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1 **ZOONOTIC ASPECTS OF ROTAVIRUSES**

2

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## Summary

Rotaviruses are important enteric pathogens of humans and animals. Group A rotaviruses (GARVs) account for up to 1 million children deaths each year, chiefly in developing countries and human vaccines are now available in many countries. Rotavirus-associated enteritis is a major problem in livestock animals, notably in young calves and piglets. Early in the epidemiological GARV studies in humans, either sporadic cases or epidemics by atypical, animal-like GARV strains were described. Complete genome sequencing of human and animal GARV strains has revealed a striking genetic heterogeneity in the 11 double stranded RNA segments across different rotavirus strains and has provided evidence for frequent intersections between the evolution of human and animal rotaviruses, as a result of multiple, repeated events of interspecies transmission and subsequent adaptation.

## 1 **Introduction**

2 Rotaviruses are enteric pathogens causing acute watery dehydrating diarrhea in various host  
3 species, including birds and mammals. Rotaviruses account for ~611,000 child deaths each year,  
4 mainly in developing countries (Parashar *et al.*, 2006). Likewise, rotavirus-associated enteritis is  
5 a major problem in young calves (Saif *et al.*, 1994), weaning and post-weaning piglets (Saif and  
6 Fernandez, 1996) and foals (Conner and Darlington, 1980). Vaccines against the most important  
7 serologic group of rotaviruses, GARVs, are available for the prevention of rotavirus diseases in  
8 cows, pigs and horses, and, more recently, they have been made available for the prevention of  
9 rotavirus disease in infants and young children (Heaton and Ciarlet, 2007).

10  
11 Rotaviruses are classified into an individual genus within the family *Reoviridae*. Rotaviruses are  
12 70-75 nm in diameter, icosahedral, triple-layered, and nonenveloped. The genome consists of 11  
13 segments of double-stranded (ds)RNA (Estes, 2001; Kapikian *et al.*, 2001). These 11 genome  
14 segments encode at least 6 structural proteins (VP1 to VP4, VP6 and VP7) and, depending on  
15 strain, 5 or 6 non-structural proteins. The virion is complex, and by electron microscopy, its  
16 structure resembles a wheel (from Latin *rota*). The genome is associated with two sub-core  
17 proteins, the RNA dependent RNA polymerase, VP1, and the guanylyltransferase, VP3. This  
18 structure is encased in the core made up by the VP2 protein. The VP2 layer is surrounded by a  
19 middle-layer, containing the serogroup specific antigen, VP6. The outer protein layer is made up  
20 by two proteins, the VP4 and the VP7. Because both surface antigens induce neutralizing  
21 antibodies and segregate in a dependent manner, they formed the basis of a widely accepted  
22 binomial nomenclature, developed for GARVs. In this system, the VP4 is referred to as the P  
23 (protease-sensitive) antigen, and the VP7 as the G antigen (glycosylated) (Estes, 2001; Kapikian  
24 *et al.*, 2001; Matthijnssens *et al.*, 2008b). The various G and P types tend to segregate according

1 to species-specific patterns across the various animal species (Table 1 and 2).

2

3 Genetically, rotaviruses are diverse, and different gene segments are peculiarly distributed across  
4 various animal species, suggesting existing host species barriers and host range restriction.

5 However, a number of gene segments, mostly those encoding the neutralizing antigens (defining

6 G and P types), have been identified repeatedly in humans in different parts of the world during

7 surveillance studies (Santos and Hoshino, 2005; Gentsch *et al.*, 2005), providing evidence that

8 animals may act as a source of virus and/or of genetic material for diversification of human

9 rotaviruses. These findings warrant rotaviruses to be handled as potential zoonotic pathogens. As

10 most data are related to a single rotavirus serogroup (group A) our review will focus primarily on

11 these viruses, unless otherwise specified.

12

### 13 **History**

14 First records on rotaviruses date back to 1950s and 1960s, when virus particles resembling

15 reoviruses were identified in the intestinal tissue of mice and rectal swab of captive monkeys by

16 using electron microscopy. In 1969, viruses with similar morphology were identified in fecal

17 samples of diarrheic cattle and serial passage of this virus revealed its etiologic role in diarrhea.

18 First human cases were diagnosed only in 1973, when intestinal mucosa and then stool extracts of

19 diarrheic children were examined by EM for viral pathogens (Bishop *et al.*, 1973). Based on the

20 characteristic wheel shaped virion morphology, the rotavirus name was proposed in this same

21 time period (Flewett *et al.*, 1974).

22

23 Subsequent improvements in diagnostic assays, particularly those that were based on direct

24 antigen detection from stool samples allowed rotaviruses to be characterized as an important

1 cause of gastroenteritis in infants and young children (Kapikian *et al.*, 1996). Combined use of  
2 electron microscopy, genomic RNA analyses (electropherotyping) and various antigen-based  
3 methods not only revealed the potential impact of rotaviruses on human health, but also allowed  
4 to gain some insight into the genetic and antigenic composition of rotaviruses and revealed that  
5 rotavirus strains circulating in humans and animals share a common group antigen. Since late  
6 1970s, however, several atypical rotavirus strains have been described that shared the virion  
7 morphology but lacked the common group antigen and/or displayed unusual genomic RNA  
8 electropherotypes. These antigenically divergent strains represented various serogroups of  
9 rotaviruses (Saif and Jiang, 1994).

10

11 To date, seven serogroups (A to G) of rotavirus have been determined (Saif and Jiang, 1994)  
12 (Table 3). Although each rotavirus serogroup has been associated with diarrhea, their distribution,  
13 epidemiology and impact shows remarkable differences in various host species. GARVs have  
14 been shown to be important cause of diarrhea in humans and a variety domesticated and captive  
15 mammals as well as poultry. Non-GARVs are relatively more often detected in healthy animals  
16 but an association with disease has been also reported. Group B and C rotaviruses have been  
17 identified in some mammalian host species, including humans, while group E rotaviruses have  
18 been detected only in pigs. Thus far, group D, F and G rotaviruses have been identified  
19 exclusively in poultry (Saif and Jiang, 1994). Representatives of a novel human non-group A-C  
20 rotavirus have been recently described (Yang *et al.*, 1998; Yang *et al.*, 2004; Alam *et al.*, 2007).  
21 The question whether they represent a new serogroup or belong to one of the known non-group  
22 A, -B, and -C rotaviruses is unclear, as no serologic data are available for this new strain and no  
23 sequence data are available for comparison for reference strains within serogroups D to G.

24

## 1 **Impact of rotaviruses on human health**

2 GARV infections heavily impact on human health. In humans, GARVs are detected in up to 50-  
3 60 % of all childhood hospitalizations due to acute gastroenteritis each year. They cause annually  
4 an estimated 130 million primary infections among children <5 y of age. Of these, every 5<sup>th</sup> and  
5 65<sup>th</sup> cases require medical visit and hospital admission, respectively, and 1 in 293 cases is fatal  
6 (~611,000 per year). More than 80% of fatal rotavirus infections occur in developing countries,  
7 where poor hygiene and sanitation, malnutrition, higher incidence of infections seriously  
8 affecting the immune status have detrimental effect on the outcome of rotavirus infections  
9 (Parashar *et al.*, 2003, 2006). The epidemiology of GARVs is complicated. As with other enteric  
10 infections, GARV are transmitted mainly via fecal-oral route. The stability of GARVs in the  
11 environment accounts for the possibility of water- or food-born outbreaks. GARVs show year-  
12 around activity in tropical areas, but show marked seasonal activity in countries with temperate  
13 climate, where virus activity peaks during winter and spring. A gradual shift of rotavirus peak  
14 activity from south-western to north and north-eastern direction has been described in North  
15 America and Europe (LeBaron *et al.*, 1990; Koopmans and Brown, 1999). Recent reviews of  
16 surveillance studies summarized global distribution of G-P combinations for 16,474 and 18,516  
17 strains, respectively, drawing the main conclusion that majority of medically important strains  
18 (90% or so) belong to 5 major surface G and P antigen combinations, including G1P[8], G2P[4],  
19 G3P8], G4P[8], and G9P[8]. Other strains may be periodically and locally important, such as  
20 G5P[8] strains in Brazil during the 1990s (Santos and Hoshino, 2005; Gentsch *et al.*, 2005). The  
21 strain prevalence usually changes year-by-year and a particular genotype that is predominant in  
22 one season may be less active or absent in the next season. Conversely, strains that are undetected  
23 in one year may become important in the next year (Bányai *et al.* 2005; Rahman *et al.* 2005; De  
24 Grazia *et al.* 2007).



1  
2 Non-GARVs are considered to have considerably less public health importance. However, a large  
3 water-borne gastroenteritis outbreak in the 1980s in China having affected ~1 million people has  
4 been linked to infection with group B rotaviruses, affecting mainly adults (Hung *et al.*, 1984).  
5 More recently, group B rotaviruses were identified from sporadic cases of infantile diarrhea  
6 outside China and these recent strains were genetically different from the Chinese strain (Ahmed  
7 *et al.*, 2004; Kelkar *et al.* 2004), suggesting that various group B rotavirus strains are circulating  
8 in humans, or, are transmissible to humans. Group C rotaviruses are considered endemic in most  
9 geographic areas and cause usually <5 % of gastroenteritis-associated hospitalizations in  
10 childhood (Bányai *et al.*, 2006). However, group C rotaviruses may also cause outbreaks  
11 associated with consumption of contaminated food or water. The limited genetic variability of  
12 group C rotaviruses in humans contrasts with the diversity currently seen in pigs (Martella *et al.*,  
13 2007b). It is unclear whether this low diversity among human strains reflects a more recent  
14 introduction of group C rotaviruses from an animal reservoir and their subsequent global spread  
15 in various populations or just a sort of genetic constraints against diversification. Nonetheless, the  
16 interspecies barrier even for group C rotaviruses seems not to be absolute as demonstrated by a  
17 recent report describing porcine-related group C rotavirus strains in Brazilian children (Gabbay *et*  
18 *al.*, 2008). The source of strain ADRV-N identified in an outbreak of diarrhea in China or a  
19 related strain reported from a sporadic adult case in Bangladesh (Alam *et al.*, 2007) has not yet  
20 been determined.

21

## 22 **Rotavirus disease in domestic animals**

23 Infection by GARVs is considered the major cause of calf diarrhea worldwide. Rotavirus  
24 infection usually affects calves within the first 4 weeks of life, causing important economic losses

1 related to death treatment costs and reduction in weight gain of affected animals. The etiology of  
2 the disease involves diverse infectious agents (virus, bacteria and protozoa) and is worsened by  
3 several factors including herd management, environment, and host nutritional and immunological  
4 conditions (Saif *et al.*, 1994; Bendali *et al.*, 1999).

5 Porcine GARVs are associated with weaning and post-weaning enteritis in piglets (Lecce and  
6 King, 1978; Will *et al.*, 1994). GARVs are one of the most frequently detected viral agents  
7 associated with diarrhoea affecting piglets between 1 and 8 weeks of age (Saif *et al.*, 1994).  
8 GARV may also be detected in non-diarrheic piglets (Lecce and King, 1978). GARV infection of  
9 pigs has been recognised in both enzootic and epizootic forms of diarrhoea resulting in economic  
10 losses in commercial piggeries (Saif and Fernández, 1996). Co-infections by other enteric  
11 pathogens (viruses, bacteria or parasites) likely trigger mechanisms of synergism, worsening the  
12 disease in piglets. About 70.8% of 1-3 months-old pigs from 12 porcine herds with enteritis  
13 outbreaks were found to be positive for rotavirus but 50.7% of the GARV-positive animals were  
14 also positive for either calicivirus or group C rotavirus (Martella *et al.*, 2007a).

15 Equine GARVs are the main cause of diarrhea in foals up to 3 months of age, causing severe  
16 economic loss due to morbidity and mortality in studs. Typically, GARV-induced disease is  
17 manifested by profuse watery diarrhea, dehydration, anorexia, abdominal pain, and depression.  
18 Although the disease is self-limiting, dehydration may be fatal, especially in young foals (Conner  
19 and Darlington, 1980). Serological surveys have detected antibody in most adult horses,  
20 suggesting that equine rotaviruses are ubiquitous (Conner and Darlington, 1980, Pearson *et al.*,  
21 1982).

22 GARVs are not regarded as major enteric pathogens of cats and dogs. Rotavirus-like particles  
23 have been detected at low frequency from both symptomatic and asymptomatic domestic

1 carnivores (Marshall *et al.*, 1984; 1987). Diarrhoea has been reproduced in neonatal gnotobiotic  
2 dogs infected experimentally with a canine GARV (Johnson *et al.*, 1983).

3 Rotavirus infection has been seen in several avian species, including chickens, turkeys, guinea  
4 fowls, pheasants, partridges and pigeons (Battilani *et al.*, 2003; Legrottaglie *et al.*, 1997). Signs  
5 include mild to severe diarrhea, dehydration, poor weight gain, increased mortality.  
6 Asymptomatic infections may also occur. Avian rotaviruses appear genetically heterogeneous, as  
7 evidenced by the broad diversity of e-types. Also, avian GARVs appear distantly related to  
8 mammalian GARVs (Ito *et al.*, 2001; Matthijnsens *et al.*, 2008b). In a 2005-2006 large-scale  
9 survey in USA, GARVs were detected by RT-PCR in 46.5% of the chicken flocks and 69.7% of  
10 the turkey flocks tested (Pantin-Jackwood, *et al.*, 2008).

#### 11 **Evidence for interspecies infections by GARVs**

12 Although rotaviruses infect particular species preferentially for which they have been defined as  
13 the homologous strains, heterologous rotavirus infections may occur in both, natural and  
14 experimental conditions. Studies in the rabbit and mouse model have demonstrated that only  
15 homologous viruses replicate efficiently and spread horizontally (Ciarlet *et al.*, 2000, Feng *et al.*,  
16 1994). Based on a Jennerian approach, animal strains that are naturally attenuated in humans  
17 have been exploited for the construction of candidate rotavirus vaccines for humans. In a number  
18 of field trials with such candidate rotavirus vaccines, the rhesus rotavirus (RRV) strain  
19 MMU18006 and the bovine strains NCDV, UK and WC3 were shown to replicate to a lower  
20 extent in humans than in their homologous hosts but to induce immune responses (Clark *et al.*,  
21 1996; Clements-Mann *et al.*, 2001; Kapikian *et al.*, 1996; Vesikari *et al.*, 1984; Vesikari, 1996).

22

23 Conversely, a number of studies have also proven that under experimental conditions, rotavirus

1 strains can infect and/or induce diarrhoea in a heterologous animal model. Human GARV strains  
2 have been shown to cause disease in several newborn animals (Kapikian *et al.*, 2001). In the  
3 piglet model, virulent human GARV strains induced diarrhoea and viraemia, while attenuated  
4 human GARV strains did not (Azevedo *et al.*, 2005). In the rabbit model, RRV has been shown  
5 to replicate efficiently and transmit horizontally (Ciarlet *et al.*, 2000). Also, a pigeon rotavirus  
6 strain (PO-13) was shown to infect and cause diarrhoea in mice (Mori *et al.*, 2001).

7  
8 Genetic analysis by RNA-RNA hybridization and full-length genome sequencing of field animal  
9 and human GARV strains has provided several examples of direct interspecies transmission  
10 under natural conditions. Complete genome sequence analyses has revealed that the G3P[3]  
11 human strains Ro1845 and HCR3A are closely related to the canine strains CU-1, K9 and A79-10  
12 and to the feline strain Cat97 in all the genome segments (Tsugawa and Hoshino, 2008). Also,  
13 the G3P[14] human strain B4106, detected from a child with enteritis, has been shown to share a  
14 high degree of genetic conservation in all the genome segments with the G3P[14] lapine strain  
15 30/96 (Matthijssens *et al.*, 2006a) (Table 4).

### 17 **Reassortment and interspecies transmission may generate novel human GARVs**

18 The mechanisms driving rotavirus diversification include positive accumulation of single point  
19 mutations, inter-segmental recombination, rearrangement, and notably reassortment (Estes,  
20 2001). Reassortment of animal viruses with human strains may create chimeric viruses bearing  
21 dsRNA segments of both the parental viruses. Presumably, when rotaviruses cross the host  
22 species barrier, they are not naturally able to efficiently infect or spread in a new host. By  
23 acquiring human GARV-derived dsRNA segments, such chimeric viruses would gain more  
24 chances to efficiently infect and spread among the population of the new host. Certain genome

1 segments are more likely involved in rotavirus adaptation to new hosts under natural conditions  
2 than others.

3  
4 Attempts to investigate the genetic relationships among the various GARV strains have been  
5 made using RNA-RNA hybridization analysis (Nakagomi *et al.*, 1989). By extensive use of  
6 RNA-RNA hybridization, it has been shown that rotaviruses recovered from the same animal  
7 species constitute a separate genogroup and usually share a high degree of overall genome  
8 homology. At least 3 genogroups have been identified for human GARVs, namely Wa-like, DS-  
9 1-like and AU-1-like (Nakagomi *et al.*, 1989). RNA-RNA hybridization has provided molecular  
10 evidence to show close interspecies relationships between human and some animal strains, or  
11 confirm the existence of naturally occurring rotavirus reassortant strains, but the extent of the  
12 relationship among the human and animal genogroups could not be completely elucidated  
13 (Nakagomi *et al.*, 1989; Nakagomi and Nakagomi, 2002).

14  
15 Animal-like GARVs, either as sporadic cases or as large epidemics have been detected in several  
16 occasions. There is evidence that heterologous GARVs of porcine origin or natural porcine-  
17 human GARV reassortants may have occurred and spread successfully throughout human  
18 populations in more occasions. In Latin America, unusual G5 rotavirus strains have been detected  
19 in children in Brazil since the early 1980s and subsequently in Argentina and Paraguay (Bok *et*  
20 *al.*, 2001; Carmona *et al.*, 2004; Coluchi *et al.*, 2002; Gouvea *et al.*, 1994; Mascarenhas *et al.*,  
21 2002; Santos *et al.*, 1998), that were shown to be, by either RNA-RNA hybridization or sequence  
22 analysis, naturally occurring reassortants between Wa-like human and porcine viruses (Alfieri *et*  
23 *al.*, 1996). In South East Asia, in the 1987-1988 season, an epidemic of infantile gastroenteritis  
24 by unusual strains was reported in Manipur, India (Gosh *et al.*, 1989). Sequence analysis of one

1 such strains, RMC321, revealed G9P[19] specificities, with at least 9 genome segments clearly of  
2 porcine origin, including the VP4 gene (Varghese *et al.*, 2004). In a subsequent epidemiological  
3 study (1989–1992), such strains were still circulating within the local population at a low  
4 frequency (2.1%) (Krishnan *et al.*, 1994). In the meantime, in 1989, the G9P[19] strains Mc323  
5 and Mc345 were isolated in Chiang Mai, Thailand, and shown to be genetically more related to  
6 porcine than to human rotaviruses by RNA-RNA hybridization and sequence analysis (Okada *et*  
7 *al.*, 2000; Urasawa *et al.*, 1992), suggesting that G9P[19] strains spread throughout Southern Asia  
8 in those years. In Europe, human GARVs resembling porcine P[6] strains in the VP4 have been  
9 identified in a scattered fashion but continuously (Martella *et al.*, 2006; Bányai *et al.*, 2004;  
10 Martella *et al.*, 2008). Porcine-like P[6] strains have been also identified in African and Asian  
11 children (Esona *et al.*, 2009; Ahmed *et al.*, 2007)

12  
13 Bovine GARVs have also contributed to the generation of novel human strains in several  
14 occasions. Strains with bovine-like VP7 and VP4 specificities G6, G8 and G10 have been  
15 detected worldwide in conjunction with a variety of P types, P[1], P[2], P[4], P[6], P[8], P[9],  
16 P[11] and P[14] (Santos and Hoshino, 2005). The unusual African G8P[6] and G8P[8] GARV  
17 strains may have arisen through several reassortment events involving human G2P[4] strains,  
18 DS-1-like, and strains carrying the G8, P[6] and P[8] genotypes (Matthijnsens *et al.*, 2006b).  
19 The bovine-like strains, G10P[11], are regarded as common human enteric pathogen in the Indian  
20 subcontinent, and a G10P[11] candidate vaccine has been developed (Ward *et al.*, 2008). Such  
21 viruses were first identified in 1993 in Bangalore, India (Dunn *et al.*, 1993) and have been  
22 detected frequently in subsequent epidemiological studies (Kelkar and Ayachit, 2000; Iturriza-  
23 Gómara *et al.*, 2004). The prototype G10P[11] Indian strain I321 by RNA-RNA hybridisation  
24 and sequence analysis was shown to have the genes encoding NSP1 and NSP3 of human origin

1 and the other dsRNA segments derived from bovine strains (Dunn *et al.*, 1993; Das *et al.*, 1993).

2

3 Human rotaviruses emerging globally in the last decade, such as G9 and G12, are likely to have  
4 originated from animal species by gene reassortment. In these particular cases, the major surface  
5 antigen, the VP7, is thought to have originated from animal GARVs, since GARVs with similar  
6 G9 and G12 VP7 specificities have been observed in piglets (Gosh *et al.*, 2006; Hoshino *et al.*,  
7 2005; Teodoroff *et al.*, 2005). Although several genetic lineages of both antigens have been  
8 described, only a single lineage from each was able to adapt to and spread in various human  
9 populations. These modern lineages of G9 and G12 specificities are now circulating on all  
10 continents, and particularly, the G9 strains were seen to completely change the local strain  
11 prevalence (Matthijssens *et al.*, 2008c; Rahman *et al.*, 2007).

12

13 Complete genome sequencing of GARV strains appears pivotal to better understand the genetic  
14 relationships among the various strains, the role of each gene segment in host range restriction  
15 and the mechanism of rotavirus evolution. To deal with the classification of the increasing  
16 amount of complete rotavirus genomic data, an extended classification and nomenclature system  
17 was developed recently (Matthijssens *et al.*, 2008a). This classification system was based on a  
18 nucleotide cut-off value for the ORF of each of the eleven gene segments, which resulted in  
19 appropriate genotypes for each of the 11 rotavirus gene segments. In line with the G- and P-  
20 genotypes for VP7 and VP4 respectively, a one-letter code was assigned for each of the gene  
21 segments, and successive numbers for the different genotypes. To apply, maintain and update this  
22 rotavirus classification system, a set of guidelines was published, and a Rotavirus Classification  
23 Working Group (RCWG) was formed (Matthijssens *et al.*, 2008b) (Table 4). This new  
24 classification system revealed a close evolutionary relationship between human Wa-like and

1 porcine rotavirus strains, and between human DS-1-like and bovine rotavirus strains, suggesting  
2 that these two major human genogroups might have an animal origin (Matthijssens *et al.*,  
3 2008a). Further studies have shown that an unusual human G6P[6] rotavirus strain, B1711, was  
4 most likely the result of a reassortment between a human DS-1-like rotavirus and bovine  
5 rotaviruses (Matthijssens *et al.*, 2008d) and that human P[14] strains might be the result of  
6 multiple interspecies transmissions and reassortment events from sheep or other ruminants to  
7 humans (Matthijssens *et al.*, 2009) (Table 4).

8

### 9 **Rotavirus vaccines**

10 Vaccines for prevention of rotavirus disease in calves, piglets and foals have been available since  
11 many years. Prevention of rotavirus disease in these animals is based on parenteral administration  
12 of either inactivated or attenuated vaccines. In order to provide a strong immunity of maternal  
13 origin, the vaccines are administered to the mothers in the late stage of pregnancy. This  
14 immunization strategy requires proper assumption of colostrum by the newborns in order to  
15 transfer adequate levels of passive immunity.

16

17 Although the development of human vaccines has started decades ago, only in recent years  
18 vaccines of prevention of rotavirus diarrhea in infants and children have been released. Initial  
19 vaccine studies concentrated on the classical "Jennerian" approach because this approach has the  
20 advantage that animal virus strains are often naturally attenuated in humans, or can be attenuated  
21 by relatively few tissue culture passages. This approach has been applied using several animal  
22 virus strains as vaccine candidates, including rotavirus strain RIT4237 (derived from the bovine  
23 rotavirus NCDV strain), bovine rotavirus strain WC3, and the rhesus rotavirus (RRV)-derived  
24 strain MMU18006 (Ward *et al.*, 2008). All of these candidate vaccines were well tolerated and



1 provided some cross-protection against human rotavirus strains; however, the protection against  
2 severe disease varied widely across studies (Offit *et al.*, 2003; Heaton and Ciarlet, 2007). While  
3 commercial pursuit of the RIT4237 vaccine was abandoned, further research focused on the RRV  
4 and WC3 strains to develop multivalent vaccines, using a modified Jennerian approach by taking  
5 advantage of the natural property of rotaviruses to reassort in cell culture, composed of human-  
6 animal reassortants containing an animal rotavirus genetic background with human rotavirus  
7 surface VP4 and VP7 proteins representing the most common G and/or P types worldwide (Offit  
8 *et al.*, 2003; Heaton and Ciarlet, 2007).

9  
10 The first multivalent live-attenuated oral rotavirus vaccine produced was the rhesus-human  
11 reassortant vaccine, RotaShield™, which consisted of RRV (G3) and three RRV-based  
12 reassortant (G1, G3, G4) strains (Offit *et al.*, 2003). The vaccine demonstrated 49-83% efficacy  
13 against all rotavirus gastroenteritis and 70-95% efficacy against severe disease (Heaton and  
14 Ciarlet, 2007; Ward *et al.*, 2008). After more than 15 years of development and clinical trials,  
15 RotaShield™ was licensed by the United States Food and Drug Administration and incorporated  
16 into the US infant immunization program in 1998. In July 1999, the Centers for Disease Control  
17 recommended postponing any further administration of RotaShield™ due to the possible  
18 association of the vaccine with intussusception (a bowel obstruction in which one segment of  
19 bowel becomes enfolded within another segment), and RotaShield™ was removed from the  
20 market in October 1999 (Ciarlet and Estes, 2001; Offit *et al.*, 2003; Heaton and Ciarlet, 2007).

21  
22 Despite the observation of intussusception with RotaShield™, two other oral rotavirus vaccine  
23 candidates, RotaTeq™ (Merck & Co., Inc. Whitehouse Station, NJ) and Rotarix™

1 (GlaxoSmithKline [GSK], Rixensart, Belgium), were developed and are now licensed in several  
2 countries worldwide. However, very large Phase III clinical trials were required to show that  
3 these vaccines were safe, well tolerated, and that there was no association with intussusception  
4 (Vesikari *et al.*, 2006; Ruiz-Palacios *et al.*, 2006). RotaTeq™ is a pentavalent combination  
5 vaccine of five live-attenuated human-bovine reassortant rotavirus strains (containing human  
6 serotypes G1, G2, G3, G4, and P1A[8] and bovine serotypes G6 and P7[5] (Heaton and Ciarlet,  
7 2007). Rotarix™ is based on the attenuated human G1P1A[8] rotavirus strain (Ward *et al.*, 2008).  
8 Both RotaTeq™ and Rotarix™ have been shown to be highly efficacious in developed countries  
9 and Latin America (Heaton and Ciarlet, 2007; Ruiz-Palacios *et al.*, 2006; Vesikari *et al.*, 2006;  
10 Ward *et al.*, 2008)

11  
12 Another oral rotavirus vaccine, the Lanzhou Lamb Rotavirus (LLR) vaccine, is licensed in China  
13 since 2000. The LLR vaccine was developed directly from an ovine animal strain, Lp14  
14 (G10P[15]) (Ciarlet *et al.*, 2008). The LLR vaccine was shown to be efficacious; however, the  
15 data have not been confirmed postlicensure (Ward *et al.*, 2008). Several other live rotavirus  
16 vaccine candidates are under development: the bovine (UK strain)-human reassortant vaccine, the  
17 human neonatal RV-3 strain, and the natural bovine-human reassortant neonatal 116E strain have  
18 progressed to different stages (Ward *et al.*, 2008). Novel approaches in the development of  
19 rotavirus vaccines include, recombinant *E. coli*-expressed VP6 proteins, inactivated vaccines, and  
20 virus-like particles (VLPs) have been tested in several animal models but none have been  
21 evaluated in humans (Ciarlet *et al.* 1998; Bertolotti-Ciarlet *et al.* 2003; Ward *et al.*, 2008).

22

## 23 **Conclusions**

24 Evidence for interspecies transmission and for genetic reassortment between human and animal

1 rotaviruses has been continuously accumulating in the literature and, in particular, some animal  
2 species, cows, pigs, cats and dogs, appear to contribute frequently to the antigenic/genetic  
3 diversity found in human rotaviruses, presumably because of the close interactions between  
4 humans and these animals driven either by cultural and/or economic forces. Reassortant GARV  
5 strains bearing mixed genome constellations (dsRNA segments derived from both human and  
6 animal viruses) seem to be more successful than completely heterologous GARV strains (with all  
7 the genome segments derived from animal viruses). Improved adaptation to the new host,  
8 coupled with the lack of specific pre-existing population immunity against the new strain, might  
9 account for the quick spread of the new GARV strains, and for their persistence in human  
10 populations. There is concern whether the introduction of rotavirus vaccines for children could  
11 alter the forces and balances that drive rotavirus evolution. However, the widespread emergence  
12 of the G9 (and G12) genotypes in humans in the absence of a rotavirus vaccine indicates that  
13 these events may occur with or without the introduction of a new rotavirus vaccine. Continuous  
14 epidemiological surveillance is critical for understanding the short- and long-term effects of the  
15 vaccines on rotavirus ecology and implementing future vaccine strategies.

16

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20 “Studio di rotavirus atipici umani ed animali”.

21

### 22 **Conflict of interest statement**

23 None.

24

1 **References**2  
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**Table 1:** Distribution of group A rotavirus G types across the various animal species. Full circles indicate that the G type is epidemiologically relevant for the species. Empty circles indicate sporadic description or low epidemiological relevance.

Species	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Humans	●	●	●	●	○	○		○	●	○	○	●								
Pig	○	●	●	●	●	○		○	●	○	●	○								
Monkey			●					○												
Cattle	○		○		○	●		●		●									○	
Sheep/Goat			○			●		●	○	●					●					
Horse			●		●			○		○			●	●						
Dog			●																	
Cat			●																	
Mouse																●				
Rabbit			●																	
Birds							●											●	●	●

**Table 2:** Distribution of group A rotavirus P genotypes across various animal species. Full circles indicate that the P type is epidemiologically relevant for the species or that it has been described only in that species to date. Open circles indicate sporadic description or low epidemiological relevance.

Genotype	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
<b>Species</b>																											
Man	○		○	●	○	●	○	●	●	●	●			●					○						●		
Pig	○				○	●	●	○			○		●						●				●			●	●
Monkey	○	●	●																					●			
Cattle	●		○		●						●			○	●		○				●						
Goat/Sheep	●		○		●			○			●			○	●												
Horse	○						○				○	●						●									
Dog			●																								
Cat			●						●																		
Mouse																●				●							
Rabbit														●									●				
Birds																											●

**Table 3:** Main features of rotavirus serogroups affecting humans.

	<b>Rotavirus serogroup</b>			
	<b>A</b>	<b>B</b>	<b>C</b>	<b>ADRV-N like strains</b>
<b>Age distribution</b>	< 5 years children	Mainly adults	All age groups	Mainly adults
<b>Seroprevalence</b>	Almost 100% antibody-prevalence by 5 years of age	?	50-60% seroprevalence by age of 60 years	?
<b>Typical setting</b>	Sporadic cases (outbreaks in adults)	Outbreaks (more recently sporadic cases)	Outbreaks and sporadic cases	Outbreaks?
<b>Geography</b>	Worldwide	East- and South-Asia	Worldwide	East- and South-Asia
<b>Seasonality</b>	Yes	?	?	?
<b>Typical mode of transmission</b>	Faecal-oral route, air-borne?	Water	Faecal-oral route, food?	?
<b>Animal host</b>	Various species of mammals and birds	Pig, Cattle, Sheep, Rat	Pig, Cattle, Dog	?
<b>Evidence for zoonotic transmission</b>	Yes	No	Yes	No

**Table 4:** Genetic relationships among group A rotavirus strains of human and animal origin. To designate the complete genetic make up of a virus, the schematic nomenclature was proposed: Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx, representing the genotypes of the VP7-VP4-VP6-VP1-VP2-VP3-NSP1-NSP2-NSP3-NSP4-NSP5 gene, respectively. The letter x indicates the number of the genotype. The colors green, red, and orange represent Wa-like, DS-1-like and AU-like gene segments, respectively. In addition, colors yellow, blue, and purple represent avian PO-13-like rotavirus gene segments, some typical porcine VP4, VP7, VP6 and NSP1 genotypes, and the SA-11-like gene segments, respectively (modified by Matthijssens *et al.*, 2008b).

Strain name	Host	VP7	VP4	VP6	VP1	VP2	VP3	NSP1	NSP2	NSP3	NSP4	NSP5
Wa	Human	G1	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
KU	Human	G1	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
DS-1	Human	G2	P[4]	I2	R2	C2	M2	V2	N2	T2	E2	H2
TB-Chen	Human	G2	P[4]	I2	R2	C2	M2	V2	N2	T2	E2	H2
Au-1	Human	G3	P[9]	I3	R3	C3	M3	V3	N3	T3	E3	H3
ST3	Human	G4	P[6]	I1	R1	C1	M1	V1	N1	T1	E1	H1
IAL28	Human	G5	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
B1711	Human	G6	P[6]	I2	R2	C2	M2	V2	N2	T2	E2	H2
Se584	Human	G6	P[9]	I2	R2	C2	M2	V3	N2	T1	E2	H3
Hun5	Human	G6	P[14]	I2	R2	C2	M2	V11	N2	T6	E2	H3
MG6	Human	G6	P[14]	I2	R2	C2	M2	V11	N2	T6	E2	H3
PA169	Human	G6	P[14]	I2	R2	C2	M2	V3	N2	T6	E2	H3
111/05-27	Human	G6	P[14]	I2	R2	C2	M2	V3	N2	T6	E2	H3
DRC88	Human	G8	P[8]	I2	R2	C2	M2	V2	N2	T2	E2	H2
69M	Human	G8	P[10]	I2	R2	C2	M2	V2	N2	T2	E2	H2
WI61	Human	G9	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
A64	Human	G10	P[14]	I2	R2	C2	M2	V3	N2	T6	E2	H3
Dhaka6	Human	G11	P[25]	I1	R1	C1	M1	V1	N1	T1	E1	H1
KTM368	Human	G11	P[25]	I5	R1	C1	M1	V1	N1	T1	E1	H1
L26	Human	G12	P[4]	I2	R2	C2	M1/M2	V2	N1	T2	E2	H1
Dhaka12-03	Human	G12	P[6]	I1	R1	C1	M1	V1	N1	T1	E1	H1
Matlab13-03	Human	G12	P[6]	I1	R1	C1	M1	V1	N1	T2	E1	H1
N26-02	Human	G12	P[6]	I2	R2	C2	M2	V2	N1	T2	E6	H2
RV176-00	Human	G12	P[6]	I2	R2	C2	M2	V2	N2	T2	E6	H2
RV161-00	Human	G12	P[6]	I2	R2	C2	M2	V2	N2	T2	E1	H2
B4633-03	Human	G12	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
Dhaka25-02	Human	G12	P[8]	I1	R1	C1	M1	V1	N1	T1	E1	H1
T152	Human	G12	P[9]	I3	R3	C3	M3	V12	N3	T3	E3	H6
BRV033	Bovine	G6	P[1]	I2	R2	C2	M2	V3	N2	T6	E2	H3
RF	Bovine	G6	P[1]	I2	R2	C2	M2	V3	N2	T6	E2	H3
Uk(tc)	Bovine	G6	P[5]	I2	R2	C2	M2	V3	N2	T7	E2	H3
WC3	Bovine	G6	P[5]	I2	R2	C2	M2	V3	N2	T6	E2	H3
OVR762	Ovine	G8	P[14]	I2	R2	C2	M2	V11	N2	T6	E2	H3
PO-13	Avian	G18	P[17]	I4	R4	C4	M4	V4	N4	T4	E4	H4
A131	Porcine	G3	P[7]	I5	R1	C2	M1	V1	N1	T1	E1	H1
Gottfried	Porcine	G4	P[6]	I1	R1	C1	M1	V8	N1	T1	E1	H1
OSU	Porcine	G5	P[7]	I5	R1	C1	M1	V1	N1	T1	E1	H1
A253	Porcine	G11	P[7]	I5	R1	C2	M1	V1	N1	T1	E1	H1
YM	Porcine	G11	P[7]	I5	R1	C1	M1	V8	N1	T1	E1	H1
SA11-5S	Simian	G3	P[1]	I2	R2	C5	M5	V5	N5	T5	E2	H5
SA11-H96	Simian	G3	P[2]	I2	R2	C5	M5	V5	N5	T5	E2	H5
SA11-Both	Simian	G3	P[2]	I2	R2	C5	M5	V5	N2	T5	E2	H5
B4106	Human	G3	P[14]	I2	R2	C2	M3	V9	N2	T6	E5	H3
30/96	Lapine	G3	P[14]	I2	R2	C2	M3	V9	N2	T6	E5	H3
Cat2	Feline	G3	P[9]	I3	R3	C2	M3	V3	N1	T6	E3	H3
Cat97	Feline	G3	P[3]	I3	R3	C2	M3	V9	N2	T3	E3	H6
CU-1	Canine	G3	P[3]	I3	R3	C2	M3	V9	N2	T3	E3	H6
K9	Canine	G3	P[3]	I3	R3	C2	M3	V9	N2	T3	E3	H6
Ro1845	Human	G3	P[3]	I3	R3	C2	M3	V9	N2	T3	E3	H6
HRC3	Human	G3	P[3]	I3	R3	C2	M3	V9	N2	T3	E3	H6