Rotavirus strains in neglected animal species including lambs, goats and camelids

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Abstract Surveillance of rotavirus infections and circulating strains in small ruminants (i.e. lambs, goats and camelids) has been a neglected research area in the past. However, recent years that have seen an intensification of surveillance in humans and livestock animals, where vaccines to reduce disease burden caused by Rotavirus A (RVA) are available, led to the efforts to better understand the epidemiology, ecology and evolution of RVA strains in other hosts, including lambs, goats and camelids. The aim of this review is to provide an update of the epidemiology and strain diversity of RV strains in these species through searching for relevant information in public data bases.

Keywords Small ruminants · Genotype · VP7 · VP4 · Surveillance

Introduction

Rotaviruses (RVs) are major enteric pathogens of humans and a wide variety of animals [13]. Clinical presentations range from asymptomatic infection to acute diarrhea that may lead to death due to severe dehydration or other complications. In livestock, RVs are commonly detected in the feces of diarrheic young animals, leading to either epizootic or enzootic forms of gastroenteritis, particularly in young calves, piglets and foals [12].

RV is a member of the Reoviridae family. Officially, the genus is divided into five species (Rotavirus A to E) and historically two additional species (Rotavirus F and G) have been distinguished based on genetic and phenotypic features. RVA, RVB, RVC, and RVE have been found to infect various animal species and humans, whereas RVD, RVF, and RVG have been isolated only from avian species [12, 34, 35]. In ruminants, most commonly identified RV strains belong to RVA, but in some settings RVB and RVC are also frequently found and implicated in severe diarrhea, particularly in young lambs and goats [14, 37, 39].

The RV genome is composed of 11 double-stranded RNA (dsRNA) segments, each encoding one protein, except segment 11, which encodes two non-structural proteins (NSP5/6). The RVA genome encodes six structural proteins (VP1–4, VP6, VP7), and five or six non-structural proteins (NSP1–NSP5/6) [13]. A binary classification system has been widely used for RVs, which is based on the configuration of the outer capsid antigens, VP7 or G types (G for glycoprotein) and VP4 or P types (P for protease sensitive
protein. The system has been adopted for all RV species. Within RVA, at least 27 G and 37 P genotypes have been reported in mammalian and avian strains [34]. The host specific distributions of G and P type specificities show peculiar patterns. For example, the most commonly reported human RVA strains have been G1P[8] globally in the pre vaccine era, whereas G5P[7], G6P[5] and G3P[12] are thought to be the predominant cause of RVA infections in swine, cattle and horses, respectively in many areas, although there is, usually, a natural fluctuation of strain prevalence [6, 27, 41]. Of note is that emerging RVA strains may reshape the distribution of genotypes in various species. For example, beginning in about 1995, G9P[8] became globally prevalent in humans [33]. Another example is the increased detection of G14P[12] strains in horses in parts of Asia, Europe and the Americas, which may be the result of a recent emergence [42].

The 11 gene based strain classification scheme recently adopted by the Rotavirus Classification Working Group (RCWG) has proven to be useful to delineate the origin and evolution of RV strains identified in various animal species. The scheme is based on nucleotide sequence identity cut-off values of each viral gene, where the scheme Gx-P[x]-Ix-Rx-Cx-Mx-Ax-Nx-Tx-Ex-Hx designates the genotype constellation of the VP7–VP4–VP6–VP1–VP2–VP3–NSP1–NSP2–NSP3–NSP4–NSP5/6 genes, respectively [31].

Recent years have seen an intensified surveillance of RV strains in various hosts. This interest is driven by new vaccine introductions and the accompanying need to monitor the impact of vaccines on disease and strain epidemiology, as well as the broad availability of PCR and nucleotide sequencing based genotyping methods. Such studies have resulted in the recognition that RV (particularly RVA) strains tend to cross host species barriers resulting in the introduction of heterologous strains in new ecologic niches by direct interspecies transmission or following reassortment with a homologous RV strain. Overall, RV surveillance and strain characterization has become routine in many laboratories and this has raised interest to study RV infection in so far neglected host species, as well. Furthermore, the expansion of studies in neglected host species may also be important as a component of understanding strain evolution in vaccine era.

In this review we collected relevant data from published studies and other databases (i.e. DNA sequence databases) to gain insight into the genetic diversity of small ruminant RVs, in particular, RVA.

Rotaviruses in sheep

An early study conducted at the US Sheep Experiment Station has shown that diarrhea accounted for 46 % of lamb mortality [47]. Diarrhea in lambs is a complex, multifactorial disease including animal susceptibility, nutritional status, environmental factors, and a variety of infectious agents. The four major infectious causes of diarrhea in lambs during the first month of life are Escherichia coli, RV, Cryptosporidium sp. and Salmonella sp. [47]. Ovine RVs belong to either RVA or RVB, but the epidemiology of lamb RVs is still largely unknown.

Several studies showed high morbidity (75–100 %) during outbreaks of neonatal diarrhea with remarkable mortality [7, 49]. In these studies RVB was detected in 16–100 % of the examined stool samples from both diarrheic and non-diarrheic lambs [7, 49]. The occurrence of ovine RVAs was reported from various countries worldwide and depending on epidemiologic setting, diagnostic assay utilized, etc. their detection rates were up to 60 % often with an estimated 10–15 % mortality [15–17, 20, 22, 26, 52, 53]. Several reports have been published from India [16, 17, 52, 53]. Wani et al. [52] reported association of RVA with lamb diarrhea in an outbreak in Kashmir, India with 25 % incidence. A later study found RVA in ~25 % of 96 diarrheic stool specimens [53].

Limited information is available on genotypes of ovine RV strains globally (Table 1). The largest data set was published in India where 500 samples collected over a period of 3 years were tested for RVs with the combination of antigen detection and molecular methods and subsequently 52 strains were genotyped for the VP7 and VP4 genes. Among the 52 strains, the most prevalent genotype was G6 (48 %) followed by G10 (36 %), and most strains had a P[11] VP4 gene [17]. At least 3 ovine RVA strains were characterized in China and G10P[15] was the only observed antigenic combination (Lp14, Lamb-NT, CC0812). The entire genomes for two of those strains, Lamb-NT and CC0812, have been sequenced [8, 48, 55], revealing conserved configurations of the backbone genes (Table 2). In Europe, a large serosurvey conducted in Spain identified neutralizing antibodies to seven G serotypes in sheep sera, with the greatest titers and prevalence against serotype G10, G3, and G6 [38]. In one Spanish strain characterization study, a single ovine RVA from an outbreak among 50–60 day-old lambs, was genotyped as G8P[1] [15]. Another Spanish RVA strain typed as G8P[14] (OVR762) [9, 32]. In the UK, four lamb RVA strains were characterized each one showing different specificities, such as LRV1, G3P[1]; LRV2a, G6P[11]; LRV2c, G9P[8] and K923, G10P[14] [14].

Rotaviruses in goats

Outbreaks of neonatal diarrhea among goats have essentially the same burden of disease as delineated for sheep.
The causes of diarrhea in goats include infectious agents including bacteria, viruses, parasites as well as management practice. Caprine RVs have been commonly implicated in diarrhea in 2–3 days old kids and the identified goat RV strains were found to belong to RVA, RVB, or RVC. The most frequently identified microorganisms causing diarrhea in goats during the first month of life are *E. coli*, *Cryptosporidium sp.* and *Salmonella sp.*
The occurrence of caprine RVA and RVB has been reported from various countries worldwide. In a study from Italy, researchers reported a ~60% detection rate for RVA in diarrheic goat samples [24], whereas in a study from Spain RVA was detected in half of the examined goat fecal specimens [20]. Other studies from Spain also reported RVB associated diarrhea among goat kids with moderate morbidity (22, 6%) and no mortality. RVA was detected in 71% (5 out of 7) of the examined samples among diarrheic goats, but could also be detected in non-diarrheic goats. Microbiological examination showed that these samples were negative for Cryptosporidium parvum, Clostridium perfringens and E. coli [37]. Muñoz et al. [39] found lower prevalence of RVB in diarrheic goats (13, 5%) and reported RVA in ~8% of samples. However, RVs could also be detected in non-diarrheic goat samples (RVA, 15%; RBV, 1%; RVC, 4%). Very few epidemiologic reports of RV in goats have been noted in Africa or Asia. A survey in Bangladesh during 2007 found RV in ~9% of diarrheic goat samples [11], though detailed microbiological examination was not performed. A report from Egypt documented RVA in 8% of samples among 3–7 weeks old goats [22]. In Turkey, the rates of RVA associated morbidity and mortality were estimated 45% (230/510) and 28% (65/230), respectively, among young goats, whereas adult animals were not affected by RVA disease [4]. A report described RVA in 21% of diarrheic fecal samples from Sudan [3]. Lately, an Indian report showed the absence of RV infection on screening of 25 diarrheic goats [28].

Information about the genotypes of caprine RVA strains globally is scanty (Table 1). Two genotype G6P[1] goat RVA strains were reported from Italy [45], one caprine RVA strain genotyped G6P[14] in South Africa [10], and a single G3P[3] RVA strain was described from Korea [23]. The G6P[1] antigen combination was identified in three goat RVA strains in Bangladesh and the full-genome of one of these strains was sequenced [18] (Table 2). Another strain found in China was not published and information about this strain is presently available only from a GenBank record [25]. Turkish goat RVA strains were found to carry genotype G6P[1] or G8P[1] antigens [4], and a single Indian goat RVA strain typed G8 [21].

Rotaviruses in new-world camelids

There are four species of South American camelids: two of them (llama and alpaca) are domesticated and two (guanaco and vicuna) are wild-living species. Studies indicate that diarrhea is an important disease in neonatal llamas, alpacas and guanacos. One epidemiological survey found that diarrhea was the most common cause of morbidity in the pre-weaning period, affecting some 23% of young animals [54]. The most common pathogens causing diarrhea in neonatal camelids are coronavirus, RV, E. coli, Cryptosporidium spp., Giardia spp. and coccidia [54]. Epidemiological data indicate the presence of RVA in all South American camelids.

The first evidence of RVA infection in llamas was derived from serological surveys conducted in Peru and Argentina [29, 43, 46]. In these studies, RVA was detected by neutralization assay. The antibody prevalence for RVA was ~88% in Argentinean llamas [46]. In the Patagonia region 95% of the serum samples collected from guanacos were positive for RVA antibodies, and two RVA strains were isolated from new-born guanacos with acute diarrhea [44]. A survey of vicunas for viral antigens conducted at the border of Argentina and Bolivia showed asymptomatic fecal shedding of RVA [29]. Blood and stool samples were collected from wild living vicunas sharing the grazing area with domesticated livestock (incl. cattle and llama). All examined sera had antibody against RVA, although virus shedding could not be detected by enzyme immunonassay [29].

Several reports describe the diversity of neutralization antigens and the genomic configuration of RVAs from new-world camelids (Table 1). Two guanaco RVAs genotyped as either G8P[14] or G8P[1] strains [44]. Both strains were found to share the same genotype constellation of the backbone genes [32] (Table 2). The G8P[1] genotype combination was also detected from the stool samples of seven young guanacos in a study in Argentina [30]. More recently, a genotype G8P[14] RVA strain was found in an Argentinean vicuna in the wild and the partial genomic constellation of this strain was also determined [5].

Rotaviruses in old-world camelids

Low reproductive rates in Old World camelids are due to infertility, pregnancy loss, udder diseases and neonatal mortality caused by a variety of infectious diseases, primarily due to diarrhea caused by E. coli, Coccidium sp., Salmonella sp., coronavirus, and RV [50].

The epidemiology of camel RV infections is not well documented. The few published studies were mainly from Sudan. One study reported the detection of RVA in 9% of samples from young (<3 month old) diarrheic camel calves [36]. RVA was detected during a 2000–2002 surveillance study in 14% (35/245) of samples and RVAs were present in both diarrheic and asymptomatic camel calves [2]. In another
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study performed during 2005–2006, the percentage of RVA positive camels was 10 %. These positive samples were collected from diarrheic camel, whereas the samples taken from non-diarrheic animals tested negative for RVA [3].

RVA genotype data from Old World camelids are very limited (Table 1). The VP7 gene of an Egyptian and a Kuwaiti camel RV strain genotyped as G10 [1, 40]. The partial genome configuration of the Kuwaiti RVA strain was also determined [40] (Table 2). More recently, the first whole genome constellation of a camel RVA was described for a Sudanese G8P[11] camel RV strain. Of interest, the Kuwaiti and the Sudanese camel RVA strains had very distinct genotype configurations, with both having several novel genotypes in their genome [19, 40] (Table 2).

Genomic and genetic relationships among strains identified in small ruminants

Molecular characterization studies have shed light on the genetic relationships of ovine, caprine and camelid RVs to both homologous and heterologous RVA strains. Initially, whole genome characterization was performed by RNA–RNA hybridization and later this method was replaced by sequencing and phylogenetic analysis of genomic RNA segments. The results of such phylogenetic analyses are described in detail in the respective studies published over the past few years. Here, we highlight some basic findings using phylogenetic trees of selected genes (Fig. 1).

The genomic configuration of small ruminant origin RVA strains is somewhat similar to the genomic configuration of bovine RVAs. These include the conserved genotype configuration of the VP1–VP2–VP3–VP6–NSP1–NSP2–NSP3–NSP5 genes which, with few exceptions, have the following composition: R2/R5-C2-M2-I2/I10-A11-N2-T6-H3 (Table 2). Other genes are more heterogenous, including four E (NSP4) types, and a wide variety of genotypes for the neutralization antigens, VP7 and VP4. In addition, genotype configurations of the backbone genes of sheep, goat and even new-world camelids were found to be more similar to each other than the gene constellation of old-world camelids identified in the eastern mediterranean and the Saharan regions.

That RVAs of small ruminant hosts harbor a variety of shared genotypes with other host species is well illustrated by phylogenetic analysis studies and the VP4, VP6, VP7, and NSP4 trees attached to this paper. For example, the G6 VP7 gene is a common bovine RVA genotype and majority of hitherto characterized caprine RVAs carry this genotype. G8 and G10 VP7 genes are shared by a variety of small ruminants, including goats, guanacos and sheep and this specificity is also present in humans, cows, pigs, and some monkeys. Similar patterns of genotype sharing are seen in the P[1] and P[14] VP4 genotypes. All of these findings reinforced previous, RNA–RNA hybridization based studies, which showed some caprine strains to be derived from reassortment events and/or interspecies transmission of canine, feline and/or simian RVAs [23]. On the contrary, some genotypes found in small ruminant hosts may be more specific to their particular host species. These include the P[15] VP4 genotype which has been found only in goat, sheep and Old-world camelids, the I10 VP6 genotype which has been described from Chinese sheep and goat RVAs, as well as the A18 NSP1 gene and the E15 NSP4 gene with only known representative strains found in Old-world camelids.

Within shared genotypes, it is sometimes possible to distinguish genetic lineages which are somewhat more typical to small ruminants. Although defining a genetic lineage may be fairly subjective, phylogenetic analysis results strongly suggest different evolutionary routes of some gene variants in their respective host species. Genetic lineages unique to small ruminants include variants of the G10 VP7 gene of camel and sheep origin and several lineages of the E2 NSP4 gene of goat and sheep origin RVA strains. Genes of small ruminant RVAs that cluster with an RVA originating in a different host species can be seen in other cases indicating that genetic interaction between goat and human RVAs (e.g., G8 VP7), guanaco and cow RVAs (e.g., G8 VP7), goat and cow RVAs (e.g., P[1] VP4) or sheep, goat, antelope and human RVAs (P[14] VP4) may occur in the nature (Fig. 1).

Concluding remarks

The first papers about RV infection in small ruminant species were published over 3 decades ago, yet epidemiological data are scarce at this time. RVs of small ruminants have remained a neglected group of enteric pathogens likely due to the greater impact ascribed to other pathogenic microorganisms and viruses and the high detection rates of RVs in asymptomatic animals that seemed to indicate that RVs have only a secondary role in acute dehydrating diarrhea in newborn and young animals. However, large RV associated gastroenteritis outbreaks with marked mortality have been periodically reported in these hosts, highlighting the need of inclusion of RV in routine laboratory diagnostics. Any indications for the need to develop appropriate intervention tools (i.e. vaccines) against RV in these animals will depend on supportive data from diagnostic laboratories.

This review of RV strain characterization studies clearly demonstrates that the amount of available information is insufficient to delineate the baseline prevalence data of RVs in various small ruminant hosts permitting only
limited conclusions to be drawn. An important observation is that in many instances the genotypes of the neutralization antigens of small ruminant origin RVAs are shared with those found in cattle. The shared genotypes between cows (sometimes horses) and other ruminants are not unexpected though, given that these animals are often pastured in the same area. These strain type data raise the question whether a vaccine developed to prevent RVA disease in calves may be effective against a shared antigen repertoire in a small ruminant host and deserves further investigation.

The importance of small ruminant RVA strain surveillance has another implication. Recently, a monovalent live oral vaccine consisting of a lamb RV strain to immunize infants and young children have been developed and distributed in China. Another RV vaccine, RotaTeq, which is based on a bovine parental RVA strain and several human RVA strains, has been shown to be shed via feces of vaccinees and to exchange genomic segments with wild type human RVA strains. Thus any concerns, if raised, vaccinees and to exchange genomic segments with wild type human RVA strains. Thus any concerns, if raised, are a vaccine developed to prevent RVA disease in calves same area. These strain type data raise the question though, given that these animals are often pastured in the same area.

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