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# Recombination and Point Mutations in Type G Rotavirus Strains: The Challenges of Vaccine Development

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## 1. Introduction

Active immunity refers to the process of exposing the body to an antigen to generate an adaptive immune response: the response takes days/weeks to develop but may be long lasting—even lifelong. Wild infection with pathogenic agents (eg. Hepatitis A Virus) and subsequent recovery gives rise to a natural active immune response usually leading to lifelong protection. In addition, some infections can be prevented by immunization with vaccines.

The term “vaccine” is derived from the Latin word “vaccinus” which means “pertaining to cows” – a reflection on Jenner’s pioneering studies using cowpox vaccinia virus to prevent human smallpox (variola) as discussed previously (Stefan, 2005; Dunn, 1996). Vaccines take advantage of using relatively harmless foreign agents to evoke protective immunity for protection against several important pathogens. Vaccine development has its early roots in the work of Edward Jenner and Louis Pasteur, who discovered how to protect people from smallpox and developed a vaccine to protect from rabies, respectively.

All vaccines contain other substances (termed excipients) that are present because they improve the immune response (an adjuvant), are necessary for ensuring stability of the product (stabilizers and preservatives), are the vehicle for delivering vaccine (carrier) or are a residual of the manufacturing process (for example antibiotics or cell culture components).

Nowadays, many types of vaccines have been proposed and used in vaccine development: Live whole virus vaccines, Killed whole virus vaccines, Subunit vaccines (purified or recombinant viral antigen), Toxoid vaccines, Synthetic vaccines, and DNA vaccines. We will discuss these vaccine types one-by-one.

### 1.1 Live, attenuated virus vaccines

They are prepared from attenuated strains that are almost or completely devoid of pathogenicity but are capable of inducing a protective immune response. They multiply in the human host and provide continuous antigenic stimulation over a period of time. Primary vaccine failures are uncommon and are usually the result of inadequate storage or administration. Another possibility is interference by related viruses as is suspected in the case of oral polio vaccine in developing countries (Giammanco et al., 1988; Drozdov & Shirman, 1961; Katz & Plotkin, 1968). Several methods have been used to attenuate viruses for vaccine production such as the use of a related virus from another animal (cowpox to prevent smallpox), the administration of pathogenic or partially attenuated virus by an unnatural route, passage of the virus in an "unnatural host" or host cell (e.g. the 17D strain of yellow fever was developed by passage in mice and then in chick embryos (Norrby, 2007) and Polioviruses were passaged in monkey kidney cells (Chezzi et al., 1998) and measles in chick embryo fibroblasts (Katz, 1958), and the development of temperature sensitive mutants (Pringle, 1996).

### 1.2 Killed/Inactivated vaccines

The term killed generally refers to bacterial vaccines, whereas inactivated relates to viral vaccines (Levine et al., 1997). They were the easiest preparations to use. The preparation was simply inactivated. For viruses, the outer virion coat should be left intact but the replicative function should be destroyed. To be effective, non-replicating virus vaccines must contain much more antigen than live vaccines that are able to replicate in the host. Preparation of killed vaccines may take the route of heat or chemicals (Turner et al., 1970). The chemicals used include formaldehyde or beta-propiolactone (Lo Grippio, 1960; Gard, 1960). The traditional agent for inactivation of the virus is formalin (Weil & Gall, 1940; Kim & Sharp, 1967). Excessive treatment with this detergent can destroy immunogenicity whereas insufficient treatment can leave infectious virus capable of causing disease. Soon after the introduction of inactivated polio vaccine, there was an outbreak of paralytic poliomyelitis in the USA due to the distribution of inadequately inactivated polio vaccine (Prevots et al., 1996). This incident led to a review of the formalin inactivation procedure and other inactivating agents are available, such as beta-propiolactone. Another problem was that SV40 was occasionally found as a contaminant and there were fears of the potential oncogenic nature of the virus (Tam et al., 2004).

### 1.3 Subunit vaccines

Originally, non-replicating vaccines were derived from crude preparations of virus from animal tissues. As the technology for growing viruses to high titres in cell cultures advanced, it became practical to purify virus and viral antigens. It is now possible to identify the peptide sites encompassing the major antigenic sites of viral antigens, from which highly purified subunit vaccines can be produced. Increasing purification may lead to loss of immunogenicity, and this may necessitate coupling to an immunogenic carrier protein or adjuvant, such as an aluminum salt. Examples of purified subunit vaccines include the HA vaccines for influenza A and B (Bachmayer et al., 1976), and HBsAg derived from the plasma of carriers (Vyas et al., 1984). Subunit vaccines can be further subdivided into those where the antigen is produced using recombinant DNA technology and those based on normal bacteriological growth processes.

Virus proteins have been expressed in bacteria, yeast, mammalian cells, and viruses. *E. Coli* cells were first to be used for this purpose but the expressed proteins were not glycosylated, which was a major drawback since many of the immunogenic proteins of viruses such as the envelope glycoproteins, were glycosylated. Nevertheless, in many instances, it was demonstrated that the non-glycosylated protein backbone was just as immunogenic. Recombinant hepatitis B vaccine is the only recombinant vaccine licensed at present (Yap et al., 1992). An alternative application of recombinant DNA technology is the production of hybrid virus vaccines. The best known example is vaccinia (Smith et al., 1983). The recombinant virus vaccine can then multiply in infected cells and produce the antigens of a wide range of viruses. The genes of several viruses can be inserted, so the potential exists for producing polyvalent live vaccines (Hauser et al., 1988; Hilleman, 1987). HBsAg, rabies, HSV and other viruses have been expressed in vaccinia (Mackett et al., 1985; Panicali et al., 1983; Paoletti et al., 1984; Perkus et al., 1985; Rice et al., 1985; Smith et al., 1983; Kieny et al., 1984; Wiktor et al., 1984).

#### **1.4 Toxoid vaccines**

Certain pathogens cause disease by secreting an exotoxin: these include tetanus, diphtheria, botulism and cholera. For these bacteria that secrete toxins, or harmful chemicals, a toxoid vaccine might be the answer. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have found that they can inactivate toxins by treating them with formalin, a solution of formaldehyde and sterilized water. Such "detoxified" toxins, called toxoids, are safe for use in vaccines. When the immune system receives a vaccine containing a harmless toxoid, it learns how to fight off the natural toxin. The immune system produces antibodies that lock onto and block the toxin. Vaccines against diphtheria and tetanus are examples of toxoid vaccines (Bizzini et al., 1970; Alouf, 1987). These vaccines are: safe because they cannot cause the disease they prevent as there is no possibility of reversion to virulence; the vaccine antigens are not actively multiplying, they cannot spread to unimmunized individuals; they are usually stable and long lasting as they are less susceptible to changes in temperature, humidity and light which can result when vaccines are used out in the community.

#### **1.5 Synthetic peptides**

The development of synthetic peptides that might be useful as vaccines depends on the identification of immunogenic sites (Milich, 1990; Hans et al., 2006; Dorothea, 1993; Jonathan, 1987). Synthetic peptide vaccines have been successfully developed for the immunoprophylaxis of infection with foot-and-mouth disease virus (Bittle et al., 1982; Brown, 1990), type A influenza virus (Muller et al., 1982), and poliovirus (Emini et al., 1983). Synthetic peptide vaccines would have many advantages. Their antigens are precisely defined and free from unnecessary components which may be associated with side effects. They are stable and relatively cheap to manufacture. Changes due to natural variation of the virus can be readily accommodated, which would be a great advantage for unstable viruses.

#### **1.6 DNA vaccines**

The demonstration by Wolff and colleagues in 1990 (Wolff et al., 1990) that protein could be expressed following direct inoculation of plasmid DNA into muscle tissue unveiled an

exciting, new era in vaccinology and gene therapy. DNA-based vaccination offers a number of advantages over other methods of immunization. It is particularly attractive compared to conventional administration of a preformed protein antigen (Ag) because the immunogen is actively synthesized *de novo* in cells transfected with DNA. The principle of DNA vaccination has been demonstrated for a variety of bacterial, viral and parasitic diseases (Ulmer et al., 1993). Immune responses have been generated by DNA vaccination against a very wide variety of viral, bacterial and protozoal pathogens and toxins (Donnelly et al., 1994; King et al., 1998). Immune responses against influenza viruses have been demonstrated in chickens, mice, ferrets and non-human primates. For humans, the major concern about DNA vaccines is whether the plasmid DNA integrates into the genome randomly, potentially leading to insertional mutagenesis. In addition, the formal acceptance of this novel technology as a new modality of human vaccines depends on the successful demonstration of its safety and efficacy in advanced clinical trials. Several trials evaluated the efficacy of a DNA vaccine targeting human immunodeficiency virus type 1 (HIV-1) for therapeutic and prophylactic applications (MacGregor et al. 1998). However, the results of these early clinical trials were disappointing. The DNA vaccines were safe and well tolerated, but they proved to be poorly immunogenic.

Vaccines may be monovalent (also called univalent) or multivalent (also called polyvalent). A monovalent vaccine is designed to immunize against a single antigen or single microorganism. A multivalent or polyvalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms. In certain cases a monovalent vaccine may be preferable for rapidly developing a strong immune response.

## 2. Rotavirus infection and common associated-genotypes

Infectious acute diarrhea is a significant cause of morbidity and mortality of infants in developing and developed countries and constitutes a major public health problem worldwide. It is estimated that in developing countries (in Africa, Asia and Latin America) 744 million to 1 billion cases of diarrhea and 2.4 to 3.3 million deaths occur annually among children less than 5 years of age, corresponding to 6600 to 9000 deaths per day (Linhares & Bresee, 2000). The viruses are the most common aetiology of these diseases, especially in developed countries, where they cause more than 80% of the cases of acute diarrhea. The most common viral causes of gastroenteritis are rotaviruses and calicivirus (norovirus).

Rotavirus, a member of the *Reoviridae* family, is a highly contagious virus that causes severe and acute dehydrating diarrhea in infants and young children as well as other young animals worldwide (Dhama et al., 2009; Kapikian et al., 2001). Mature rotavirus, non-enveloped virions, contains an 11-segmented, double-stranded RNA (dsRNA) genome enclosed in a triple-layered protein capsid (Hoshino & Kapikian, 2000). The segmented nature of the genome allows rotaviruses to reassort *in vitro* and *in vivo* (Greenberg et al., 1981; Kalica et al., 1981; Gombold & Ramig, 1986).

A dual nomenclature has been used to differentiate rotavirus strains based on their serotype specificities, which are carried by the two outer capsid antigens, VP7 and VP4 (Estes & Kapikian, 2007).



The high disease burden motivated major efforts to develop a suitable rotavirus vaccine. However, the vaccine efficacy is being challenged by the extensive strain diversity of the rotaviruses (Estes, 2001; Green et al., 1987, 1988; Hoshino et al., 1994; Kapikian et al., 2001; Linhares et al., 1999).

Reverse-transcription polymerase chain reaction (RT-PCR) is the most widely used method for rotavirus characterization in surveillance studies. Molecular methods have allowed the detection of many rotavirus G-types (Banyai et al., 2003; Cubitt et al., 2000; Cunliffe et al., 1999; Das et al., 1993a, 2003; Gentsch et al., 1996; Gouvea et al., 1994; Pongsuwanna et al., 2002). Because of the natural variation in the rotaviral gene sequences, G-type-specific-primer based RT-PCR led to the genotyping failure (Adah et al., 1997; Iturriza-Gómara et al., 2000, 2004a; Maunula & von Bonsdorff, 1998; Rahman et al., 2005b). In addition, the accumulation of point mutations through genetic drift at the type-specific primer binding sites has resulted in failures to type strains or in mistyping. For example, the accumulation of point mutations at the G9 type-specific primer binding site was reported as having an impact for the efficient genotyping of rotaviruses (Martella et al., 2004; Santos et al., 2003). Moreover, some nucleotide identity between genotypes lead to primer cross-reactivity between rotavirus strains as the case of rotavirus G3 and G10 strains using primers developed by Gouvea et al. (1990) as discussed previously (Iturriza-Gómara et al., 2004b).

In order to overcome this problem, a modified classification system for VP4, VP7, and NSP4, and a novel classification system for VP1, VP2, VP3, VP6, NSP1, NSP2, NSP3, and NSP5/6 were proposed to be used for international standardization and implementation (Matthijnssens et al., 2008a, 2008b).

Actually, VP4 and VP7 are the main targets for vaccine development strategies. In the present review we will focus on the diversity of VP7 among rotavirus strains and the effect of this variability upon vaccine development.

Similar to most of the group A rotaviruses, the VP7 nucleotide sequence is 1062 nucleotides long. The ORF starts at nucleotide 49 with an AUG (ATG) start codon and ends at nucleotide 1029 with a UAG (TAG) termination codon, comprising 981 nucleotides (Estes & Cohen, 1989; Bellamy & Both, 1990).

The gene segment coding for the VP7 glycoprotein is the basis for genotyping group A rotaviruses into at least fifteen G-genotypes. Studies of intragenotype diversity led to subdivision of the G genotypes into several lineages (two major lineages, designated I and II) and sublineages, distinctly identified by unique genomic as well as epidemiological features. Lineage I was further subdivided into four sublineages, Ia-Id.

Genotypes G1, G2, G3, G4 and G9 are the most common G-types in humans (Gentsch et al., 1996; Liprandi et al., 2003; Martella et al., 2003; Okada et al., 2000; Rao et al., 2000; Sereno & Gorziglia, 1994). Nevertheless, over past decades, type G1 rotaviruses have been the most widespread genotype causing acute gastroenteritis in children from many countries covering all continents of the world (Santos & Hoshino, 2005). Type G2 rotavirus represents a different genogroup which appears to have a cyclic pattern of occurrence and yet little information is available about its genetic variability. Type G3 rotavirus have been found in a broad range of host species, including humans, monkeys, dogs, cats, horses, rabbits, mice, sheep and pigs (Martella et al., 2001; Andrej et al., 2008; Hoshino et al., 1984; Paul et al.,

1988; Fitzgerald et al., 1995). The G9 rotavirus was first reported in the United States in the early 1980s (Clark et al., 1987). It represents the fifth most common G genotype of rotavirus infections throughout the world (Gentsch et al., 2005; Santos & Hoshino, 2005, Khamrin et al., 2006).

### 3. Rotavirus vaccines

#### 3.1 Monovalent animal and human rotavirus vaccines

*Monovalent animal rotavirus vaccines.* Research to develop a safe, effective rotavirus vaccine began in the mid-1970s, when investigators demonstrated that previous infection with animal rotavirus strains protected laboratory animals from experimental infection with human rotaviruses (Zissis et al., 1983). Researchers thought that live animal strains that were naturally attenuated for humans, when given orally, might mimic the immune response to natural infection and protect children against disease. Three nonhuman rotavirus vaccines, two bovine rotavirus strains, RIT 4237 (P6[1]G6) and WC3 (P7[5]G6), and a simian (rhesus) rotavirus reassortant vaccine (RRV) strain (P[3]G3), were studied (Christy et al., 1988; Clark et al., 1988; Vesikari et al., 1984). These vaccines demonstrated variable efficacy in field trials and gave particularly disappointing results in developing countries (Hanlon et al., 1987; Lanata et al., 1989; Penelope, 2008). Another monovalent, ovine strain vaccine produced by the Lanzhou Institute and licensed in China in 2000 (Lanzhou lamb rotavirus vaccine (LLR); P[12], G10) was available in some parts of China (World Health Organization [WHO], 2000). Few data are available about the effectiveness of this vaccine and it was not included in national immunization programs in China or elsewhere. Finally, monovalent animal strain vaccines have been mostly abandoned.

*Monovalent human rotavirus vaccines.* Rotarix®, developed by GlaxoSmithKline Biologicals, Belgium, is a monovalent, P1A[8] G1 rotavirus derived from a human G1 strain (89-12) that yielded high efficacy in early trials in the US and Finland (Bernstein et al., 2002). Its Efficacy has been confirmed in many countries (Ruiz-Palacios et al., 2006; De Vos et al., 2004).

RV3 neonatal strain vaccine, a P2A[6] G3 strain, was first isolated from newborns at the Children's Hospital in Melbourne, Australia (Barnes et al., 1997). Neonates infected with this rotavirus strain in hospital nurseries usually were asymptomatic and were later protected against severe disease in early childhood. However, serum immune responses were poor (Das et al., 1993a). Many attempts were undertaken to increase the titer of this vaccine and return to clinical trials.

Another two Indian neonatal strain vaccines 116E and I321 were proposed as candidate vaccines (Das et al., 1993a, 1993b; Iturriza-Gómara et al., 2004a). Both strains are in preclinical development and human trials are being planned in India, but with the new finding of I321-like strains causing disease in children, both careful epidemiological studies and safety monitoring will be essential prior to licensure.

#### 3.2 Polyvalent rotavirus vaccines

In view of the inconsistency of protection from monovalent animal rotavirus-based vaccines, vaccine development efforts began to use either naturally attenuated human rotavirus strains or reassortant rotavirus strains bearing a human rotavirus gene for the VP7 protein

together with the other 10 genes from an animal rotavirus strain (Midthun & Kapikian, 1996). The next generation of vaccines was formulated to include more than one rotavirus G serotype to provide heterotypic as well as homotypic immunity. The ability of rotaviruses to reassort during mixed infections in vitro allowed the production of reassortant vaccines, termed the “modified Jennerian” approach (Kapikian et al., 1996b). Reassortant viruses contain some genes from the animal rotavirus parent and some genes from the human rotavirus parent. VP7 was thought to be important for protection; therefore, human-animal reassortant rotaviruses for use as vaccines included human VP7 genes to provide protective immune responses.

*Quadrivalent RRV-based rhesus-human reassortant vaccine.* A RotaShield was the first multivalent live oral reassortant vaccine (tetraivalent, reassortant rhesus-human rotavirus vaccine, [RRV-TV]) contained a mixture of four virus strains representing the most commonly seen G types, G1 to G4: three rhesus-human reassortant strains containing the VP7 genes of human serotypes G1, G2, and G4 strains were substituted for the VP7 gene of the parent RRV, and the fourth strain comprised serotype G3 of rhesus RRV (Kapikian et al., 1996a). RRV-TV was extensively evaluated in field trials in the United States, Finland, and Venezuela and proved highly effective (80 to 100%) in preventing severe diarrhea due to rotavirus in each of these settings (Joensuu et al., 1997; Perez-Schael et al., 1997; Rennels et al., 1996; Santosham et al., 1997). Due to the proven efficacy, the RRV-TV vaccine was licensed in August 1998 for routine use in children in the United States at 2, 4, and 6 months of age (Centers for Disease Control and Prevention [CDC], 1999b). Later, this vaccine was withdrawn from the market in 1999 as a consequence of vaccine-associated intussusception in several cases of vaccinated infants (CDC, 1999a).

*Pentavalent WC3-based bovine-human reassortant vaccine.* Rotateq®, manufactured by Merck, Inc, USA, is a pentavalent vaccine containing five reassortants representing the common human VP7 types, G1-4 and the most common VP4 type, P[8] (CDC, 2006). A large efficacy trial with Rotateq® has been completed, which found 74 and 98% efficacy against all and severe disease, respectively and has efficacy against each of the common circulating serotypes. Compared with the rhesus reassortants, the bovine-human reassortants appear to cause less fever while maintaining immunogenicity (Clark et al., 2004). A large safety trial found no evidence of an increased risk of intussusceptions among vaccinees compared with placebo recipients (Vesikari et al., 2006).

Both RotaTeq and RotaRix have been shown to be effective against rotavirus gastroenteritis, however on March 22, 2010 the Food and Drug Administration (FDA) recommended that the use of the Rotarix vaccine be suspended in the United States because of some DNA from a porcine (pig) virus (porcine circovirus type 1) detected in the vaccine. Subsequently, some DNA from this and another porcine virus were also detected in Rotateq. On May 14, 2010 the FDA updated their recommendations for the use of rotavirus vaccines based on a review of the literature and the input from experts. The RotaTeq vaccine was proven to be effective in many countries such as Finland (Vesikari et al., 2010).

Whatever the type of vaccine and strategy of its development, the introduction of a new vaccine faces many hurdles, including cost, production capabilities, safety, and other programmatic issues. For rotavirus vaccines, while there is clearly a need, there are also additional challenges raised by the emergence of new rotavirus genotypes.



#### 4. The prevalence of uncommon G-type rotaviruses and challenges for vaccine development

Genetic variability has been observed for all RNA viruses examined, and their potential for rapid evolution is increasingly recognized as the basis of their ubiquity and adaptability (Holland et al., 1992; Kilbourne, 1991). The molecular mechanisms underlying RNA virus variations are: mutation, homologous and non homologous recombinations, and genome reassortment in viruses with a segmented genome such as reoviruses. The genetic evolution of viruses is an important aspect of the epidemiology of viral diseases and sometimes causes problems in the development of successful vaccines.

The effectiveness of rotavirus vaccines will be dependent upon the immunity conferred against prevalent and emergent variants causing severe diarrhoeal disease. The global effort toward the prevention of rotavirus disease to be successful, special efforts will be required in countries where new genotypes were detected such as G5, G6, G8, G10, G11, and G12 (Figure 1). Nucleotide analysis using CLUSTAL X (version 1.8) of VP7 gene of these uncommon rotaviruses showed high degree of variability with the common G-type viruses (Figure 2). Genomic similarities between rotaviruses from different animal species are regarded as evidence of interspecies transmission of rotaviruses that may occur as a whole virion or genetic reassortment. The high variability of viral sequences due to genetic reassortment and nucleotide substitution are considered the most important mechanisms of evolution for rotaviruses. The antigenic variation within a serotype was known as a mechanism by which variants of rotavirus emerge to escape host immunity. This variability represents considerable potential for impaired vaccine efficacy.

The available information in literature showed that type G5 rotavirus is an important and commonly detected pathogen of swine and has also been identified in equine (Kapikian et al., 2001). However, in 1994, Gouvea and collaborators first demonstrated the occurrence of rotavirus genotype G5 among Brazilian children with diarrhea (Gouvea et al., 1994; Timenetsky et al., 1997). The detection of rotavirus G5 among children with diarrhea has also been reported in Argentina and Paraguay, indicating the spread of this virus across South America (Coluchi et al., 2002; Bok et al., 2001). In addition, the detection of type G5 rotavirus was reported in Cameroon (Esona et al., 2004). Another genotypes, type G6 and G10 strains have been isolated from humans (Dunn et al., 1993; Gerna et al., 1992, 1994; Armah et al., 2010). Although type G6 is the commonest rotavirus G type found in cows and at low frequency in sheep and goats (Kapikian et al., 2001), it was detected from hospitalized children with acute gastroenteritis in Italy during 1987–1988 (Gerna et al., 1992), Australia (Palombo & Bishop, 1995; Cooney et al., 2001), India (Kelkar & Ayachit, 2000), USA (Griffin et al., 2002), Belgium (Rahman et al., 2003), and Hungary (Banyai et al., 2004; Banyai et al., 2003). Type G8 virus, which can be found in cows at relatively high frequency (Kapikian et al., 2001), was first isolated in a study performed between 1979 and 1981, from stool specimens collected from children with diarrhea in Jakarta and Medan (Indonesia) (Hasegawa et al., 1984), Kenya (Nokes et al., 2010), and other countries such as Finland, Italy, Nigeria, Brazil, Malawi, South Africa, Egypt, Australia, the United States, and the United Kingdom (Adah et al., 1997, 2001; Cunliffe et al., 1999; Cunliffe et al., 2000; Gerna et al., 1990; Holmes et al., 1999; Palombo et al., 2000; Parwani et al., 1993; Rao et al., 2000; Santos et al., 1998; Steele et al., 1999). Type G11 rotaviruses are believed to be circulating in pigs, albeit in low numbers mainly in Mexico in 1983 and in Venezuela in 1989 (Ciarlet et al.,

1994; Ruiz et al., 1988). Later, several reports have described the detection of G11 rotavirus strains from humans in India (Banerjee et al., 2007), Bangladesh (Rahman et al., 2005a; Rahman et al., 2007), Nepal (Uchida et al., 2006), Ecuador (Banyai et al., 2009), and South Korea (Hong et al., 2007). Type G12 rotavirus was detected in stool specimens collected from children with diarrhea in the Philippines (Taniguchi et al., 1990), Thailand (Pongsuwanna et al., 2002), USA (Griffin et al., 2002), India (Das et al., 2003), Japan (Shinozaki et al., 2004), Korea (Cheon et al., 2004), Argentina (Castello et al., 2004), Malawi (Cunliffe et al., 2009), and Saudi Arabia (Kheyami et al., 2008). Type G12 has not been detected in animals other than humans.

Furthermore, recombination between human and animal rotavirus constitutes another challenge for vaccine development. Many G-type rotaviruses are considered to be reassortants between human and bovine viruses such as the case of G8 rotaviruses (Browning et al., 1992; Ohshima et al., 1990; Adah et al., 2003). Reassortment among bovine, porcine and human rotavirus strains was also reported (Park et al., 2011).

Other important issues need to be discussed concerning the potential that the vaccine strains themselves may either cause disease or reassort with wild-type rotavirus to produce a virulent strain as reported for RotaTeq reassortant strain in association with acute gastroenteritis (Payne et al., 2010). In addition, the predominance of G2 rotaviruses in Brazil following the introduction of Rotarix (Gurgel et al., 2007; Nakagomi & Nakagomi, 2009) and the predominance of G3 rotaviruses after vaccine introduction in USA after a Surveillance From 2005 to 2008 (Hull et al., 2011) may enhance the study the effectiveness of the available vaccines and the growing need to evaluate their use.

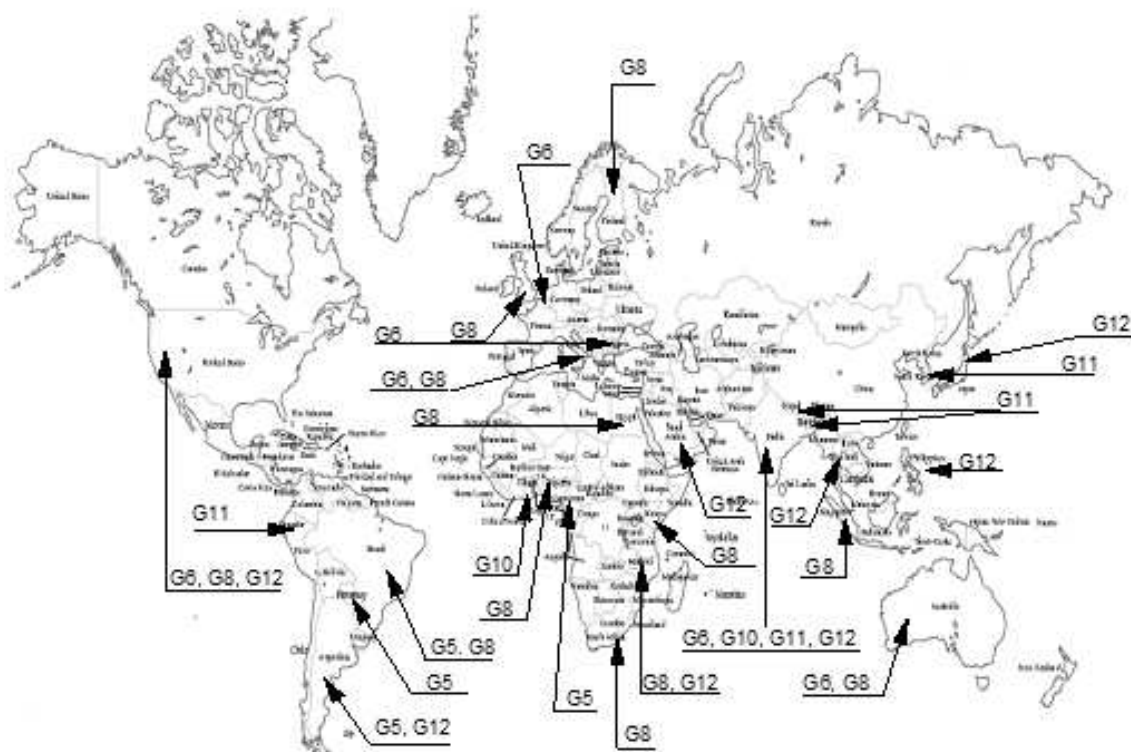


Fig. 1. Distribution of uncommon rotavirus genotypes in the world. The countries where the uncommon rotavirus genotypes were detected are shown by arrows.

|     |             |            |             |            |              |            |            |            |             |            |
|-----|-------------|------------|-------------|------------|--------------|------------|------------|------------|-------------|------------|
| G1  | GGCTTTAAAA  | GAGAGAATTT | CCGTCCTGGCT | AACGGTTAGC | TCCITTTTAAAT | GTATGGTATT | GAATATACCA | CAATTCTAAT | CTTTCTGATA  | TCATTCATTC |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | TACTCAACTA  | TATATTAATA | TCAGTGACCC  | AAATAATGGA | CTACATCATA   | TATAGATTTT | TGTTAATTTT | TGTAGCATT  | TTTGCCTTAA  | CTAAAGCTCA |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | GAACTATGGA  | CTTAATATAC | CAATAACAGG  | ATCAATGGAT | ACTGTATACT   | CCAACCTAC  | TCAAGAAGGA | GTATTTCTAA | CATCCACATT  | ATGTTTGTAT |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | TATCCAACCTG | AAGCAAGTAC | TCAAATCAGT  | GACGGTGAAT | GGAAAGACTC   | ATTATCACAA | ATGTTTCTTA | CGAAAGGTTG | GCCAAACAGGA | TCAGTCTATT |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | TCAAAGAGTA  | CTCAATATTT | GTTGATTTTT  | CCGTTGACCC | ACAATATAT    | TGCGATTATA | ATTTAGTACT | AATGAAGTAT | GATCAAAATC  | TTGAATTAGA |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | ATATCAATGG  | GATCATCATG | TACTGTGAAA  | GTGTGTCCAC | TGAATACACA   | AACGTTAGGA | ATAGTTGTC  | AAACACGAA  | TGTAGACTCA  | TTTGAACACG |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |
| G1  | TTGCTGAGAA  | TGAAAATA   | GCTATAGTAG  | ACGTCGTTGA | TGGGATAAAT   | CATAAATAA  | ATTTGACAA  | TACGACATGT | ACTATTCGAA  | ATTGTAAGAA |
| G2  |             |            |             |            |              |            |            |            |             |            |
| G3  |             |            |             |            |              |            |            |            |             |            |
| G4  |             |            |             |            |              |            |            |            |             |            |
| G9  |             |            |             |            |              |            |            |            |             |            |
| G6  |             |            |             |            |              |            |            |            |             |            |
| G8  |             |            |             |            |              |            |            |            |             |            |
| G10 |             |            |             |            |              |            |            |            |             |            |
| G11 |             |            |             |            |              |            |            |            |             |            |
| G12 |             |            |             |            |              |            |            |            |             |            |

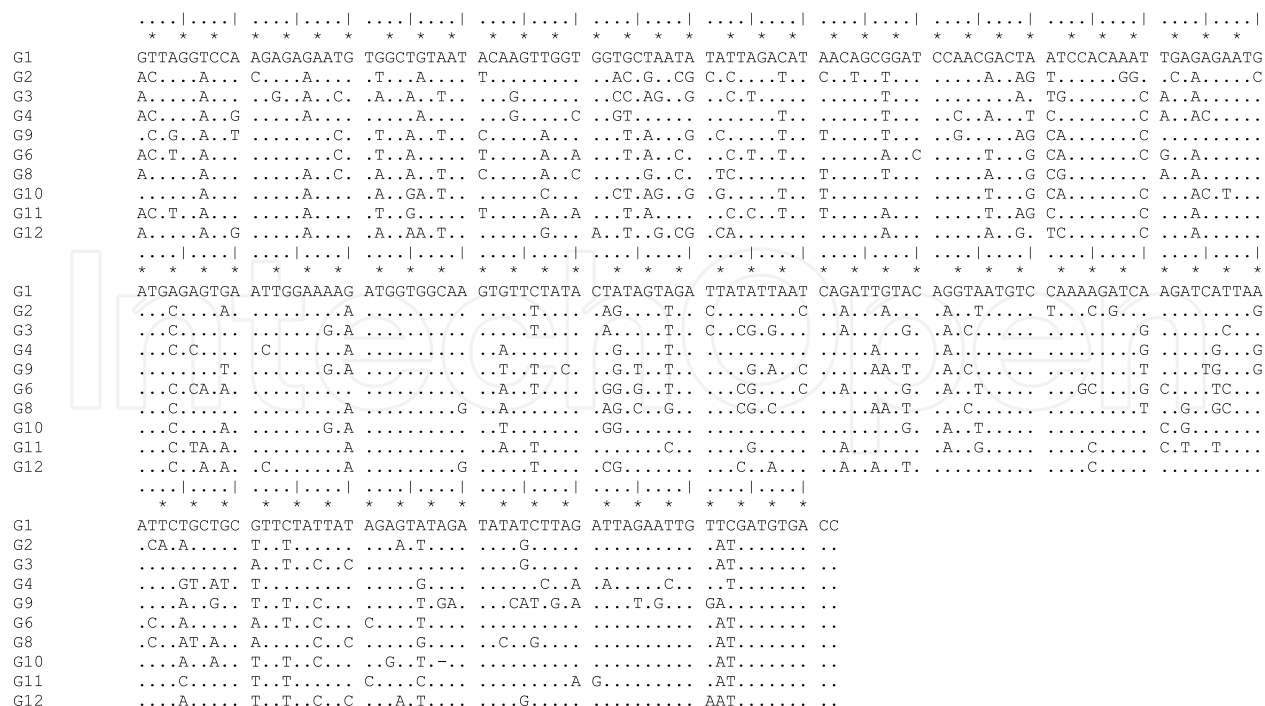


Fig. 2. Nucleotide analysis of rotavirus genotypes. Points indicated no nucleotide change. Nucleotide difference was shown by alphabetical marks. The start codon was underlined at position 49.

In addition, there is evidence of intragenic recombination in rotavirus VP7 genes. The existence of intragenic recombinations between interlineage and intersublineage in G1 rotaviruses was demonstrated (Tung et al., 2007). This variability has led to nucleotide mismatches between the actual VP7 gene and primers and consequently a failure on the detection of the G1 strains (Parra & Espinola, 2006). Other studies have reported the detection of possible new distinct sublineages for G2 genotype (Mascarenhas et al., 2010). Recombination between human rotaviruses and animal rotaviruses were well recognized in G3 rotaviruses (Nishikawa et al., 1989) and the genetic variation in their VP7 gene was reported in China and Japan accompanied with change also on the amino acid level (Wen et al., 1997). In addition, it has been postulated that amino acid substitutions at positions 96 and 213 might be involved in the emergence of G3 rotavirus strains in Japan, China, and Russia from 2001 to 2004 (Trinh et al., 2007). The diversification of rotavirus strains in phylogenetic lineages in G9 strains was reported previously (Santos et al., 2002; Hoshino et al., 2004; Cao et al., 2008; Pattara et al., 2009). Although one amino acid change at position 208 in an antigenic region C of G9 rotaviruses VP7 gene was reported, it is not clear whether this change affected the nature of the viruses in terms of antigenicity, infectivity or pathogenicity.

## 5. Conclusion

As a conclusion, the use of vaccines with broad and consistent serotype coverage would be important to help decrease the burden of rotavirus in countries with new emergent genotypes. The emergence of new rotavirus strains stresses the importance of a better knowledge of their genotypes and their mechanisms of transmission. Hence the importance



of setting up a vaccine design strategy as well as surveillance programs that should detect the diversity of rotavirus strains before, during and after the introduction of a rotavirus vaccine (Palombo, 1999) in order to detect the possible appearance of a mutants escape strains that probably reflect a selective pressure induced by the vaccine and eventually may pose a challenge to vaccine strategies. Further studies need to be carried out in order to elucidate the mechanism(s) behind the genetic recombination of rotaviruses and the emergence of new genotypes.

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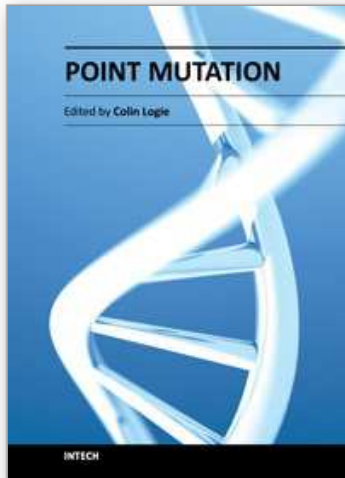
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## **Point Mutation**

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This book concerns the signatures left behind in chromosomes by the forces that drive DNA code evolution in the form of DNA nucleotide substitutions. Since the genetic code predetermines the molecular basis of life, it could have been about any aspect of biology. As it happens, it is largely about recent adaptation of pathogens and their human host. Nine chapters are medically oriented, two are bioinformatics-oriented and one is technological, describing the state of the art in synthetic point mutagenesis. What stands out in this book is the increasing rate at which DNA data has been amassed in the course of the past decade and how knowledge in this vibrant research field is currently being translated in the medical world.

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