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ZOONOTIC ASPECTS OF ROTAVIRUSES

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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.
Introduction

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

Rotaviruses are classified into an individual genus within the family Reoviridae. Rotaviruses are 70-75 nm in diameter, icosahedral, triple-layered, and nonenveloped. The genome consists of 11 segments of double-stranded (ds)RNA (Estes, 2001; Kapikian et al., 2001). These 11 genome segments encode at least 6 structural proteins (VP1 to VP4, VP6 and VP7) and, depending on strain, 5 or 6 non-structural proteins. The virion is complex, and by electron microscopy, its structure resembles a wheel (from Latin rota). The genome is associated with two sub-core proteins, the RNA dependent RNA polymerase, VP1, and the guanylyltransferase, VP3. This structure is encased in the core made up by the VP2 protein. The VP2 layer is surrounded by a middle-layer, containing the serogroup specific antigen, VP6. The outer protein layer is made up by two proteins, the VP4 and the VP7. Because both surface antigens induce neutralizing antibodies and segregate in a dependent manner, they formed the basis of a widely accepted binomial nomenclature, developed for GARVs. In this system, the VP4 is referred to as the P (protease-sensitive) antigen, and the VP7 as the G antigen (glycosylated) (Estes, 2001; Kapikian et al., 2001; Matthijnssens et al., 2008b). The various G and P types tend to segregate according
to species-specific patterns across the various animal species (Table 1 and 2).

Genetically, rotaviruses are diverse, and different gene segments are peculiarly distributed across various animal species, suggesting existing host species barriers and host range restriction. However, a number of gene segments, mostly those encoding the neutralizing antigens (defining G and P types), have been identified repeatedly in humans in different parts of the world during surveillance studies (Santos and Hoshino, 2005; Gentsch et al., 2005), providing evidence that animals may act as a source of virus and/or of genetic material for diversification of human rotaviruses. These findings warrant rotaviruses to be handled as potential zoonotic pathogens. As most data are related to a single rotavirus serogroup (group A) our review will focus primarily on these viruses, unless otherwise specified.

**History**

First records on rotaviruses date back to 1950s and 1960s, when virus particles resembling reoviruses were identified in the intestinal tissue of mice and rectal swab of captive monkeys by using electron microscopy. In 1969, viruses with similar morphology were identified in fecal samples of diarrheic cattle and serial passage of this virus revealed its etiologic role in diarrhea. First human cases were diagnosed only in 1973, when intestinal mucosa and then stool extracts of diarrheic children were examined by EM for viral pathogens (Bishop et al., 1973). Based on the characteristic wheel shaped virion morphology, the rotavirus name was proposed in this same time period (Flewett et al., 1974).

Subsequent improvements in diagnostic assays, particularly those that were based on direct antigen detection from stool samples allowed rotaviruses to be characterized as an important
cause of gastroenteritis in infants and young children (Kapikian et al., 1996). Combined use of
electron microscopy, genomic RNA analyses (electropherotyping) and various antigen-based
methods not only revealed the potential impact of rotaviruses on human health, but also allowed
to gain some insight into the genetic and antigenic composition of rotaviruses and revealed that
rotavirus strains circulating in humans and animals share a common group antigen. Since late
1970s, however, several atypical rotavirus strains have been described that shared the virion
morphology but lacked the common group antigen and/or displayed unusual genomic RNA
electropherotypes. These antigenically divergent strains represented various serogroups of
rotaviruses (Saif and Jiang, 1994).

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

GARV infections heavily impact on human health. In humans, GARVs are detected in up to 50-60% of all childhood hospitalizations due to acute gastroenteritis each year. They cause annually an estimated 130 million primary infections among children <5 y of age. Of these, every 5th and 65th cases require medical visit and hospital admission, respectively, and 1 in 293 cases is fatal (~611,000 per year). More than 80% of fatal rotavirus infections occur in developing countries, where poor hygiene and sanitation, malnutrition, higher incidence of infections seriously affecting the immune status have detrimental effect on the outcome of rotavirus infections (Parashar et al., 2003, 2006). The epidemiology of GARVs is complicated. As with other enteric infections, GARV are transmitted mainly via fecal-oral route. The stability of GARVs in the environment accounts for the possibility of water- or food-born outbreaks. GARVs show year-around activity in tropical areas, but show marked seasonal activity in countries with temperate climate, where virus activity peaks during winter and spring. A gradual shift of rotavirus peak activity from south-western to north and north-eastern direction has been described in North America and Europe (LeBaron et al., 1990; Koopmans and Brown, 1999). Recent reviews of surveillance studies summarized global distribution of G-P combinations for 16,474 and 18,516 strains, respectively, drawing the main conclusion that majority of medically important strains (90% or so) belong to 5 major surface G and P antigen combinations, including G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]. Other strains may be periodically and locally important, such as G5P[8] strains in Brazil during the 1990s (Santos and Hoshino, 2005; Gentsch et al., 2005). The strain prevalence usually changes year-by-year and a particular genotype that is predominant in one season may be less active or absent in the next season. Conversely, strains that are undetected in one year may become important in the next year (Bányai et al. 2005; Rahman et al. 2005; De Grazia et al. 2007).
Non-GARVs are considered to have considerably less public health importance. However, a large water-borne gastroenteritis outbreak in the 1980s in China having affected ~1 million people has been linked to infection with group B rotaviruses, affecting mainly adults (Hung et al., 1984). More recently, group B rotaviruses were identified from sporadic cases of infantile diarrhea outside China and these recent strains were genetically different from the Chinese strain (Ahmed et al., 2004; Kelkar et al. 2004), suggesting that various group B rotavirus strains are circulating in humans, or, are transmissible to humans. Group C rotaviruses are considered endemic in most geographic areas and cause usually <5 % of gastroenteritis-associated hospitalizations in childhood (Bányai et al., 2006). However, group C rotaviruses may also cause outbreaks associated with consumption of contaminated food or water. The limited genetic variability of group C rotaviruses in humans contrasts with the diversity currently seen in pigs (Martella et al., 2007b). It is unclear whether this low diversity among human strains reflects a more recent introduction of group C rotaviruses from an animal reservoir and their subsequent global spread in various populations or just a sort of genetic constraints against diversification. Nonetheless, the interspecies barrier even for group C rotaviruses seems not to be absolute as demonstrated by a recent report describing porcine-related group C rotavirus strains in Brazilian children (Gabbay et al., 2008). The source of strain ADRV-N identified in an outbreak of diarrhea in China or a related strain reported from a sporadic adult case in Bangladesh (Alam et al., 2007) has not yet been determined.

**Rotavirus disease in domestic animals**

Infection by GARVs is considered the major cause of calf diarrhea worldwide. Rotavirus infection usually affects calves within the first 4 weeks of life, causing important economic losses
related to death treatment costs and reduction in weight gain of affected animals. The etiology of
the disease involves diverse infectious agents (virus, bacteria and protozoa) and is worsened by
several factors including herd management, environment, and host nutritional and immunological
conditions (Saif et al., 1994; Bendali et al., 1999).

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

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

GARVs are not regarded as major enteric pathogens of cats and dogs. Rotavirus-like particles
have been detected at low frequency from both symptomatic and asymptomatic domestic
carnivores (Marshall et al., 1984; 1987). Diarrhoea has been reproduced in neonatal gnotobiotic
dogs infected experimentally with a canine GARV (Johnson et al., 1983).

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

Evidence for interspecies infections by GARVs

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

Conversely, a number of studies have also proven that under experimental conditions, rotavirus
strains can infect and/or induce diarrhoea in a heterologous animal model. Human GARV strains have been shown to cause disease in several newborn animals (Kapikian et al., 2001). In the piglet model, virulent human GARV strains induced diarrhoea and viraemia, while attenuated human GARV strains did not (Azevedo et al., 2005). In the rabbit model, RRV has been shown to replicate efficiently and transmit horizontally (Ciarlet et al., 2000). Also, a pigeon rotavirus strain (PO-13) was shown to infect and cause diarrhoea in mice (Mori et al., 2001).

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

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

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

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

Animal-like GARVs, either as sporadic cases or as large epidemics have been detected in several occasions. There is evidence that heterologous GARVs of porcine origin or natural porcine-human GARV reassortants may have occurred and spread successfully throughout human populations in more occasions. In Latin America, unusual G5 rotavirus strains have been detected in children in Brazil since the early 1980s and subsequently in Argentina and Paraguay (Bok et al., 2001; Carmona et al., 2004; Coluchi et al., 2002; Gouvea et al., 1994; Mascarenhas et al., 2002; Santos et al., 1998), that were shown to be, by either RNA-RNA hybridization or sequence analysis, naturally occurring reassortants between Wa-like human and porcine viruses (Alfieri et al., 1996). In South East Asia, in the 1987-1988 season, an epidemic of infantile gastroenteritis by unusual strains was reported in Manipur, India (Gosh et al., 1989). Sequence analysis of one
such strains, RMC321, revealed G9P[19] specificities, with at least 9 genome segments clearly of porcine origin, including the VP4 gene (Varghese et al., 2004). In a subsequent epidemiological study (1989–1992), such strains were still circulating within the local population at a low frequency (2.1%) (Krishnan et al., 1994). In the meantime, in 1989, the G9P[19] strains Mc323 and Mc345 were isolated in Chiang Mai, Thailand, and shown to be genetically more related to porcine than to human rotaviruses by RNA-RNA hybridization and sequence analysis (Okada et al., 2000; Urasawa et al., 1992), suggesting that G9P[19] strains spread throughout Southern Asia in those years. In Europe, human GARVs resembling porcine P[6] strains in the VP4 have been identified in a scattered fashion but continuously (Martella et al., 2006; Bányai et al., 2004; Martella et al., 2008). Porcine-like P[6] strains have been also identified in African and Asian children (Esona et al., 2009; Ahmed et al., 2007).

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

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

Complete genome sequencing of GARV strains appears pivotal to better understand the genetic relationships among the various strains, the role of each gene segment in host range restriction and the mechanism of rotavirus evolution. To deal with the classification of the increasing amount of complete rotavirus genomic data, an extended classification and nomenclature system was developed recently (Matthijnssens et al., 2008a). This classification system was based on a nucleotide cut-off value for the ORF of each of the eleven gene segments, which resulted in appropriate genotypes for each of the 11 rotavirus gene segments. In line with the G- and P-genotypes for VP7 and VP4 respectively, a one-letter code was assigned for each of the gene segments, and successive numbers for the different genotypes. To apply, maintain and update this rotavirus classification system, a set of guidelines was published, and a Rotavirus Classification Working Group (RCWG) was formed (Matthijnssens et al., 2008b) (Table 4). This new classification system revealed a close evolutionary relationship between human Wa-like and
porcine rotavirus strains, and between human DS-1-like and bovine rotavirus strains, suggesting that these two major human genogroups might have an animal origin (Matthijnssens et al., 2008a). Further studies have shown that an unusual human G6P[6] rotavirus strain, B1711, was most likely the result of a reassortment between a human DS-1-like rotavirus and bovine rotaviruses (Matthijnssens et al., 2008d) and that human P[14] strains might be the result of multiple interspecies transmissions and reassortment events from sheep or other ruminants to humans (Matthijnssens et al., 2009) (Table 4).

**Rotavirus vaccines**

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

Although the development of human vaccines has started decades ago, only in recent years vaccines of prevention of rotavirus diarrhea in infants and children have been released. Initial vaccine studies concentrated on the classical "Jennerian" approach because this approach has the advantage that animal virus strains are often naturally attenuated in humans, or can be attenuated by relatively few tissue culture passages. This approach has been applied using several animal virus strains as vaccine candidates, including rotavirus strain RIT4237 (derived from the bovine rotavirus NCDV strain), bovine rotavirus strain WC3, and the rhesus rotavirus (RRV)-derived strain MMU18006 (Ward et al., 2008). All of these candidate vaccines were well tolerated and
provided some cross-protection against human rotavirus strains; however, the protection against severe disease varied widely across studies (Offit et al., 2003; Heaton and Ciarlet, 2007). While commercial pursuit of the RIT4237 vaccine was abandoned, further research focused on the RRV and WC3 strains to develop multivalent vaccines, using a modified Jennerian approach by taking advantage of the natural property of rotaviruses to reassort in cell culture, composed of human-animal reassortants containing an animal rotavirus genetic background with human rotavirus surface VP4 and VP7 proteins representing the most common G and/or P types worldwide (Offit et al., 2003; Heaton and Ciarlet, 2007).

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

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

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

Conclusions

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

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Conflict of interest statement
None.
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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.

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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 |
|-----------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Species   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Man       | ○ | ○ | • | • | ○ | • | • | • | • | *  | *  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pig       | ○ | ○ | • | • | • | ○ | ○ | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Monkey    | ○ | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cattle    | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Goat/Sheep| • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Horse     | ○ | ○ | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dog       | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cat       | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mouse     | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Rabbit    | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Birds     | • | • | • | • | • | • | • | • | • |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
### Table 3: Main features of rotavirus serogroups affecting humans.

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

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<th>NSP2</th>
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