greater capacity to induce the formation of antibodies) have been described, four of which have been detected in humans. Serotypes G are the most frequent in the world, and serotype G1 prevails in Argentina, Brazil, Chile, Costa Rica, Ecuador, Honduras, Mexico, Panama, and Venezuela Dóró et al., 2014.

A classification system based on the analysis of genome nucleotide has also been proposed for RVA. This system assigns a specific genotype for each of the 11 RNA segments of the virus. Comparison of the individual sequences of RNA segments of the rotavirus belonging to Group A to the individual sequences of RNA segments of other viruses has shown that RVA resembles influenza viruses. Substitutions or rearrangements of bases between different RNA segments occur, and many of these mutations take place mainly in segment 11, which codes for two Non-structural proteins, NSP5 and NSP6 (GIAMBIAGI et al., 1994; SCHNEPF et al., 2008). Such mutations often alter the conformation of protein VP6, present in the intermediate capsid, and are the basis for the classification of subgroups I and II. Most importantly, chronic infection in immunodeficient children has been suggested to favor the rearrangement of RVA strains, which allows the virus to replicate for long periods Troupin et al., 2011.

The current rotavirus nomenclature designates each RNA fragment, VP7-VP4-VP6-VP1-VP2-VP3 and NSP1 to NSP5/6, by letters, Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx, where "x" represents the arabic number starting from 1 (CARVALHO-COSTA, 2019).

From 2007 to 2012, identification of the genotypes revealed that 46,967 rotavirus strains belonging to Group A existed in 81 countries. Of this total number of strains, 8,224 were characterized in Africa, 2,341 in the Eastern Mediterranean region, 6,756 in the Americas, 14,438 in Europe, 5,728 in Southeastern Asia, and 9,480 in the Western Pacific region Dóró et al., 2014.

The rotavirus genotype has been reclassified by methodologies based on the sequencing of gene VP6 and metagenomic studies, which has allowed eight rotavirus groups to be designated as distinct species A–H Matthijnssens et al., 2012. Rotavirus A prevails in mammals and birds; Rotavirus B, Rotavirus C, Rotavirus E, and Rotavirus H occur in mammals; Rotavirus D, Rotavirus F, and Rotavirus G emerge in birds only; and Rotavirus I (RVI) has been described in dogs Trojnar et al., 2013.

Survival and transmission

The gastrointestinal tract and feces of infected humans are the reservoir of the rotavirus. The virus primarily replicates in the small intestine, particularly in the jejunum, a process that involves the top cells of the intestinal villi.

The rotavirus can be transmitted by fecal-oral dissemination or through person-to-person contact. About 10 particles of the virus are excreted per gram of feces, and the maximum viral excretion occurs on the third and fourth days since the onset of the first symptoms. During the acute phase of the disease, viral elimination may begin two days before the onset of diarrhea and may persist for 10 days after the onset of the symptoms. If we consider immunodeficient individuals, the virus can be detected for over 30 days after infection (GRAY, 2011; DENNEHY, 2012). Only 10 to 100 viral particles are necessary to infect humans, increasing the potential risk of infection and making epidemics common (GRAY, 2011).

Other sources of the virus such as airway secretions, objects, surfaces, toys, water, and food have been pointed out in most emissions from pre-schools and schools. In addition, because the rotavirus can

survive for weeks or even months on non-disinfected surfaces, it is also an important cause of nosocomial diarrhea (DENNEHY, 2012).

The rotavirus can recognize different cell receptors, but carbohydrates of the cell surface, which are evolutionarily conserved in humans and some animals, are probably the main receptors for the rotavirus (LIU et al., 2016b). Other binding sites including sialic acid (CIARLET et al., 2002), heat shock proteins (Zárate et al., 2003), and integrins (GRAHAM et al., 2003), may allow the virus to penetrate into the host cell. Zoonotic transmission of rotavirus genotypes (Table 1) resulting from intimate contact between humans and animals or from contamination of water or food reservoirs by excreta from infected animals has been reported (DHAMA et al., 2009; MARTELLA et al., 2010; TSUGAWA; HOSHINO, 2008; GUERRA et al., 2016; NGUYEN et al., 2016; MARTON et al., 2017; KOMOTO et al., 2016). This reveals that there are natural sources of viral genomes where mutations and creation of new viral genotypes of unpredictable virulence take place.

Table 1 - Distribution of the rotavirus genotypes identified in human or animal infections.

Rotavirus Genotype	Source	Detected in infection of	Reference
G3	Feline, canine, swine and equine	Humans	Dhama et al., 2009; Martella et al, 2010
G3P[3] (Ro1845 and HCR 3A)	Canine or feline	Humans	Tsugawa and Hoshino, 2008
G3P[8]	Equine	Humans	Guerra et al., 2016
G3P[9]	Feline	Humans	Nguyen et al., 2016
G4, G5, G6 e G8	Swine	Humans, calves and camels.	Dhama et al., 2009; Martella et al., 2010
G5	Swine and equine	Humans	Dhama et al., 2009; Martella et al., 2010
G6, G8, and G10	Bovine	Humans	Dhama et al., 2009; Martella et al., 2010
G8P[14]	Bovine or ovine	Humans	Marton et al., 2017
G9	Swine and lambs	Humans	Dhama et al., 2009; Martella et al., 2010
NSP2	Bovine	Humans	Komoto et al., 2016

Source: Prepared by the authors.

Clinical manifestations and physiopathology of the disease

Rotavirus infection usually begins with low-grade, acute fever and vomiting. After 24 to 48 hours, watery diarrhea (10 to 20 evacuations/day) starts, and symptoms may persist from three to eight days. Dehydration and electrolyte disturbances are the main and most frequent sequelae of rotavirus infection (DENNEHY, 2012).

The rotavirus represents the main etiological agent of severe gastroenteritis among infants and children aged less than five years worldwide. The aggravating effects of the disease have been related to complications such as necrotizing enterocolitis, intussusception, and biliary atresia, which contribute to episodes of prolonged diarrhea and intolerance to carbohydrates and lactose in some children. Other systemic infections, viremias, and even aggravation of autoimmune diseases can happen in patients infected with the virus (DENNEHY, 2012).

When humans ingest food and water contaminated with the virus, protein VP4 on the external surface of the rotavirus is fractionated by the enzymes pancreatin, trypsin, or elastase into two smaller proteins (VP5 and VP8). Subsequently, the virus adheres to and infects enterocytes, destroying enzymes like maltase, sucrose, and lactase. This destruction prevents disaccharides from breaking and being absorbed, thereby increasing the osmolarity of the intestinal lumen and raising the influx of liquid (LIU et al., 2016b). Furthermore, intestinal bacteria may act on unabsorbed sugar, which results in elimination of feces with acid pH and may accentuate the diarrhea of osmotic nature. The viral enterotoxin (protein NSP4, which resembles the cholera toxin) also decreases the activity of Na/K ATPase, which underlies the intestinal absorption of sodium coupled to glucose, reducing the absorption of sodium and water. Activation of the enteric nervous system by infection can also induce diarrhea, to culminate in secretion of intestinal fluid, electrolyte liquid, and thus diarrhea (LUNDGREN, 2000; BALL et al., 1996).

Epidemiology

Almost all children aged five years are estimated to have had an episode of rotavirus gastroenteritis. This virus accounts for about 5% of infant mortality per year worldwide. About two million admissions and over 500,000 thousand deaths are attributed to this virus every year (GRAY, 2011).

Liu et al. (2016a) reported that children's first exposure to a rotavirus infection during the first six months of life often results in severe illness that requires hospitalization. Interestingly, the number of hospitalizations decreases among infants aged less than three months probably because they receive passive maternal antibodies through breastfeeding.

Rotavirus infection involving older children and adults was related to outbreaks or to population groups that are at risk of contracting the infection such as travelers to endemic areas, individuals working in enclosed spaces like day care centers and hospitals, individuals who may be in contact with sick children, the elderly, and immunocompromised patients. Between 30 and 50% of the adults that come into contact with infected infants become infected, as well (Ford-Jones et al., 2000). However, the disease is asymptomatic in most of these adults because they present neutralizing antibodies previously acquired during natural primary and/or secondary infections (LUCHS; TIMENETSKY, 2016).

The seasonality of rotavirus outbreaks is more evident in countries with temperate climate and is less visible in countries with tropical climates. Patel et al. (2013) reported that the level of development of a country influences the intensity of the disease more than season, latitude, or geographical location. In African, Asian, and South American countries, where seasonal variation is smaller, incidence of the rotavirus is high as compared to more developed countries in Europe, North America, and Oceania.

In the United States, the rotavirus is estimated to cause 20 to 60 deaths, 55,000 to 70,000 hospitalizations, 205,000 to 272,000 visits to emergency units, and 410,000 outpatient consultations annually, with total expenditures estimated at one billion dollars (Fischer et al., 2007). Fischer et al. (2007) reported that American children infected with the virus develop episodes of gastroenteritis, which often leads parents to skip work to provide care for their sick children. In Brazil, the rotavirus was first recorded in 1976, when the virus was the main cause of severe diarrhea in children aged less than five years. If we consider the average positivity indexes by region, the northern region stood out with an index of 36.5% up to the year 2000 (LINHARES; BRESEE, 2000). By 2006, about 2,500 children under the age of five had died each year (MASUKAWA et al., 2014).

In recent years, the rotavirus disease has developed differently across continents. Steele et al. (2016) reported that the incidence of the rotavirus in unvaccinated children aged between two and six months is approximately twice as high in Africa as compared to Europe; an opposite trend emerges during the second year of life. According to these authors, the natural immunity rate to the wild-type infection acquired at

a younger age is higher in unvaccinated children from low- to middle-income nations as compared to children living in high-income countries.

In the United Kingdom, the rotavirus accounts for 45% of hospitalizations for acute gastroenteritis and for 20% of emergency care (HUNGERFORD et al., 2016). In China, the total annual expenditure on the treatment of cases of rotavirus gastroenteritis is USD 365 million, with the virus underlying 18.4–54.0% of cases of acute diarrhea in children aged less than five years (LIU et al., 2016a).

Prevention of infection and post-vaccine impact

Before the rotavirus vaccine was introduced, rotavirus infection was primarily treated with oral rehydration and adequate feeding of liquids; the adjuvant action of selected probiotics has also been reported. Additionally, frequent hand hygiene has been described as one of the most important procedures to minimize transmission of the rotavirus (DENNEHY, 2012). However, disinfectants such as chlorhexidine are ineffective against the virus, and soap and water do not remove all the viral load; in contrast, agents containing alcohol are more effective against the virus.

Vaccination is undoubtedly the major strategy to control rotavirus infection. The vaccine consists mainly of attenuated viral particles whose oral administration stimulates the individual's immune system against the virus. The first human rotavirus vaccine (RotaShield, RRV-TV) was licensed in 1998. It was a tetravalent vaccine that contained four strains of the virus represented by the most commonly disseminated types G. Although the efficacy of the vaccine was between 80 and 100%, it was discontinued 14 months after its introduction because cases of intussusception associated with vaccination were reported (world rate of 1–10,000) (CENTERS FOR DISEASE CONTROL AND PREVENTION, 1999).

Subsequently, other vaccines were licensed and are currently in the market; e.g., RV5 (RotaTeq®), a live oral vaccine manufactured by Merck (three doses, at two, four, and six months of age) that was licensed in 2006; RV1 (Rotarix®), a live oral vaccine manufactured by Glaxo Smith Kline (two doses, at two and four months of age) that was licensed in 2008; and RIX4414 (RV1), licensed in 2006, which consists of attenuated virus of strain G1P, which is the most common in humans (DENNEHY, 2012).

The worrying data about the rotavirus have led the WHO to coordinate the Rotavirus Global Surveillance Network since 2008. The Network advocates that rotavirus be tested in infants and children aged less than five years that are hospitalized for acute gastroenteritis. One of the original objectives of the Network was to provide data to describe the epidemiology of the disease, to establish a platform to measure the impact of vaccination, and to identify viral strains and their distribution (WHO, 2010).

Among the regions assessed by the WHO in 2009, the Americas had the lowest rate of rotavirus detection: 25%. In Brazil, immunization with the oral rotavirus vaccine, was licensed in 2005 and introduced into the national immunization program in 2006, under the trade name Rotarix®. In 2008, immunization in children reached a rate of 82% and has increased ever since. From its implementation in 2006 until 2011, the vaccine prevented 1,804 deaths, 91,127 hospitalizations, and 550,198 outpatient visits each year, which reduced the general health costs related to rotavirus gastroenteritis by 76% (AMBROSINI; CARRARO, 2012; CARVALHO-COSTA et al., 2019).

By 2012, rotavirus vaccines had been licensed in 125 countries and had been included in the National Immunization Program of 29 (15%) out of 193 countries worldwide, mostly in Latin America (50%). However, by 2012 no low-income country had been included in the immunization program even though these countries represented a large proportion of cases of high-severity diseases caused by the rotavirus (DENNEHY, 2012). Fortunately, other 60 countries introduced either RV1 (monovalent vaccine) or RV5 (pentavalent vaccine) in their child immunization programs in May 2014 (DÓRÓ et al., 2014).

One of the first African countries to introduce the rotavirus vaccine in its national immunization

program was Malawi in 2012, which lowered hospitalization costs related to the virus-infected population by 43% (NAKAGOMI et al., 2013). In other African countries, such as the Democratic Republic of Congo, Ethiopia, and Nigeria, vaccines have prevented from 28 to 31% of rotavirus-associated deaths (KOLLARITSCH et al., 2015).

In the US, Kaufman and Chen (2016) suggested that vaccination effectively diminished rotavirus infections among infants and children by reducing the rate of rotavirus positivity in the post-vaccine period by 73.3%.

Studies in Panama, Brazil, and Mexico reported a reduction of between 22 and 50% in deaths caused by diarrhea and estimated that the vaccine (RV1) prevents 1,800 deaths in Mexico and Brazil and nearly 27,000 deaths in India per year. Concerning the European continent, the rate of hospitalization due to the rotavirus decreased by 60% in Germany. In Belgium, where vaccination coverage is high, vaccination is 90% effective. In Austria, one of the first countries to implement vaccination in 2007, hospitalization due to rotavirus infection decreased by 70% as compared to the pre-vaccination period (2001-2006) (WHO, 2010).

Overall, 85–98% of the different rotavirus vaccines available worldwide are effective: hospitalization, medical visits, mortality from acute gastroenteritis, and the number of positive laboratory results have decreased (WHO, 2010; GRAY, 2011; HUNGERFORD et al, 2016). Nevertheless, implementation of the vaccines has led to replacement of existing serotypes, so rotavirus infection still prevails in many countries despite the efficacy of rotavirus vaccines.

In Latin America (Table 2), serotype G2 has emerged after vaccination (LINHARES et al., 2011), but other genotypes also circulate in Latin American countries. In Argentina, strain G12P[8] emerged in 2008, and strain G2P[4] re-emerged and became predominant again in 2011 (MANDILE et al., 2014). In Brazil (Table 2), introduction of the vaccine elicited replacement of genotypes G1P[8] and G9P[8] with genotype G2P[4] in several regions of the country (Carvalho-Costa et al., 2019). In the years 2012, 2013, and 2014, genotypes G3P[8] and G12P[8] reappeared throughout the country (AMBROSINI; CARRARO, 2012; Dóró et al., 2014). In 2008, G9P[8] was the predominant rotavirus genotype in Cuba, Chile, and Bolivia (RIBAS et al., 2011; DÓRÓ et al., 2014). However, in Colombia and Paraguay, infections caused by genotype G2P[4] increased from 2008 to 2011 (MARTÍNEZ et al., 2010; PELÁEZ-CARVAJAL et al., 2014). Vizzi et al. (2017) reported that genotype G1P[8] re-emerged after the vaccine was introduced in Venezuela and, together with genotype G2P[4], caused most of rotavirus infection in the country.

In North America, strains G1, G2, G3, G4, and G9 were commonly identified after the vaccine was implemented (MAST et al., 2010). In the United States, the most prevalent serotype was G3 a few years ago; G3P[9] was the most common line, and G12 and G14 were possibly emerging strains (DÓRÓ et al., 2014). The predominant genotype has now changed: the genotype with the highest prevalence is G12 (Bowen, 2014; Wylie, Weinstock and Storch, 2015). In Canada, genotypes G1P[8], G3P[6], G3P[8], G2P[4], G9P[8], G4P[8], and G9P[4] have been reported (CHETRIT et al., 2013).

The African continent has the highest rates of the rotavirus, which is understandable if we remember that the conditions in which the population lives, including health services and sanitation, among others, determines the occurrence of diseases with preventable causes. Between 2006 and 2016, types G (G1, G2, G3, G9, and G12) were the most common in Africa; G1 prevailed. Among types P, P[8] predominated especially in North Africa, followed by P[6] and P[4]. The combination G1P[8] was the most found, but G2P[4], G9P[8], and G2P[6] was also reported (OUERMI et al., 2017).

G12 is an emerging genotype in Cameroon, but a different sub-lineage predominates there (Table 2) (DÓRÓ et al., 2014). G1P[8] prevails in Ghana (DÓRÓ et al., 2014), but Agbemabiese et al. (2016) pointed out the evolution of G2P[4] in the country. In Malawi, G12, sub-lineage G12P[6], has increased

progressively (Nakagomi et al., 2017). According to Motayo et al. (2016), G1, G8, and G9 are the common strains in Nigeria. Apart from genotype G1P[8], other strains also circulate in Kenya, where the dominant lineage is G9P[8] (DÓRÓ et al., 2014). Genotype G1P[8] is the most frequent in Tunisia, but G3P[8] also circulates in this country (DÓRÓ et al., 2014; MOUSSA et al., 2016).

In Asian countries (Table 2), the predominant strains are G1, G2, G3, and G9. In China, strain G1, and no longer G3, prevailed in 2011 (DÓRÓ et al., 2014). Zhang et al. (2017) reported that strains G1 and G2 nowadays circulate and predominate along with strain G9. According to Asada et al. (2016), in Japan strain G3 prevailed from when the vaccine was implemented until 2015 (DÓRÓ et al., 2014; FUJII et al., 2019), but strains G1 and G2 are currently prevalent. In South Korea, the predominant strains are also G1 and G2 (CHUNG et al., 2015). In Thailand (DÓRÓ et al., 2014), the prevalent genotype is G1P[8] followed by G2P[4] and G3P[8]. Do et al. (2017) reported that strain G1 also prevails in Vietnam, where sub-lineage G1P[8] stands out (Table 2).

In the case of European/Eurasian countries (Table 2), G9P[8], G2P[4], G1P[8], and G4P[8] prevailed. In Austria, genotype G2P prevailed after the vaccine was implemented in 2007, but serotype G2P[4] emerged in 2011 (DÓRÓ et al., 2014). Furthermore, infection by genotype G2P[4] occurred in Belgium even after vaccine RV1 was implemented (PITZER et al., 2015). Genotypes G4P[8] and G1P[8] predominate in Greece, whereas genotype G9P[8] predominated in 2012 in Hungary (DÓRÓ et al., 2014; KOUKOU et al., 2015).

In India, genotype G1P[8] followed by genotype G9P[8] prevailed a few years ago (BABJI et al., 2018; GUPTA et al., 2019), but Chitambar et al. (2014) reported the emergence of G9P[4]. Pradhan et al. (2016) reported that G9P[4] is the most frequent genotype in India.

In countries like Ireland, Collins et al. (2015) indicated the prevalence of G1P[8] and reported changes in circulating patterns with the re-emergence of G2P[4]; in Italy, the predominant genotype is G1P[8] (DÓRÓ et al., 2014).

Based on the report by Anca et al. (2014), the predominant genotype in Romania has changed from G9P[8] and G4P[8] to G1P[8] since the vaccine was introduced. In Russia (LOBZIN et al., 2017), genotype G1P[8] also prevailed. In contrast, the prevalence of rotavirus genotype has changed from G1P[8] to G4P[8] along with G2P[4] in Slovenia (Steyer et al., 2014).

In Turkey, the rotavirus strains were classified into genotypes G1–G4 between 2000 and 2010, but recent studies have pointed the increased prevalence of G9P[8] (DÓRÓ et al., 2014; TAPISIZ et al., 2019).

Circulating and predominant genotypes have also changed in Australia (Table 2). G1P[8] was the predominant genotype in this country, but genotype G12P[8] followed by genotype G3P[8] has become the most frequent recently (DÓRÓ et al., 2014; ROCZO-FARKAS et al., 2017; ROCZO-FARKAS, COWLEY ;BINES, 2019).

In the Orient, the most frequent strains are G1 and G9. In Israel, the predominant strain is G1P[8]; strain G3P[8] is the second most common strain in the country, but it has not been detected in other Eastern countries (MUHSEN et al., 2016). In Lebanon, G1P[8] along with G9P[8] was also prevalent a few years ago (Ali et al., 2016), whilst strains G1P[4] and G1P[6] prevail in Pakistan (DÓRÓ et al., 2014). In Saudi Arabia, the most common strain – G1P[8] – has declined, whereas strain G2P[4] has emerged and significantly increased in rotavirus cases (DÓRÓ et al., 2014; Al-Ayed et al., 2017).

Table 2 - Worldwide distribution of circulating and predominant rotavirus genotypes.

	Main Genotypes			
Countries by continent	**Pre-vaccination Genotype**	**Post-vaccination genotype**	**Currently in circulation**	**References**
AMERICA SOUTH / NORTH				
Argentina	G1P[8]	G2P[4]	G12P[8]; G2P [4]; G9P[8]; G1P[8]	Dóró et al., 2014; Mandile et al., 2014
Brazil	G1P[8]	G12P[8]	G2P[4]; G9P[8]; G1P[8]; G12P[8]; G3P[8]	Dóró et al., 2014; Luchs and Timenetsky, 2016; Patel et al., 2013; Carvalho-Costa et al., 2019
Bolivia, Cuba, Chile, and Peru	NA[a]	G9P[8]	G9P[8]	Dóró et al., 2014; Ribas et al., 2011
Colombia and Paraguay	NA[a]	G2P[4]	G2P[4]	Peláez-Carvajal et al., 2014; Martínez et al., 2010
Venezuela	G1P[8]	G2P[4]	G2P[4]; G1P[8]; G9P[8]; G3P[8]; G2P[6]	Vizzi et al., 2017
USA	G3P[8]	G12P[8]	G1P[8]; G12P[12]; G9P[6]; G12P[8]; G3P[8]; G3P[9]	Dóró et al., 2014; Mast et al., 2010; Wylie, Weinstock and Storch, 2015; Bowen et al., 2014
Canada	G1P[8]	G9P[8]	G9P[8];G1P[8]; G2P[4]; G3P[8]; G3P[6]; G4P[8]; G9P[4]	Chetrit el al., 2013
AFRICA				
Cameroon	G1P[8]	G12P[8]	G1P[8]; G12P[6]; G12P[8]; G1P[6]; G3P[6]; G2P[4]; G8P[6]; G2P[6]; G3P[8];	Dóró et al., 2014; Ouermi et al., 2017
Ghana	G1P[8]	G2P[4]	G2[6]; G3P[6]; G6P[6]; G2P[4]	Dóró et al., 2014; Ouermi et al., 2017; Agbemabiese et al., 2016
Malawi	G1P[8]	G12P[6]	G12P[6]; G2P[4]; G8P[6]; G12P[8]	Ouermi et al., 2017; Nakagomi et al., 2017
Nigeria	G12P[8]	G1P[8]	G1[P8]; G3[P8]; G1P[5]; G6P[8]; G3P[6]	Ouermi et al., 2017; Motayo; Adeniji and Faneye, 2016
Kenya	G1P[8]	G9P[8]	G9P[8]; G1P[8]; G2P[4]; G3P[8]; G4P[8]; G12P[8]	Dóró et al., 2014; Ouermi et al., 2017
Tunisia	G2P[4]	G1P[8]	G3P[8]; G9P[8]; G4P[8]; G2P[4]; G12P[6]; G12P[8]	Dóró et al., 2014; Moussa et al.; 2016
ASIA				
China	G3P[8]	G9P[8]	G3P[8]; G9P[8]; G2P[4]; G1P[8]	Dóró et al., 2014; Zhang et al., 2017

►►

Table 2 - Worldwide distribution of circulating and predominant rotavirus genotypes (cont.).

Japan	G3P[8]	G1P[8]	G1P[8]; G2P[4]; G3P[8]	Dóró et al., 2014; Fujii et al., 2019
South Korea	G1P[8]	G2P[4]	G2P[4]; G1P[8]; G3P[8]; G4P[8]; G9P[8]	Chung et al., 2015
Thailand	NA[a]	G1P[8]	G2P[4]; G1P[8]; G3P[8]	Dóró et al., 2014
Vietnam	G3P[8]	G1P[8]	G2P[4]; G1P[8]; G3P[8]; G9P[19]; G10P[14]	Do et al., 2017
EUROPE / EURASIA				
Austria	NA[a]	G2P[4]	G2P[4]; G2P[4]	Dóró et al., 2014
Belgium	G1P[8]	G2P[4]	G3P[8]; G4P[8]; G9P[8]; G2P[4]; G1P[8]	Pitzer et al., 2015
Greece	G1P[8]	G4P[8]	G4P[8]; G1P[8]; G12P[8]; G3P[8]; G12P[6]	Dóró et al., 2014; Koukou et al., 2015
Hungary	NA[a]	G9P[8]	G9P[8]; G2P[4]; G1P[8]; G4P[8]	Dóró et al., 2014
India	G1P[8]	G9P[4]	G1P[8]; G9P[4]; G2P[4]; G1P[6]	Gupta et al., 2019; Babji et al., 2018; Pradhan, Walimbe and Chitambar, 2016
Ireland	G1P[8]	G9P[4]	G9P[4]; G1P[8]; G3P[4]; G2P[4]; G2P[8]	Collins et al., 2015
Italy	G1P[8]	G2P[4]	G1P[8]; G2P[4]; G9P[4]; G9P[8]	Dóró et al., 2014
Romania	G2P[4]	G9P[8]	G9P[8]; G4P[8]; G1P[8]	Anca et al., 2014
Russia	G4P[8]	G1P[8]	G4P[8]; G1P[8]; G3P[8]; G9P[8]; G2P[4]; G4P[4]	Lobzin et al., 2017
Slovenia	G1P[8]	G4P[8]	G4P[8]; G1P[8]; G2P[4]	Steyer et al., 2014
Turkey	G9P[8]	G1P[8]	G9P[8]; G1P[8]; G3P[8]; G2P[4]	Dóró et al., 2014; Tapisiz et al., 2019
OCEANIA				
Australia	G1P[8]	G12P[8]	G12P[8]; G3P[8]; G1P[8]	Dóró et al., 2014; Roczo-Farkas et al.; Roczo-Farkas, Cowley and Bines, 2019
ORIENT				
Israel	G1P[8]	G3P[8]	G1P[8]; G3P[8]; G2P[4]; G4P[8]; G9P[8]	Muhsen et al., 2016
Lebanon	G1P[8]	G9P[8]	G1P[8]; G9P[8]; G2P[4]	Ali et al., 2016

Pakistan	G1P[8]	G1P[4]	G1P[4]; G1P[8]; G1P[6]; G2P[4]; G2P[8]; G9P[8]	Dóró et al., 2014
Saudi Arabia	G1P[8]	G2P[4]	G2P[4]; G1P[8]; G1P[6]; G9P[8]	Al-Ayed et al., 2017

a: not applicable

Source: Prepared by the authors.

Final considerations

The current global challenge regarding rotavirus infection is to ensure protection against the disease through immunization. Changes in the prevalence of circulating genotypes and re-emergence of serotypes have been reported worldwide. In addition, the virus can easily infect several animal species other than humans, as evidenced by reports of cross-infection of strains, which have served as warning that new virus genotypes have been generated.

Immunization helps to reduce health-related expenses and to reduce mortality due to the rotavirus, thus improving health indicators and significantly contributing to the promotion of health throughout the world.

The promotion of health should be inserted in the context of raising awareness of the importance of controlling infections caused by gastroenteric agents such as the rotavirus, which empowers populations. Inter-sectoral actions that encompass not only the health sector, but also all the socio-economic sector including the government, researchers, teachers, health agents, and communities are relevant. Such actions shall decrease health-related expenditures and reduce mortality caused by the rotavirus, thereby improving health indicators and promoting health around the world.

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