Molecular characterization of genotype G6 human rotavirus strains detected in Italy from 1986 to 2009

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A B S T R A C T

Group A human rotavirus (HRV) strains with a bovine-like (G6) major outer capsid protein VP7 were first detected in Palermo, Italy, in the late 1980s, and subsequently worldwide. During a 25-year rotavirus surveillance period, additional HRV G6 strains, associated with either a P[9] or P[14] VP4 genotype, have been detected sporadically, but repeatedly, in Palermo. Whether these G6 HRVs were transmitted to humans directly from an animal reservoir or could have circulated at low prevalence in susceptible individuals is uncertain. Upon sequence analyses of the VP7, VP4, VP6, NSP4 and NSP5 gene segments, all the Italian HRV strains displayed a conserved genotype constellation, G6-P[9]/[14]-I2-E2-H3. Intra-genotypic lineages and/or sub-lineages were observed among the various HRV strains, with some lineage/sublineage combinations being retained over time. Interestingly, two epidemiologically unrelated G6[P9] viruses, collected in the same rotavirus season, were found to have a clonal origin. In conclusion, our results indicate not only diverse origin of animal derived G6 HRVs in Palermo but also suggest human-to-human transmission of certain strains.

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1. Introduction

Group A rotaviruses (RVs) are important enteric pathogens in young children and livestock animals worldwide (Estes and Kapikian, 2007). Complete RV virions are approximately 100 nm in diameter, icosahedral, triple-layered, and non-enveloped. The genome consists of 11 segments of double-stranded (ds)RNA (Estes and Kapikian, 2007). The outer protein layer is made up by two proteins, the spike and viral attachment protein VP4 and the major shell glycoprotein VP7, both of which form the basis for a binomial nomenclature. The VP4 is referred to as the P (protease-sensitive) antigen, and the VP7 as the G (glycosylated) antigen (Estes and Kapikian, 2007). The majority (>90%) of medically important human RV (HRV) strains belong to five major surface G and P genotype combinations, G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] (Ciarlet and Schodnel, 2009; Matthijnssens et al., 2008b; Santos and Hoshino, 2005). Strains with unusual G/P genotype combinations, mostly considered animal-like (zoonotic) RV strains, are usually detected in a sporadic fashion in humans; however, they can reach an epidemiological relevance in some geographical settings, likely as the result of a process of adaptation via accumulation of mutations or exchange of genomic segments via reassortment (Martella et al., 2010). Several unusual and emerging HRVs (G8, G10, G11 and G12) are believed to have an animal origin and to have been introduced into the human population through multiple events of interspecies transmission followed by gene reassortment (Ciarlet et al., 2008; Martella et al., 2010; Matthijnssens et al., 2008c, 2010b; Santos and Hoshino, 2005). In an attempt to standardize RV classification and to better understand the evolutionary mechanisms behind the emergence of novel RV strains, a new classification system based on a nucleotide cut-off value for open reading frame (ORF) of each of the 11 gene segments, has been proposed by the Rotavirus Classification Working Group (RCWG), assigning a one-letter code to each of the gene segments, and successive numbers for the different genotypes (Matthijnssens et al., 2008a,b). Upon full-length genome sequence analyses a close evolutionary relationship has been observed between human Wa-like and porcine RV strains, and between human DS-1-like and bovine RV strains, suggesting that these two major human genogroups might have an animal origin (Matthijnssens et al., 2008a). The increasing number of sequence data of field strains continuously deposited to databases

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and the capability to produce laboratory strains through in vitro cultivation and reassortment aided by newly established reverse genetics system require new standards and uniformity in rotavirus nomenclature and prompted the RCWG to propose a novel standardized system to name RV strains according to the following scheme: RV group/species of origin/country of identification/ common name/year of identification/G- and P-type (Matthijssens et al., in press).

Bovine-like HRV G6 strains, RVA/Human-tc/ITA/PA151/1987/G6P[9] and RVA/Human-tc/ITA/PA169/1988/G6P[14], respectively, were first identified in 1987 and 1988 from children hospitalised with acute gastroenteritis in Palermo, Italy (Gerna et al., 1992). Since then, G6P[9] and G6P[14] HRV strains have been detected in children with gastroenteritis from several countries (Bányai et al., 2003, 2009a, b; Chandrasahen et al., 2010; Cooney et al., 2001; Griffis et al., 2002; Martini et al., 2008; Matthijssens et al., 2009a). In addition, G6 HRVs with other P types have been identified in several parts of Europe (G6P[4], G6P[6], G6P[8], and G6P[11]) (Iiturritza-Gomara et al., 2010; Rahman et al., 2003). To date complete genomes have been determined for a discrete number of G6 HRVs, including six G6P[14] strains from Australia, Belgium, Hungary and Italy, one G6P[9] strains from the USA, and a single probable human-animal reassortant G6P[6] strain from Belgium (Heiman et al., 2008; Matthijssens et al., 2008d, 2009a). A close genetic relatedness between human G6P[14] strains from a global collection and animal G6P[14] and G8P[14] viruses (from ruminants and ungulates) has been described, suggesting that these animals may act as reservoirs of G6 RV strains for humans (Bányai et al., 2009a, b; 2010; Matthijssens et al., 2009a).

Uninterrupted surveillance for HRVs has been carried out in Palermo, Italy, for 25 years, thus providing a unique archival collection suitable for the study of epidemiologic trends and evolution of HRVs (Arista et al., 2006; De Grazia et al., 2007, 2009). During this surveillance activity, a total of seven G6 HRV strains have been detected and found to possess either a P[9] or P[14] VP4 genotype specificity. In order to gather information on the genetic constellation of HRV G6 strains, and to investigate the genetic relationships between the HRV G6 strains and other human and animal RVs, the sequence of the VP7, VP4, VP6, NSP4 and NSP5 genes was determined.

2. Materials and methods

The seven Italian G6 HRV strains were detected over a 15 years time span from 1987 to 2003. They were collected in November 1987 (RVA/Human-tc/ITA/PA151/1987/G6P[9]), February 1988 (RVA/Human-tc/ITA/PA169/1988/G6P[14]), January 1989 (RVA/Human-wt/ITA/PA5/1989/G6P[14]), November 1993 (RVA/Human-wt/ITA/PA27-GV1/1993/G6P[9]), May 2002 (RVA/Human-wt/ITA/P77/2002/G6P[14]) and November 2003 (RVA/Human-wt/ITA/PA17/2003/G6P[9] and RVA/Human-wt/ITA/PA43/2003/G6P[9]). All the strains were detected in stool samples from children <5 years of age, who were hospitalised with acute gastroenteritis. The PA151 and PA169 strains were successfully adapted to growth in MA104 cell cultures according to previously reported procedures (Gerna et al., 1992). The G6 typing was performed by EIA using type 1-2-3-4-5-6- and 9-specific neutralizing monoclonal antibodies reactive with viral protein VP7 or by RT-PCR for VP7-genotyping (Arista et al., 1990; Gouvea et al., 1990).

For this study the VP7, VP4, VP6, NSP4 and NSP5 genes of HRV strains PA5-89, PA27-GV1-93, PA77-02, PA17-03 and PA43-03 were amplified by RT-PCR (Gentsch et al., 1992; Gouvea et al., 1990; Iiturritza-Gomara et al., 2002, 2004; Lee et al., 2000; Mohan and Atteya, 2001). The PCR amplicons generated were used to obtain partial gene sequences whose length varied from 715 to 843 nucleotides (nt) for VP4, from 232 to 247 nt for VP6, from 950 to 1026 nt for VP7, from 631 to 722 nt for NSP4 and from 480 to 588 nt for NSP5. Sequence alignment was performed using CLUSTAL W (Thompson et al., 1994) and phylogenetic analysis was carried out using the software MEGA 4.0 (Kumar et al., 2004). For the purpose of comparison and completeness, the sequences of the prototype G6 HRV strains PA151-87 and PA169-88 were retrieved from GenBank (Gerna et al., 1994; Matthijssens et al., 2009a; Nakagomi et al., 1993), with the exception of the VP6 and NSP5 gene sequences of strain PA151-87, which were determined in this study. The accession numbers of the nucleotide (nt) sequences obtained in this study are as follows: JF793931–JF793936 (VP6), JF793942–JF793946 (VP7), JF793937–JF793941 (VP8*), EU659855, JF793926–JF793930 (NSP4) and EU659852, JF793921–JF793925 (NSP5) for the Italian HRV G6 strains, respectively.

3. Results and discussion

During a 25-years uninterrupted surveillance for HRVs conducted in Palermo, Italy, a total of seven G6 strains were identified. The Italian G6 HRV strains displayed a conserved genomic constellation, G6-P[9]/P[14]-I2-E2-H3, differing only in the VP4-coding gene. However, upon phylogenetic analysis, a more complex picture emerged. For VP7, the strains belonging to genotype G6 have been divided into eight (I-VIII) major lineages (Fig. 1a) based on this and previous studies (Chandrasahen et al., 2010; Rahman et al., 2003). The Italian G6P[9] HRV strains clustered in G6-lineage I together with HRV strains isolated in USA (RVA/Human-tc/USA/Se584/1998/G6P[9]) (Belgium (RVA/Human-wt/BEL/B1711/2002/G6P[6]), Hungary (RVA/Human-wt/HUN/Hun8/1998/G6P[9]) and France (RVA/Human-x/FR/RA353/ XXXX/G6P[9]), while the HRV G6P[14] strains segregated in G6-lineage II together with other HRV strains isolated in Italy (RVA/Human-tc/ITA/111-05-27/2005/G6P[14]) (Australia (RVA/Human-tc/AUS/MG6/1993/G6P[14]), Australia (RVA/Human-tc/AUS/MG6/1993/G6P[14]), France (RVA/Human-tc/AUS/MG6/1993/G6P[14]), Belgium (RVA/Human-tc/19025/1997/G6P[14]) and Hungary (RVA/Human-wt/HUN/BP1879/2003/G6P[14]) and with animal RVAs identified in South Africa (RVA/Goat-tc/ZAF/Cap455/XXX/G6P[14] and RVA/antilope-wt/ZAF/RC-18/2008/G6P[14]). A number of sub-lineages within G6 lineages I and II could be further discriminated (1a to Id and lla to lle) (Fig. 1a). Most bovine RVs, including the G6-component of RotaTeq (RVA/Vaccine/RotaTeq-Wt79-4/1992/G6P1A[8]), clustered in lineage IV, showing only 80.9–84.9% nucleotide identity to the Italian HRV G6 strains. By analysis of the VP8* portion of VP4, the Italian G6P[9] HRVs clustered together with feline, human AU-1-like, and human G6P[9] RV strains detected in Hungary, Israel, Japan, Italy, France, Russia, and USA (Fig. 1b). The Italian G6P[14] HRV strains PA5-89 and PA77-02 clustered together with the prototype HRV G6P[14] strain PA169-88, and with G6/G8/G10 HRV and ungulate RV strains from various parts of the world, including the human strains 111-05-27 (Italy), B10925 (Belgium), Hun5 (Hungary), EGY3399 (Egypt) PR-1300-04 (Italy), A64 (England), MG6 and WAG8.1 (Australia), the ovine strains OVR762 (Spain) and Cap455 (South Africa), and the lama guanaco strain Chubut (Argentina), the bovine strain RUBV3 (India), and the antelope strain RC-18-08 (South Africa). Five discrete lineages (a–e) were observed among P[9] strains and nine lineages (a–i) were identified among P[14] viruses.

The I-genotypes (VP6), E-genotypes (NSP4) and H-genotype (NSP5) were also investigated, revealing that all the G6P[9] and G6P[14] Italian HRV strains belonged to the 12, E2 and H3 genotypes. The VP6 genotype I2 strains were further classified into 5 lineages (Fig. 1c), the NSP4 genotype E2 strains into 7 lineages (Fig. 1d), and the NSP5 genotype H3 strains into 7 lineages (Fig. 1e).
Fig. 1. Phylogenetic analysis of nucleotide sequences of the VP7 (a), VP4 (b), VP6 (c), NSP4 (d) and NSP5 (e) genes. Filled triangles indicate G6P[14] strains from this study; open triangles G6P[14] strains from previous studies; filled circles G6P[9] strains from this study and open circles G6P[9] strains from previous studies. Rotavirus nomenclature has been used according to the Rotavirus Classification Working Group (RCWG) (Matthijnssens et al., in press). Bootstrap values above 70%, estimated with 1000 pseudoreplicate data sets, are indicated at each node.
<table>
<thead>
<tr>
<th>Sample ID</th>
<th>VP7-VP4-VP6-NSP4-NSP5 genotype</th>
<th>VP7</th>
<th>VP4</th>
<th>VP6</th>
<th>NSP4</th>
<th>NSP5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA151-87</td>
<td>G6-P[9]-I2-E2-H3</td>
<td>95%: B1711 (EF504087)</td>
<td>89%: Bo/KN-4 (D12710)</td>
<td>98%: PAI58-96 (GU296427)</td>
<td>93%: PAI58-96 (GU296429)</td>
<td>97%: PA169 (EF554135)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99%: MG6 (U220011)</td>
<td>97%: B10925-97 (EF554118)</td>
<td>91%: SI-R230-07 (DQ384061)</td>
<td>97%: PA169-96 (GU296417)</td>
<td>97%: PAI58-96 (GU296419)</td>
</tr>
<tr>
<td>PA169-88</td>
<td>G6-P[14]-I2-E2-H3</td>
<td>99%: MG6 (U220011)</td>
<td>88%: Bo/RUBV319</td>
<td>96%: B10925 (EF554119)</td>
<td>97%: PA169 (EF554135)</td>
<td>97%: Bo/XJX-07/Ch (EU828786)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>97%: An/RC18-08-08 (RC1818)</td>
<td>96%: B10925 (EF554124)</td>
<td>97%: PAI58-96 (GU296417)</td>
<td>97%: Bo/XJX-07/Ch (EU828786)</td>
<td>97%: PAI58-96 (GU296419)</td>
</tr>
<tr>
<td>PA5-89</td>
<td>G6-P[14]-I2-E2-H3</td>
<td>98%: 111-05-27 (EF554142)</td>
<td>97%: An/RC18-08-08 (RC1818)</td>
<td>96%: B10925 (EF554119)</td>
<td>97%: PAI58-96 (GU296417)</td>
<td>97%: Bo/XJX-07/Ch (EU828786)</td>
</tr>
<tr>
<td>PA27-GV1-93</td>
<td>G6-P[9]-I2-E2-H3</td>
<td>96%: PA151 (L20881)</td>
<td>88%: Bo/KN-4 (D12710)</td>
<td>99%: Hun2 (AJ481137)</td>
<td>95%: 111-05-27 (EF554141)</td>
<td>97%: Bo/FR/ Dijona282/07 (GU259607)</td>
</tr>
<tr>
<td>PA77-02</td>
<td>G6-P[14]-I2-E2-H3</td>
<td>98%: 111-05-27 (EF554142)</td>
<td>94%: Ov/Cap455 (AY128708)</td>
<td>90%: Guanaco (FJ347103)</td>
<td>97%: PAI58-96 (GU296417)</td>
<td>97%: Bo/XJX-07/Ch (EU828786)</td>
</tr>
<tr>
<td>PA17-03</td>
<td>G6-P[9]-I2-E2-H3</td>
<td>98%: Hun7 (AJ488134)</td>
<td>89%: Bo/KN-4 (D12710)</td>
<td>96%: Fe/BA222 (GU827409)</td>
<td>97%: BPI819/03/HUN (AM992580)</td>
<td>97%: PAI136-96 (EF554135)</td>
</tr>
<tr>
<td>PA43-03</td>
<td>G6-P[9]-I2-E2-H3</td>
<td>97%: Bu1711 (EF504087)</td>
<td>86%: Bo/KN-4 (D12710)</td>
<td>97%: Fe/BA222 (GU827409)</td>
<td>99%: BPI819/03/HUN (AM992580)</td>
<td>97%: PAI136-96 (EF554135)</td>
</tr>
</tbody>
</table>

Bo = bovine, Ov = ovine, An = antilope, Gu = guanaco, Fe = feline, Si = simian.
Detailed comparison of the Italian G6 HRV strains with a selection of G6 RV strains of different origin is shown in Table 1. By comparing with sequences in the online databases using a BLAST search (http://www.ncbi.nlm.nih.gov/BLAST), the Italian G6 HRV strains appeared closely related to HRV strains that were in most cases regarded as zoonotic viruses, in all the analysed genome segments, but mainly in the VP4, VP6 and VP7 genes. Interestingly, the Italian HRV G6P[9] strains of this study displayed close similarity, mostly in their NS5P segment, with multi-reassortant G3P[9] RVs (PAH136 and PAI58) detected in Palermo in 1996. These G3P[9] strains seem to have originated by multiple sequential reassortment events involving human/feline-like RVA/Human-tc/AU-1/1982/G3P[9], RVA/Cat-tc/AUS/Cat-2/1984/G3P[9]-like viruses and RVs from ruminants (De Grazia et al., 2010; Martella et al., 2010) or may alternatively be a distinct feline/ canine genogroup (Martella et al., 2011).

Unlike other studies, in which G6P[9] HRV strains were detected in older children (Bánayai et al., 2009a; Griffin et al., 2002), in the present study, the G6P[9] and G6P[14] HRV strains were all detected in infants and young children (less than 5 years of age). The G6 HRV strains detected in Palermo had no apparent epidemiological relationships to each other. An exception to this was represented by 2 distinct infections caused by G6P[9] HRV strains, which occurred in 2003 within 3 days. The two isolates, PA17-03 and PA43-03, were highly similar to each other, sharing ≥99.5% nt identity in all the five gene segments analysed, indicating a likely clonal origin (Table 2). Nosocomial transmission was ruled out since the stool samples were collected on the first day following admission to the same hospital. Although there was no apparent relation between the two cases, it is reasonable to assume that the two children might have been exposed to a common virus source or that the G6P[9] HRV strain was transmitted directly or indirectly among the two patients. These findings may provide evidence of secondary human-to-human transmission of G6 RV strains, and may constitute an exception to previous observations (Bánayai et al., 2009a; Matthijssens et al., 2009a).

Two G6P[9] HRV strains, PA151-87 and PA27-GV1-93, detected 6 years apart in Palermo were found to share not only the same genotype constellation, but also the same phylogenetic lineage in three out of five genomic segments analysed (Table 2). G6P[9] HRV strains retaining the same constellation for 4 genes (VP4, VP6, VP7, and NSP4) over a 7-years time span were also described from Hungary (Bánayai et al., 2009a). High genetic conservation of some genome segments may suggest that these strains are able to successfully infect and cause disease in a human host although they are not transmitted at high efficiency.

Detection of genotype P[14] HRV strains has been described in different geographic areas (Iturriza-Gómez et al., 2009, 2010; Matthijssens et al., 2009a). Upon complete genome analysis, five HRV G6P[14] strains revealed closer genetic relatedness to ovine and antelope RV strains, suggesting repeated interspecies transmission from sheep or other ungulates to humans (Matthijssens et al., 2009a). Despite their widespread geographic distribution, HRV P[14] strains display a remarkable overall-conserved genotype constellation. In our study, the same genome make up was retained in the three G6P[14] HRV strains detected over 14 years (Table 2). Moreover, two of these strains PA5-89 and PA77-02, collected 13 years apart, shared the same lineage/sublineage in four genomic segments. These findings reinforce the observations that defined genome constellations may be required for transmission of G6P[14] HRVs from the animal reservoirs to humans.

4. Conclusions

In this study, we determined and characterized the genotype constellation of seven G6 HRV strains detected in the geographic area where the HRV G6 prototypes were first detected. Two G6P[9] clones were identified in 2003, providing possible evidence for human-to-human transmission. The transmission may not be very efficient, since similar viruses were not detected anymore in or after 2003 in Palermo. Circulation in humans, even at low rates, may provide a good opportunity for animal-like RVs to reassort with HRVs, generating novel strains that could, theoretically, be better adapted to the human host than most animal RVs. However, this has not been observed yet. Epidemiological surveillance for HRV G and P genotypes throughout the world has been used to define appropriate vaccine formulations to prevent RV infections in paediatric populations. At present, G6 HRVs are considered occasional human pathogens, transmitted sporadically from animal sources. One of the two licensed and worldwide distributed rotavirus vaccines, the pentavalent rotavirus vaccine, RotaTeq® (Merck & Co., Inc. Whitehouse Station, NJ), contains five human-bovine reassortant strains, each expressing a different VP7 or VP4 rotavirus surface protein, on the backbone of the naturally attenuated tissue culture-adapted parental bovine rotavirus strain WC3 (G6P[7]I) (Matthijssens et al., 2010). The efficacy of the vaccines has been assessed in large clinical trials, indicating that they are generally well tolerated, immunogenic and highly efficacious (Armah et al., 2010; Madhi et al., 2010; Ruiz-Palacios et al., 2006; Tate et al., 2010; Vesikari et al., 2006, 2010; Zaman et al., 2010).

In Italy, the two licensed rotavirus vaccines RotaTeq® and Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) have been available since 2006 and 2007, respectively. However, rotavirus vaccine coverage is limited, and in 2008, only <0.4% of children between 12 and 24 months of age had received either rotavirus vaccine (Istituto Superiore di Sanità, 2009). The first

### Table 2
Partial genomic constellations of the G6P[9] and G6P[14] Italian human rotavirus (HRVs) included in this study. Segments genetically related within the same lineage or sublineage (as evidenced in the phylogenetic trees) are shown with different shades of grey, to underline common patterns.

<table>
<thead>
<tr>
<th>Italian G6P[9] HRV</th>
<th>VP7</th>
<th>VP4</th>
<th>VP6</th>
<th>NSP4</th>
<th>NSP5</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>G6</td>
<td>P[9]</td>
<td>I2</td>
<td>E2</td>
<td>H3</td>
</tr>
<tr>
<td>PA151-87</td>
<td>(d)</td>
<td>c</td>
<td>b</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>PA27-GV1-93</td>
<td>(c)</td>
<td>b</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>PA17-03</td>
<td>(a)</td>
<td>d</td>
<td>b</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>PA43-03</td>
<td>(a)</td>
<td>d</td>
<td>e</td>
<td>b</td>
<td>b</td>
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<tbody>
<tr>
<td></td>
<td>Lineage (sublineage)</td>
<td>Lineage</td>
<td>Lineage</td>
<td>Lineage</td>
<td>Lineage</td>
</tr>
<tr>
<td>PA169-88</td>
<td>(b)</td>
<td>b</td>
<td>c</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>PA5-89</td>
<td>(d)</td>
<td>d</td>
<td>a</td>
<td>c</td>
<td>a</td>
</tr>
<tr>
<td>PA77-02</td>
<td>(d)</td>
<td>h</td>
<td>a</td>
<td>c</td>
<td>a</td>
</tr>
</tbody>
</table>
encouraging data on the impact of RV vaccination on the prevalence of disease caused by RV infections are becoming available (Chang et al., 2009; Clark et al., 2009; Tate et al., 2009; Zeller et al., 2010). Also there is evidence that the vaccines provide good homotypic and, in general, good heterotypic protection. For example, the recombinant components of the G1–G4 and P[4] strains included in the vaccine (Matthijsens et al., 2010) were proved efficacious against circulating G1–G4 and P[8] strains even though they are not genetically closely related. Similarly, the VP7 sequences of the G6 strains circulating in humans are not very closely related to that of the G6 backbone strain in RotaTeq® (Ciarlet et al., 2002; Matthijsens et al., 2010). However, the “lineage independent” efficacy demonstrated for the common HRV strains is encouraging and hopefully a similar level of efficacy will be reached against G6 HRVs where these strains are of medical importance. Ultimately, a better understanding of vaccine efficacy against various zoonotic or animal-derived HRVs, including the HRV G6P[9] and G6P[14] strains, requires continuous surveillance of HRV in the post rotavirus vaccine era.

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