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The Emergence of New Rotavirus Strains in America

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Rotavirus infections are the most common causes of infectious diarrhea in young children and animal worldwide. In some countries in Latin American specifically in Central American and Caribbean countries, rotavirus infections are not subject to specific surveillance. This review is about the unusually strains detected and potential zoonotic of rotavirus in Latin American. Although, interspecies transmission has not been documented to occur directly, an increase of the number of reports of atypical rotavirus genotypes; apparently derived from transmission between animal of farm, domestic and wild with humans, has been reported in some Latin American countries and the world. We consider that the rapid increase in the detection of new unusual strains with genetic heterogeneity, raises interesting questions about the evolution of rotavirus in The Latin American region. The emergence of novel strains derived from interspecies transmission has implications for the design and implementation of successful human rotavirus vaccine strategies.

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1. INTRODUCTION

Rotaviruses are the world's leading cause of childhood gastroenteritis [1]. Rotavirus is an endemic pathogen in many regions of the world [1]. It has been considered one of the causes of death in children under five years of age; worldwide it produced more than 500,000.00 deaths [2]; it has also been proven to be the cause of death in mammals and birds [3].

Rotavirus is classified as a genus of the Reoviridae family, which is a naked virus and has a segmented genome [4]. The rotavirus that causes acute gastroenteritis in children worldwide belongs to group A; antigenetic, rotaviruses are classified into serogroups, subgroups, and serotypes. Till this date, 8 serogroups are known, defined by the epitopes present in the VP6 protein, each of which has been assigned a letter: groups A, B, C and H have been isolated in both humans and animals; whereas groups D, E, F and G have only been isolated in animals [3, 4].

Most rotavirus infections are caused by group A rotavirus [4]. Serogroup A is typically associated with diarrhea in people and young animals. The VP6 protein is the predominant antigen of the group; it constitute 51% of the virion [4].

Rotaviruses from group A have the existence of two external capsid proteins, highly reactive against neutralizing antibodies: VP7 and VP4 proteins. Therefore, the classification of rotaviruses is a binary system that distinguishes different serotypes of the VP7 and VP4 proteins. The internal capsid or nucleus has the viral genome that is made up of 11 segments of double-stranded RNA (dsRNA). Each segment encodes a specific viral protein; six structural proteins called viral proteins (VP), VP1, VP2, VP3, VP4, VP6 and VP7 and six non-structural proteins (NSP): NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6 [4]. Since VP7 is a glycoprotein, the VP7 serotype is also known as G-serotype or G-type. In the case of VP4, because it is a protein sensitive to proteases, it is called P-serotype or P-type [4].

Until now, 32 genotypes of G (VP7) and 47 genotypes of P (VP4) are known respectively [5]. Knowledge of the genetic relationships between human and animal strains has been possible thanks to the sequence of the complete analysis of the rotavirus genome [3, 6].

2. PATHOGENESIS AND CLINICAL MANIFESTATIONS

Rotavirus infection follows the fecal-oral route [4], this virus is very stable in the environment, being able to survive for long periods of time [4]. Studies have shown that the respiratory tract is also involved, as is the case with the influenza virus, the detection of rotavirus in drinking water for human consumption [7] contaminated water, swimming pools [8, 9], in food [10] and in contaminated objects; it is well documented [4].

Other observations that suggest environmental contamination as a source of infection are: the persistence of infections in nurseries and the high frequency of nosocomial rotavirus infections [11]. In a controlled study it was shown that if the surface contaminated with rotavirus was sprayed with detergent, infection did not occur [12].

There are reports in Latin America and the world on the role of animals as the source of infectious rotavirus humans, that consider rotavirus as possible potential zoonotic [13-22].

2.1 Rotavirus Replication

Rotaviruses infect mature cells of the intestinal villi, especially from the duodenum and ileum [23]. Rotavirus infection shows a marked tropism and is mainly restricted to the intestinal mucosa [4, 23]. Viruses infect the cell after interaction with a receptor; on the other hand, the rotavirus triple layer particle (TLPs) binds to the enterocytes of the small intestine villi [23]. The rotavirus TLPs first attach to sialo-glycans on the host cell surface, followed by interactions with other cellular receptors, including integrins and Hsc70; upon contact with the cellular receptor, the VP4 spikes of rotavirus TLPs undergo conformational changes in such a way that thelipophilic domains of VP5* which are normally hidden below VP8*are exposed on the surface in form of a ‘post-penetration umbrella’conformation [23]. The virus particles are transported by endosomes where the low level of calcium [24], leads to the loss in the lining of the TLPs, transforming them into doble layer particles

(DLPs), become transcriptionally active synthesizing non-polyadenylated RNA strands by the biochemical activity of the viral VP1 and VP3 enzymes [23]. Viroplasm is formed around the cell nucleus as early as two hours after virus infection [24]. The newly made DLPs bind to NSP4, which serves as an endoplasmic reticulum receptor, and bud into the endoplasmic reticulum NSP4 also acts as a viroporin to release Ca2+ from intracellular stores, the transient membranes are removed as the outer capsid proteins VP4 and VP7 assemble, resulting in the maturation of the TLPs [23, 24]. Replicate in the cytoplasm, lyse the cell, atrophy the villi and decrease the absorption capacity, acting mainly on disaccharidases; as a result of infection, crypt cell hyperplasia occurs which, at the same time, stimulates secretory activity with increased excretion of water and electrolytes. There are problems in the ion transport function in the jejunum and ileum during diarrhea [23].

2.2 Enterotoxin Non-structural Protein (NSP4)

The most important histopathological change is atrophy of the intestinal villi with poor differentiation of the epithelial cells of the small intestine. There is an alteration to actively transport sodium and chloride, with a glucose-mediated sodium ion transport defect [23]. Also, recently, other mechanisms of rotavirus pathogenicity have been identified, which are the cytotoxic activity of the non-structural protein NSP4 that occurs in the initial phase of the viral replication cycle [24] and the activation of the enteric nervous system (ENS) [24]. Both mechanisms produce diarrhea without producing any histopathological alteration. In the first mechanism, enterotoxin (NSP4) alters calcium homeostasis, causing an increase in intracytoplasmic calcium that activates chlorine channels, and increases chlorine secretion, accompanied by water, into the intestinal lumen. In the second mechanism, the ENS, which controls bowel movements and fluid absorption and secretion, produces secretory diarrhea when stimulated by the virus [25].

3. EPIDEMIOLOGICAL PATTERNS OF ROTAVIRUS

Knowledge of the epidemiology of rotavirus is essential for the control of this disease; especially since it has been observed that it presents differences between developed and developing countries, as well as between temperate and tropical climate regions [26]. These differences could be associated with risk factors that have not yet been established, but have been linked to socioeconomic status, home overcrowding, low maternal education, and low birth at weight [26]. For example, this virus presents differences in the severity of the disease between developed and developing countries. Rotavirus diarrhea is much more severe in populations of low socioeconomic status; the majority of deaths caused by rotavirus occur in less developed countries [26, 27].

Rotavirus presents differences in seasonal behavior; changes in the seasonal pattern of rotavirus disease have also been observed after vaccine introduction [28].

This seasonal behavior influences the age at which the first rotavirus infection occurs [26]. In countries without marked seasonality, the age at which the first infection appears is very early (<6 months of age), because all born children are exposed to the virus, regardless of the date of birth, and this is the case in most tropical countries; while at countries with marked seasonality or temperate countries, the first infections occur in later ages (9-15 months of age) [26, 29].

4. ROTAVIRUS INDUCED IMMUNITY

Rotaviruses produce a local infection that mainly affects the mature cells of the intestinal villi [23]. The incubation period (1-3 days) is relatively short, which induces a partial and short-lasting immunity [30]. This type of infection is similar to the one produced by respiratory viruses and contrasts with the immunity produced by systemic viruses, such as polio, rubella, chickenpox and measles, which have a longer incubation period (7-14 days) , and produces lifelong immunity [30]. Mucosal immunity constitutes a very important defense in intestinal infections caused by rotavirus [23, 31].

With the increasing number of infections, the degree of protection is increased, but at least two symptomatic or asymptomatic infections are needed, to prevent rotavirus disease of any severity [32]. In other words, natural infection does not protect against reinfection but significantly reduces the severity of the disease [33].

4.1 Clinical Manifestations

The scope of rotavirus infection ranges from asymptomatic to mild-moderate clinical condition, to profuse, watery diarrhea that can cause dehydration and death [30]. After an incubation period of 1 to 3 days, the picture begins abruptly with vomiting and fever, followed by profuse watery diarrhea leading to dehydration; the temperature drops rapidly, vomiting subsides within 24 to 48 hours, and diarrhea within two to seven days [30]. Approximately 30 to 40 percent of the viral infected children developed slight fever, vomiting which last one or two days, and gastrointestinal symptoms that last three or seven days, but that may occasionally last from two to three weeks [30, 31]. Without a suitable liquid replacement, pathological conditions can cause dehydration. Moreover, high frequency vomiting leads to a high health risk to small kids [31].

There is passive immunity, which comes transplacentally and via breastfeeding [4], occasionally fatal gastroenteritis occurs, this because dehydration is not treated in time [4].

4.2 Antibody-Mediated Immunity and Protection

Rotavirus infection induces immunity mediated by specific antibodies, IgM, IgG and IgA, that can be detected in serum, saliva, duodenal contents, and feces, 7 to 28 days post-infection [34,35]. In this way, viruses that infect the mucosa, such as rotaviruses and respiratory viruses, induce a local secretory IgA response (IgA-s), a primary factor in the defense of the intestinal mucosa or respiratory tract, as the case may be. On the other hand, the proteins of the outer layer, VP4 and VP7, induce neutralizing antibodies (IgG) [36] and the VP6 protein, located in the intermediate layer, as well as the non-structural NSP4 protein, which are also immunogenic [23].

In general, VP7 homotypic neutralizing antibodies (IgG) and to a lesser extent VP4 homotypic neutralizing antibodies, appear after the first infection [34, 37]. Instead, re-infection stimulates the appearance of heterotypic antibodies against VP7 and VP4 [31, 34, 37]. Which means that the immunity produced during the first contact with the virus is mainly homotypic and the heterotypic immune response appears with age as a result of subsequent exposures to the virus, both in naturally infected children and in vaccinated children [23, 34]. These results indicate or support the need to suffer at least 2 infections to produce a broad spectrum immune response, which would imply the need to administer two doses of the vaccine [37].

5. ROTAVIRUS VACCINES

In development of rotavirus vaccines, we licensed the first vaccine in the US RotaShield®, a human-rhesus vaccine [38]; but, this vaccine demonstrated to be associated with intestinal intussusception events, which was confirmed 12 months after its use in the United States [39].

New candidates were designed afterwards. One was RotaTeq ® (RV5; Merck & Co. Inc., USA), an antigenic component vaccine that includes five rearranged bovine-human strains, and Rotarix® (RV1, GlaxoSmithKline, Belgium), a single attenuated strain for humans. They were introduced into immunization programs in Latin America and the Caribbean in 2006 [33, 40] where 88 deaths occur annually for every 100,000 children under 5 years of age [41]. None of these vaccines demonstrated in studies the possibility of association with intestinal intussusception [42].

The following vaccines are approved against rotavirus: RotaTeq®, Rotarix® Rotavac®, and Rotasiil® [43]. The Lanzhou Lamb vaccine in China and Rotavin-MI® in Vietnam. Rotavac® includes the neonatal strain of rotavirus 116E, a naturally occurring human-bovine rearranged strain of the G9P [11] serotype [44]. The Lanzhou Lamb vaccine, based on a rotavirus strain obtained in 1985 from a local lamb with diarrhea and attenuated through serial passage , was licensed in China in 2000 [45]. Rotavin-MI® is similar to Rotarix® in that it is an attenuated G1P strain [8] obtained from a Vietnamese child [46]. Rotasil® is a UK bovine regrouping vaccine composed of five regrouped strains, with the added benefit of thermal stability, developed in collaboration with researchers from the USA, India and Brazil [47].
In 2015, 1.31 million children died due to diarrhea, of which 500,000 were children under the age of five. From 2005 to 2015, the number of cases of diarrhea in children under five years of age decreased by approximately 10%. Deaths from diarrhea decreased by about 34% and deaths due to rotavirus decreased by 44% [2]. The efficacy of Rotarix® and RotaTeq® reduced hospitalizations and visits to the emergency room

associated with rotavirus gastroenteritis [33]. In the Latin American and Caribbean region, the study described a 90% efficacy of these vaccines; there was no risk of intestinal intussusception, nor risk of death among the children in the study [33]. WHO recommends keeping rotavirus vaccines in all national immunization programs worldwide [48]. Currently, 19 countries in Latin America and the Caribbean include rotavirus vaccines in their national immunization programs [49].

6. DISTRIBUTION OF UNUSUAL GENOTYPES AND STRAINS WITH ZOONOTIC POTENTIAL IN AMERICA AND THE CARIBBEAN

Group A rotavirus, discovered in Australia by Bishop RF, et al. [50], is the most frequent cause of the illness, and has been responsible, between 2000 and 2006, for nearly 611,000 deaths per year in children under the age of five, globally [23,51]. After the development and application of the Rotarix ® vaccine, according to the World Health Organization; these figures have decreased, according to studies by the World Health Organization (WHO), to 215,000 deaths yearly, between 2013 and 2016, to 215,000 death worldwide [48]. In Latin American countries, diarrheal diseases continue to be one of the most important public health problems [52].

The worldwide distribution of genotypes G (VP7) and P (VP4) shows a number of combinations associated with diarrhea: G1 P[8]; G2 P[4]; G3 P[8]; G4 P[8] being these, considered the most common in the history of the study of rotavirus worldwide. Nevertheless, the latest investigations have revealed that strains that were considered emergent and unusual as the case of G9 P [8], are considered today, among the most common genotypes occupying the fifth place; as we can also not omit the case of the G12 P [8] genotype, strain that was what considered emerging, and has been expanding in several countries in Latin America and around the world [53-58].

6.1 Central America and Caribbean Countries

In Central America, in 2001, Nicaragua was the first Central American country to initiate molecular epidemiology studies in rotavirus for the VP7 and VP4 proteins [59], detecting common genotypes such as and unusual such as: G1P[4], G3 P[6] and G2 P[8] [59, 60,61]. After conducting these first studies, for the first time, an epidemiological surveillance network on rotavirus was formed, where in addition to Nicaragua, other Central American countries like Costa Rica, Panama, Honduras and Guatemala participated under the sponsorship of the Research and Training of Tropical Diseases in Central American (NeTropica), countries such as: Costa Rica, Panama, Honduras and Guatemala [62, 63]. Simultaneously to this study a genotyping surveillance of circulating rotavirus strains before the introduction of the rotavirus vaccine (Rotarix® Glaxo Smithkline) was performed for the first time in these countries, Panama, Costa Rica and the Dominican Republic [64]. In this sense, Nicaragua was the first country in Central America to introduce the rotavirus vaccine [65].

For the first study carried out in Panama, Costa Rica and the Dominican Republic during the year 2000-2003; it was detected common genotypes [64]. Once this investigation was carried out, the presence of unusual strains (Table. 1. B.), was reported in these three countries [64].

During the year 2002-2003 in Honduras, samples of children with gastroenteritis were analyzed to detect the presence of rotavirus by means of RT-PCR for VP7 and VP4, where the G1P[8] genotypes were determined with a frequency of 96% and G2 P[4] with a lower frequency of 4% (Annabelle Ferrera, unpublished data [66]. However, in Nicaragua, since the first molecular detection of rotavirus carried out in 2003 to date, many circulating, common and unusual genotypes have been detected [57, 59, 61, 65, 67, 68, 69, 70, 71], as well as mutant strains, such as the one found in Nicaragua (G4 P [8]), which revealed the insert of the amino acid asparagine as a residue in position 76 combined with additional mutations [67]. The researchers propose that this genotype, which was considered a common strain, emerged from countries in South America [67]. It is important to add and clarify that during the outbreak of this strain there were deaths of children due to diarrhea in this country and they were attributable to this G4 P [8] strain [67]. This genotype was found associated with other genotypes reported as common strains [67]. During these years of characterization studies of rotavirus strains in Central America, there have been deaths of children due to diarrhea attributed to rotavirus [26, 67]. Again, for the year 2005 and 2006, samples were analyzed in Costa Rica,

Nicaragua, Honduras, Guatemala and the Dominican Republic, where common genotypes such as G1 P[8] were detected circulating in these countries [64, 66, 67]. G9 P [8] was detected circulating in Costa Rica, Nicaragua, Honduras and also the G9 P [4] strain circulating in Costa Rica for that same year (Table. 1. B.). In the Dominican Republic strains possessing a G3 (VP7) gene of putative equine origin (EQL-G3) have been detected in humans and gene recombinant gene (G4P[6-8_R]) from bovine and porcine detected in humans [13,16, 66], we found that for the year 2012, in this country the G3 genotype was circulating in stools with diarrhea, revealing in these strains rotavirus of human origin, with segments of bat genes with high homology for VP7 and VP4 proteins [72], being this, another evidence of the possibility of zoonosis, in the region.

Another investigation reveals a G8 P [14] strain detected in a child with evidence of simian and bovine origin in Guatemala, which represents that genetic rearrangement exists in our countries and that these strains originate from possible zoonotic potentials (Table. 1. B.) [18]. Also in Guatemala, investigations carried out in 2009 reveal genotype, G9 P [4] followed by G9 P[8] (32%), and (G3, P [4-8]) (2%). We agree with the hypothesis formulated by Quaye O, et al. [73] where they emphasize that probably this (G9 P [8-4]) genotype arose from mixed G9 P [4] infections with G9 P [8]. Also in Honduras for the year 2010, a strain of rotavirus defecated by a child identified as G10 P[14] was determined, where it reveals that with the VP7 protein, it has 85% homology with genes derived from sheep, horses and cattle, revealing a possible zoonosis (Table. 1. B.) [22]. Another research in Nicaragua also demonstrates the possibility of zoonotic transmission, because gene sequences of bovine rotavirus in a child with diarrhea were revealed; all segments were sequenced and show detection of sequence segments of animal rotavirus in rotavirus that cause diarrhea in children [74].

For the year 2012 it was reported in Haiti rotavirus circulation, common genotypes [75]. Some genotype detection studies have been carried out in Cuba, Jamaica and Puerto Rico where common genotypes were also detected [76, 77, 78, 79, 80]. In Barbados, strains of humans have also been detected with segments of animals of porcine origin G4 P [14]; the authors consider that this strain arose by genetic rearrangement between humans and animals [17].

There is no information on molecular surveillance of rotavirus in Central American and Caribbean countries such as: El Salvador, Belize, Aruba and Curacao. It is important to emphasize that few researchers in our region receive financial grants from the state to carry out research on public health diseases and the availability of international resources for Central American scientists is limited [62, 63], which happens as well, in Caribbean countries; even though, there is available data that rotaviruses are still today considered one public health problem.

6.2 South America Countries

Studies carried out in South America reveal that in Colombia, for example, the presence of common rotavirus genotypes and a variety of unusual G and P combinations have been detected [81]; however, no investigations were found to reveal in humans, the detection of strains with animal segments. In Peru, studies have revealed the detection of unusual rotavirus strains such as G12 declared as emerging strains [82]; few studies have been conducted in this country, so the epidemiological behavior of the circulating genotypes is unknown. In Ecuador, studies also show the presence of common genotypes and unusual considered as potential emerging [83, 84, 85, 86]. Possible potential rotavirus zoonosis has been detected by detecting segments of porcine-human origin detected in a child with diarrhea in Ecuador (Table. 1. C.) (G11 P [6]); [84]. Researchers recommend modifying these primers, because there are in the region, many cases of positive samples to rotavirus by ELISA; and when genotyping time via RT-PCR comes, it is difficult to identify the genotypes for VP7 and VP4 [87]. In the case of Bolivia, few studies have been carried out on rotavirus genotyping, in which common genotypes have been detected and rare strains [88]. Research carried out in Chile indicates that unusual strains have appeared, which share homology with strains from Europe and Asia, like (G8 P [8]) [89, 90, 91]. In the case of Argentina, studies have been carried out where the G4 P [6] genotype has been detected in humans with segments of porcine origin (Table. 1. C.) [92]; as well as, common and rare genotypes [93]. Studies carried out in Uruguay for the detection of rotavirus in wastewater reveal the presence of common strains and emerging ones like G12P [8] and genotype G3P [3]; a very rare combination detected in humans in the surveillance system [94, 95]. In Paraguay, there has been detected, in the rotavirus defecated by

a child, bovine rotavirus segments detecting the G8 P [1] strain [96]. Another study reveals the presence of the G4 P[6] strain in a Paraguayan child, where genomic analysis reveal a genome similar to that of pigs; which suggests a direct transmission from animal to human [21]. Uncommon genotypes have also been detected circulating in this country, G9 P[6] and G12 P[9], that are associated with transmission of feline rotavirus segments, where possibly inter-species transmission occurred from feline to human population (Table. 1. C.) [97]. In Venezuela, rare combinations of rotavirus genotypes have also been detected G8P [14], G8P [4], G1P [4], G4P [4], G2P [6], and mixed infections [98, 99]. In Surinam, the characterization of an unusual rotavirus strain G20 P [28], detected in a 24-month-old child, is described; three of the eleven gene segments (VP7, VP4, VP6) were similar to sequences of related human rotavirus genes similar to bats (Table. 1. C.) [100].

In Brazil, various investigations have been carried out, where the association of rotavirus as zoonotic potential, have been documented [3, 101, 102, 103]. An investigation shows a genotype G10 of bovine rotavirus defecated by a Brazilian child [20]; another research shows, for the first time in Latin America (Brazil), a strain of canine rotavirus in a one-year-old child with diarrhea [14]. A study done in this country, reveals rare strains in humans that contain segments of equine rotavirus for (VP4) P8 [104, 105]. A G3P[9] sample from a child with acute gastroenteritis revealed in the study of phylogeny a closer relationship with genes of animal origin, such as the chiroptera, alpaca, horse and monkey [106]. Other studies on indigenous children from Brazil, revealed a strain considered unusual, (G8 P [6]) [107]; Phylogenetic studies of these strains revealed segments of bovine, porcine and goat rotavirus [107] (Table. 1. C). Various investigations show that the growing study of the genetic diversity found in porcine rotavirus would provide a platform to monitor the role of animals as possible genetic reservoirs for emerging human rotavirus strains [108]. Another study with indigenous people from Mato Grosso in southern Brazil suggests that a possible genetic rearrangement occurred between cattle-bats and that it was possibly transmitted to humans [20].

6.3 North America

In Mexico, since the years between 2000-2019, little research has been devoted to monitor circulating strains of rotavirus in this country [109, 110, 111]; There is a report on the rotavirus, in which genetic sequences share homology closest canine and porcine strains, study that evidences the possible zoonotic potential in this country [112]. It is shown that although few studies on the epidemiology of rotavirus strains circulating in this country have been carried out; some researchers have concentrated efforts on the biology of rotavirus regarding its entry and exit from the cell [113]. We are not omitting on this review, that in North Carolina, in the United States, a child with diarrhea was reported, which had the genotype G3 P [8] that shares high homology with equine segments [114]. Another study in this country evidenced bovine and equine segments in humans identified as the (G14 P [24]) strain [115]. In Houston, Texas, a Hispanic patient from Mexico was treated with diarrhea, being the first case in the United States where a human rotavirus (G24 P [14]) was detected with high homology in bovine segments [116]; also, the G8 P [14] strain with bovine and simian segments identified for the first time in the United States (Table. 1. A.) [117].

Although it is difficult to have exact estimates of epidemiological data and viral load of rotavirus disease in Latin American children; it is clear that rotavirus diarrhea is common in Latin America and the Caribbean; after vaccination programs, deaths and hospitalizations due to diarrhea in children under five years of age have decreased considerably [33,52].

Phylogenetic studies carried out worldwide for the rotavirus VP7 and VP4 protein demonstrate differences in the lineage and sub-lineage of genotypes that affect humans and also reveal a great genetic variability of rotavirus genotypes [118]. The identification of unusual strains of rotavirus has been largely detected in developing countries [87]. Although interspecies transmission has not been documented to occur directly, an increase of the number of reports of atypical rotavirus strains, apparently derived from transmission between pigs and cattle bovine and cattle, bovine with humans, pigs with humans and between humans, has been reported globally [6,119]. The main means of zoonotic transmission is human-animal contact [3]. The risk of such transmission is also present in the contamination of water or food reservoirs by feces of infected animals [8, 9, 10, 14, 119, 120]. However, studies on rotavirus zoonosis have a limitation because there are not full study reports

in Latin America, on the sequencing of the rotavirus genotypes in animals such as: sheep, goats, pigs, dogs and cats; where there is an information bank of circulating strains that allows epidemiologically correlate among strains detected in humans and animals. Therefore, the study of the zoonotic event of a certain strain of rotavirus is confirmed only on the basis of phylogenetic evidence [14].

Table 1. Unusually Strains and Evidence of Potential Zoonotic of Rotavirus in American Countries

A. North America

Rotavirus Strains	Country	References
*G3P8	United States (USA)	Perkins C et al., 2017
*G14P24	United States (USA)	Mijatovic-Rustempasic S et al., 2016
*G8P14	United States (USA)	Mijatovic-Rustempasic S et al., 2015
G9P4	Mexico	Felix-Valenzuela et al., 2016
*G24P14	Mexico	Ward ML et al., 2016

**Relationship to animal rotaviruses*

B. Central America and Caribbean Countries

Rotavirus Strains	Country	References
G1 P4	Dominican Republic	Bourdett-Stanziola L et al., 2008
G1P6	Costa Rica and Dominican Republic	Bourdett-Stanziola L et al., 2011
G2P8	Costa Rica	Bourdett-Stanziola L et al., 2011
G3P6	Dominican Republic	Bourdett-Stanziola L et al., 2011
G9P4	Costa Rica	Bourdett-Stanziola L et al., 2011
*G4P[6-8_R]	Dominican Republic	Esona MD et al., 2017
*EQL-G3P[8]	Dominican Republic	Katz EM et al., 2019
*G10P14	Honduras	Quaye O et al., 2018
*G8P14	Guatemala	Gautam R et al., 2015
*G4P14	Barbados	Tam KI et al., 2014

**Relationship to animal rotaviruses*

C. South America

Rotavirus Strains	Country	References
*G11P6	Ecuador	Bányai K et al., 2009
G1P6	Bolivia	Rivera R et al., 2013
G2P6	Bolivia	Rivera R et al., 2013
*G4P6	Argentina, Paraguay	Degiuseppe JI et al., 2013; Martínez M et al., 2014
G3P3	Uruguay	Tort LF et al., 2015
*G8P1	Paraguay	Martínez M et al., 2014
*G12P9	Paraguay	Martínez M et al., 2010
*G9P6	Paraguay	Martínez M et al., 2010
*G20P28	Suriname	Esona MD et al., 2018
*G10	Brazil	Lunch A and Timenetsky Mdo C. 2014
*G3P9	Brazil	Bezerra DA et al., 2017
*G8P6	Brazil	Luchs A et al., 2015
G8P8	Chile	Lucero Y et al., 2019

**Relationship to animal rotaviruses*

If it is taken into consideration that many genetic rearrangements of this virus derive from the introduction of new strains [118]; it is possible that the emergence of new genotypes in these countries could be due to the introduction of new genes, since our tropical countries are a tourist attraction for immigrants from all over the world. The idea that this migration flow may lead to an exchange of rotavirus strains is speculation; however, an additional in depth complete analysis is required, of gene sequences of rotavirus strains collected to completely validate this hypothesis.

7. STUDIES THAT EVIDENCE REASSORTMENT OF HUMAN GENOTYPE ROTAVIRUS IN ANIMALS IN AMERICA

Very little research has been devoted to monitoring circulating strains of rotavirus A in animals in Latin America; some investigations have been carried out in Costa Rica, Brazil, Peru, Uruguay and Argentina where they suggest the occurrence of co-infections and genetic rearrangement, the detection of human genotypes in bovine, swine, alpaca, bat, equine, can be considered evidence of the zoonotic potential of rotaviruses, because rotavirus a may be zoonotic, excretion of into the environment can result in transmission causing interspecies infections and allowing the emergence of new reassorted viruses. Phylogenetic analysis showed that some of the rotavirus genotypes found in this animals had high percentages of identity when compared with reference strains from humans [121, 122, 123, 124, 125, 126, 127].

8. INTERSPECIES TRANSMISSION

The major source of zoonotic transmission is the contact between humans and animals [3]. Moreover, the ingestion of contaminated food and drink leads to rotavirus infection feed [8, 9, 10, 14, 119, 120]. The viral infection of millions of people, every year, is due to the rotavirus transmission by animals of farming communities (horses, bovine, pigs, and poultry), and also by wild animals, which leads, on the other hand, to the infection of new rotavirus strains [20, 66, 123, 126].

Molecular studies carried out in the Dominican Republic revealed that the rotavirus detected in children belongs to the G3 virus genotype containing genes for the VP7 bat rotavirus (≥97%) [72]. In Surinam, a research lead to the detection of an uncommon human rotavirus strains (G20P) [28], which was also identified, in 2006, at an Ecuadorian strain. Both rotavirus strains had very high similarity with a bat rotavirus strain [100]. Simsek et al. [127] suggested that the bats are main transmitters of the rotavirus in humans, but this needed to be scientifically determined in further investigations. Few studies have been carried out on the detection of rotavirus strains in bats in the world; however, new genotypes never before reported have been recently identified in bats, where it is interesting and important to emphasize that some of these new rotavirus genotypes have a close relationship with other mammals [127, 128, 129].

It is likely that peculiar human rotavirus strains have emerged by genetic rearrangements among animal and humans' co-infections. Rotaviruses have segmented genome, as the influenza, that prompt new strains during viral replication. A key prerequisite for the great strain's diversity is the co-circulation of different rotavirus strains at the same population that favors the interspecies transmission [119].

Luchs A, Timenetsky Mdo [20] and Bourdett-Stanziola L, et al. [66], suggest that inter-species transmission happens frequently, because many people in Latin American countries live in poor hygiene conditions and some, also they live closely with animals. We agree with this hypothesis given that in many Latin American and Caribbean countries the inhabitants live in extreme poverty and in many cases live together with wild and farm animals; and on some sites, they share the same source of water for consumption.

We consider that the rapid increase in the detection of new unusual strains with emerging zoonotic potential of rotavirus in Latin America and the Caribbean, in association with genetic heterogeneity, raises interesting questions about the evolution of rotavirus in the Latin American region.

9. CONCLUSION

The results of the molecular characterization of these strains would contribute in the future new knowledge about the possible genetic rearrangements of rotavirus. The emergence of strains derived from interspecies transmission has implicated and inspired the study of different

vaccine strategies. The selective pressure of the vaccine could increase the pressure of rare strains circulation and consequently reduce the effectiveness of the current vaccine.

In response to the surveillance reports of unusual strains with zoonotic potential carried out in the Latin American Region, little information is evidenced. Therefore, we consider urgent, the need to maintain molecular surveillance of rotavirus strains in the region; as well as the reinforcement in the maintenance and consolidation in the unification of the protocols of detection and characterization of rotavirus in the laboratories of Central America, the Caribbean and the rest of the countries of America, with the intention of evaluating the impact of vaccine in the future.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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