Bovine-like coronaviruses in domestic and wild ruminants

Haitham Mohamed Amer

Department of Virology, Faculty of Veterinary Medicine, Cairo University, 11221 Giza, Egypt

Abstract

Coronaviruses (CoVs) produce a wide spectrum of disease syndromes in different mammalian and avian host species. These viruses are well-recognized for their ability to change tissue tropism, to hurdle the interspecies barriers and to adapt ecological variations. It is predicted that the inherent genetic diversity of CoVs caused by accumulation of point mutations and high frequency of homologous recombination is the principal determinant of these competences. Several CoVs (e.g. Severe acute respiratory syndrome-CoV, Middle East respiratory syndrome-CoV) have been recorded to cross the interspecies barrier, inducing different disease conditions in variable animal hosts. Bovine CoV (BCoV) is a primary cause of gastroenteritis and respiratory disease in cattle calves, winter dysentery in lactating cows and shipping fever pneumonia in feedlot cattle. Although it has long been known as a restrictive cattle pathogen, CoVs that are closely related to BCoV have been recognized in dogs, humans and in other ruminant species. Biologic, antigenic and genetic analyses of the so-called ‘bovine-like CoVs’ proposed classification of these viruses as host-range variants rather than distinct virus species. In this review, the different bovine-like CoVs that have been identified in domesticated ruminants (water buffalo, sheep, goat, dromedary camel, llama and alpaca) and wild ruminants (deer, wild cattle, antelopes, giraffes and wild goats) are discussed in terms of epidemiology, transmission and virus characteristics. The presented data denote the importance of these viruses in the persistence of BCoV in nature, spread to new geographical zones, and continuous emergence of disease epidemics in cattle farms.

Introduction

Coronaviruses (CoVs) form a large group of enveloped viruses that harbour the largest genome among all RNA viruses (26.4–31.7 kb in length). CoVs occupy the entire subfamily of Coronavirinae within the family Coronaviridae, order Nidovirales. Traditionally, CoVs were classified into three groups depending on their antigenic and genetic properties (Brian and Baric, 2005). However, these groups have been recently replaced with four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The first two genera include only mammalian CoVs, while all avian CoVs are members of the other two genera (de Groot et al., 2012).

CoVs infect a wide diversity of animal and bird species causing respiratory, enteric, neurologic and hepatic disorders. Since SARS-CoV was identified in 2003, a significant increase in the number of emerging CoVs has been shown in people and animals as a result of the growing interest in CoV research and the development of improved diagnostic tools (Woo et al., 2009; Peck et al., 2015). The accumulated information has confirmed the ability of CoVs to adapt new tissue tropisms, to jump host-species barriers and to acclimatize variable ecological niches (Decaro et al., 2010b). These abilities were believed to be attributed to: (1) the high mutation rate (a single mutation/genome/round of replication) caused by low fidelity of the viral RNA polymerase (Drake and Holland, 1999), and (2) the exceptional tendency for homologous recombination mediated by random template switching during RNA replication (Woo et al., 2006; Decaro and Buonavoglia, 2008). Cross-species transmission of CoVs was previously recorded for many CoVs (e.g. SARS-CoV in palm civet and human beings (Song et al., 2005); Middle East respiratory syndrome CoV (MERS-CoV) in camels and people (Drosten et al., 2014)). Bovine CoV (BCoV) represents an excellent example of a CoV that extensively crosses the interspecies barrier. Several bovine-like CoVs were identified as aetiologic pathogens of enteric and/or respiratory diseases in a diverse spectrum of ruminant species (Saif, 2010), dogs (Decaro et al., 2007; Erles et al., 2007; Lorusso et al., 2009) and even human beings (Zhang et al., 1994).

Bovine CoV

BCoVs are commonly identified in the respiratory and intestinal tracts of healthy cattle, and contribute to different disease syndromes (Fulton et al., 2015). The virus is involved as a major cause of calf diarrhoea (CD) during the first 3 weeks of life in both dairy and beef cattle herds.
(Boileau and Kapil, 2010). High mortalities are mostly attributed to BCoV infections because they affect both small and large intestines, destroying villi and leading to severe, often bloody, diarrhoea (Torres-Medina et al., 1985). Enteric BCoV infection is also associated with winter dysentery (WD) in adult dairy cattle, causing dramatic decrease in milk production and significant economic losses (Natsukai et al., 2007). Respiratory tract infection in growing (2-16 weeks of age) and feedlot calves has been frequently attributed to BCoV (Storz et al., 2000; Decaro et al., 2008b; Saif, 2010). The widespread distribution of BCoV could be explained by two main factors: (1) rapid transmission of the virus via faecal–oral and respiratory routes (Heckert et al., 1990; Decaro et al., 2008a), and (2) existence of carrier animals within infected herds. These carriers shed the virus in faeces, particularly during the stress of winter season and parturition, and serve as a source of infection to their neonates and reservoirs for reinfection on the farm (Carman and Hazlett, 1992).

Bovine-like CoVs

In 2008, the Coronavirus Study Group of the International Committee of Taxonomy of Viruses has proposed taxonomic grouping of six CoVs of people, cattle, pigs, horses and dogs [human CoV OC43 (HCoV-OC43), human enteric CoV, BCoV, porcine haemagglutinating encephalomyelitis virus, equine CoV and canine respiratory CoV] in a new virus species named Beta-coronavirus 1 (de Groot et al., 2011; Lau et al., 2012). For instance, HCoV-OC43 likely evolved from ancestral BCoV strains that crossed the interspecies barrier and established an infection in human beings around 1890 (Vijgen et al., 2005; Vijgen et al., 2006).

Several CoV strains have been identified in the faeces, intestinal contents and sometimes in the respiratory secretions of a diverse group of domestic and wild (captive and free-range) ruminant species (Tables 1 and 2). Most of these viruses have demonstrated extensive biologic, antigenic and genetic similarities with BCoV and consequently they were termed as bovine-like CoVs (Tsunemitsu et al., 1995). Experimental transmission of bovine-like CoVs to gnotobiotic and colostrum-deprived cattle calves suggest that cattle may be reservoirs for CoV strains to infect other domestic and wild ruminants and vice versa, in a process that helps maintain and evolution of CoVs in these species (Tsunemitsu et al., 1995; Hasokuzu et al., 2007). It has been proposed that the broad host range of BCoV may be attributed to the presence of haemagglutinin-esterase protein that enables the virus to bind to different cell types (Saif, 2010).

Bovine-like CoVs in domestic ruminants

Water buffalo (Bubalus bubalis)

The domestic Asian buffalo (commonly named as water buffalo) is a large bovid originated from Southeastern Asia and tamed approximately 5000 years ago. It is used in many countries as a source of good quality meat, milk and leather, and as a labour animal in agriculture farms. The population of water buffalo in the world was estimated to be 172 million head with 95% living in Asia (mostly in India, China and Pakistan), 2.4% in South America (principally in Brazil), 2.3% in Africa (only in Egypt), 0.3% in Europe and 0.02% in Australia (Borghese, 2011). The first description of bovine-like CoVs in water buffalo dated back to 1985, when BCoV antibodies were detected using virus neutralization (VN) and haemagglutination inhibition (HI) assays in 52.9% of sera collected from water buffaloes of different age groups in Bulgaria. Seven faecal samples of diarrhoic buffalo calves showed haemagglutinating activity that was suppressed by BCoV-specific antiserum (Muniappa et al., 1985). In the early 1990s, bovine-like CoVs were detected in the faeces of suckling buffalo calves with profuse diarrhoea in Egypt using monoclonal antibody (Mab)-based enzyme-linked immunosorbent assay (ELISA) and immunoperoxidase assays (Abd El-Karim et al., 1990). The CoV particles were identified in two further studies in Egypt using negative-contrast transmission electron microscopy (EM) in 20 and 55.2% of the faecal samples collected from diarrhoic buffalo calves, and 8.3 and 19.1% of the faecal samples collected from apparently healthy buffalo calves, respectively (Byomi et al., 1996; Abd El-Rahim, 1997). The epidemiological data presented by the Tri-national Health Research Project, USAID, indicated that CoV is the second most-common pathogen causing diarrhoea in buffalo calves in Egypt with a prevalence rate of 37.7% (Saleh, 1994; Garbe et al., 1995).

An outbreak of CD and neonatal mortality was later described in a herd of water buffaloes in Campania (Southern Italy) between October 2006 and April 2007. Bovine-like CoVs were identified in the intestinal contents of buffalo calves with severe diarrhoea (two dead and 17 alive) by conventional and real-time reverse transcription polymerase chain reaction (RT-PCR) assays. A virus strain (designated as 179/07-11) was isolated from HRT-18 cells, producing the typical cytopathic effects of BCoV. This strain shared many similarities with BCoVs including: (1) haemagglutination of mouse erythrocytes, (2) receptor-destroying enzymatic activity, (3) cross-reactivity with BCoV antisera in immunofluorescence (IF) assay, and (4) genomic organization. However, the inability of strain 179/07-11 to replicate in MDBK cells and to agglutinate chicken erythrocytes, along with the existence of considerable genetic distance between both bovine and buffalo strains, suggested the assignment of strain 179/07-11 as a prototype of a novel host-range variant of BCoV (named as bubaline CoV) (Decaro et al., 2008c). Four further bubaline CoV strains were isolated afterwards and all showed similar biologic and antigenic characteristics to the prototype strain 179/07-11. Nevertheless, the genetic analysis showed that three of these strains were closely related to the prototype strain whereas the fourth shared higher genetic similarity to recent BCoV reference strains (Decaro et al., 2010a). It is proposed that the bubaline CoV may be originated from interspecies transmission of a BCoV strain; however, no cattle, sheep or goat contact to the water buffalo herd was demonstrated at the time of the outbreak.

The first complete genome sequence of a bubaline CoV was retrieved from two strains identified in Bangladesh in 2014 (BuCoV HKU26 strains B1-24F and B1-28F). The overall nucleotide homology with BCoVs was ranged from 98 to 99%, which supports the taxonomic relevance of both types of CoVs. Nevertheless, the nature of the three accessory proteins that located between spike (S) and envelope (E) varies distinctively. The 4.9 kDa protein of BCoV was replaced with 2.9 kDa protein in BuCoV HKU26, a result of premature stop codon, and the 4.8 kDa protein was replaced with 3.2 and 5.1 kDa proteins in strains B1-24F and B1-28F, respectively, a result of frameshift deletion mutation (Lau et al., 2016).
Table 1. A collective summary of bovine-like CoVs in domestic ruminants

| Animal species | Country (state)          | Samples                  | Test(s) of choice         | Positive samples | Reference                           |
|----------------|--------------------------|--------------------------|---------------------------|------------------|--------------------------------------|
| Water buffalo  | Bulgaria                 | Serum                    | VNT, HI                   | 155              | 52.9                                 | Muniappa et al. (1985)             |
| Water buffalo  | Egypt                    | Faeces                   | ELISA, IP                 | ND               | ND                                   | Abd El-Karim et al. (1990)         |
| Water buffalo  | Egypt                    | Faeces                   | NC-EM, HA                 | 8                | 14.7                                 | Byomi et al. (1996)                |
| Water buffalo  | Egypt                    | Faeces                   | NC-EM                     | 39               | 29.6                                 | Abd El-Rahim (1997)                |
| Water buffalo  | Italy                    | Faeces – intestinal      | Conventional and real-time RT-PCR | 19              | 100                                  | Decaro et al. (2008c, 2010b)        |
| Water buffalo  | Bangladesh               | Faeces                   | RT-PCR                    | 2                | ND                                   | Lau et al. (2016)                  |
| Sheep          | USA (Idaho, Montana)     | Faeces                   | EM                         | 1                | 3.6                                  | Harp et al. (1981)                 |
| Sheep          | Chile                    | Intestinal contents      | ELISA, EM                 | 6                | 6.1                                  | Reinhardt et al. (1995)            |
| Sheep, goat    | Spain                    | Faeces                   | Blocking ELISA            | 0                | 0                                    | Muñoz et al. (1996)               |
| Sheep, goat    | Turkey                   | Intestinal contents      | IHC                        | 1                | 3.3                                  | Ozmen et al. (2006)                |
| Sheep          | Sweden                   | Serum                    | ND                         | 41               | 18.8                                 | Trávén et al. (1999)              |
| Goat           | South Korea              | Serum                    | HI                         | 8                | 1                                    | Yang et al. (2008)                 |
| Dromedary camel| USA (Wisconsin)          | Faeces                   | EM, IHC                    | 1                | 100                                  | Wunschmann et al. (2002)           |
| Dromedary camel| UAE (Dubai)              | Faeces                   | RT-PCR, VNT, IFA          | 14               | 4.8                                  | Woo et al. (2014, 2016)            |
| Dromedary camel| Saudi Arabia             | Nasal/rectal swab        | RT-PCR                    | 331              | 25.3                                 | Sabir et al. (2016)               |
| Llama, alpaca  | USA (Oregon)             | Faeces                   | ND                         | 19               | 42                                   | Cebra et al. (2003); Jin et al. (2007) |
| Alpaca         | Peru                     | Faeces                   | IC                         | 3                | 23                                   | López et al. (2011)               |
| Alpaca         | Peru                     | Intestinal lavage        | RT-PCR                    | 20               | 40                                   | Rojas et al. (2016)               |
| Alpaca         | USA (Georgia)            | Faeces                   | RT-PCR                    | 1                | 100                                  | Genova et al. (2008)              |
| Alpaca         | USA (California)         | Lung tissue              | Isolation, EM, sequencing | 1                | 9.1                                  | Crossley et al. (2010, 2012)       |

VNT, virus neutralization test; HI, haemagglutination inhibition; HEHA, haemadsorption–elution–haemagglutination assays; ND, not defined; ELISA, enzyme-linked immunosorbent assay; IP, immunoperoxidase; NC-EM, negative contrast electron microscopy; HA, haemagglutination; RT-PCR, reverse transcription polymerase chain reaction; EM, electron microscopy; IHC, immunohistochemistry; IFA, immunofluorescent assay; UAE, United Arab of Emirates; IC, immunochromatography.

**Sheep (Ovis aries)**

Bovine-like CoVs have been identified as a cause of enteritis and neonatal mortality in domestic sheep in several countries worldwide (Tzipori et al., 1978; Harp et al., 1981; Pass et al., 1982; Reinhardt et al., 1995). However, the prevalence of infection was mostly low and of minor importance. Among 545 diarrhoeic lambs originated from 12 sheep flocks in southern Idaho and western Montana, USA, bovine-like CoVs were detected in lambs of only one flock (Harp et al., 1981). As well, CoVs were detected in six (out of 98; 6.1%) dead lambs but not in healthy lambs and ewes in Chile (Reinhardt et al., 1995). Two reports from Spain and Turkey demonstrated that Cryptosporidium parvum, Giardia intestinalis, Escherichia coli and rotavirus – but not CoV – were the leading causes of neonatal diarrhoea and mortalities in domestic sheep (Muñoz et al., 1996; Ozmen et al., 2006). A nationwide screening of BCoV-specific antibodies in Swedish sheep has demonstrated that 19% of all sera samples were positive. However, it was expected that these antibodies originated from contact with infected cattle faeces rather than a natural infection with bovine-like CoV (Trávén et al., 1999).

**Goat (Capra aegagrus hircus)**

Few studies have investigated the role of bovine-like CoV in goat kids with neonatal diarrhoea. Examination of faecal samples from diarrhoeic and non-diarrhoeic kids (1–45 days old) in Spain has demonstrated complete absence of CoVs (Muñoz et al., 1996). While CoVs were detected in the faeces of one (out of 19; 3.3%) kid with neonatal enteritis in Turkey by immunohistochemistry (IHC). The positive reaction was obvious at the crypt epithelium of small intestine and in the submucosal macrophages (Ozmen et al., 2006). A large-scale serosurveillance for viral diseases has been conducted in 144 native goat farms in South Korea between 2005 and 2006. Among 804 sera samples collected from five provinces of South Korea, CoV HI antibodies were only detected in eight samples (1%), as the least prevalent viral infection in two provinces, while it was entirely absent in the other districts (Yang et al., 2008).

**Camelids**

Nowadays, six species of camelids exist. They are grouped into two tribes: Camelini that includes old world camels, and
Lamini that contains new world camels. Two species of old world camels include dromedary or one-humped camel (Camelus dromedarius) and Bactrian or two-humped camel (Camelus bactrianus). The majority of old world camels (90%) are dromedaries, which inhabit the African horn, North Africa, Middle East and Southwestern Asia. The Bactrian camel has an estimated worldwide population of 1.4 million animals living in central Asia (mostly in China and Mongolia) (Frankin, 2011). Few wild dromedary and Bactrian camels are still living in Australia and Gobi Desert, respectively (Saalfeld and Edwards, 2008; Animal Information Organization, 2018).

On the other hand, the new world camels include two wild species: guanaco (Lama guanicoe) and vicuna (Vicugna vicugna), and two domesticated species: llama (Lama glama) and alpaca (Vicugna pacos). All of these species are living in South America (mostly in the Andean highlands) and are used for food, textile and transport (Hirst, 2017). About 2.5–3.0 million llamas are currently distributing in Bolivia (70%), Chile, Peru, and Argentina. Similarly, a world population of 3.88 million alpacas are mostly concentrated in Peru (77%), Bolivia (13%), Chile and Argentina. Breeding of llama and alpaca for commercial uses is expanding outside South America, particularly in the USA, Australia and many European countries (Crossley et al., 2010; Thomas and Morgan, 2013; La Vigna Alpacas, 2018).

### Old world camels
The role of dromedary camels (DCs) as the most likely source of human infection with MERS-CoVs is gradually establishing with continuous appearance of new evidence (Alagaili et al., 2014; Muhairi et al., 2016; Sabir et al., 2016; Miguel et al., 2017). Because MERS-CoV has never been identified in cattle (Hemida et al., 2013; Reusken et al., 2013a, 2013b) and has many unique antigenic and genetic characteristics that make it distinct from BCoVs (Hemida et al., 2013), it will not be discussed further in this review.

Although DCs are normal inhabitants of Northern and Eastern Africa and Southwestern Asia, the first report of bovine-like CoV infections in DCs came from the USA (Wünschmann et al., 2002). A case of severe lethal gastroenteritis was recorded in a 6-week-old female camel calf in Wisconsin. CoV particles with typical club-shaped projections were identified in the faeces of the diarrhoeic camel calf by EM. The virus showed specific reactivity with two MAbs, prepared against BCoV S and nucleocapsid (N) proteins, in the epithelial cells of colonic crypts by IHC. The nature and origin of the CoV were not elucidated; however, the role of interspecies transmission was proposed because individuals of other animals like horses, zebras and reindeer were kept with the camel calf in the same barn at the time of infection.

In 2013, a novel CoV, designated as DcCoV UAE-HKU23, was identified in 14 (4.8%) leftover DC faecal samples (four with diarrhoea) in the Central Veterinary Research Laboratory, Dubai, UAE. Complete genome analysis of DcCoV UAE-HKU23 in three faecal samples has classified the virus as a member of lineage A1 of Betacoronaviruses (Woo et al., 2014). However, genetic distance analysis and codon usage bias of polymerase, S and N genes of DcCoV UAE-HKU23 strains have demonstrated that it is distantly separated from other members of Betacoronavirus 1 and may form a unique cluster within the group (Woo et al., 2013).
Recombinant N protein of DcCoV UAE-HKU23 has been generated and utilized for the detection of the virus-specific antibodies in sera of 59 camels originated from Sudan, Saudi Arabia, Oman and Pakistan (Woo et al., 2014). Antibodies to the recombinant protein were identified in 98.3 and 100% of the tested sera samples using IF and VN assays. Immunization of mice with the recombinant N proteins of DcCoV UAE-HKU23 and MERS-CoV has confirmed minimal cross-antigenicity between both viruses in Western blot (WB) and VN assays (Woo et al., 2016). These results demonstrate that a Betacoronavirus, other than MERS-CoV, is circulating among DCs in different countries of Middle East and may contribute to pathological conditions of diarrhoea, particularly in camel calves.

Table 3. Betacoronavirus 1 strains used in the phylogenetic analysis

| Virus strain | Animal species | Year  | Country | GenBank Accession | Clinical form          | Reference                  |
|--------------|----------------|-------|---------|------------------|------------------------|----------------------------|
| BubCoV HKU26 B1-24F | Water buffalo | 2014  | Bangladesh | KU558922 | Winter dysentery | Lau et al. (2016) |
| BubCoV HKU26 B1-28F | Water buffalo | 2014  | Bangladesh | KU558923 | Winter dysentery | Lau et al. (2016) |
| DcCoV UAE-HKU23-265F | Dromedary camel | 2013  | UAE | KF906249 | Sporadic diarrhoea | Woo et al. (2014) |
| DcCoV UAE-HKU23-265F | Dromedary camel | 2013  | UAE | KF906250 | Sporadic diarrhoea | Woo et al. (2014) |
| DcCoV UAE-HKU23-262F | Dromedary camel | 2013  | UAE | KF906250 | Sporadic diarrhoea | Woo et al. (2014) |
| DcCoV UAE-HKU23-268F | Dromedary camel | 2013  | UAE | KF906251 | Sporadic diarrhoea | Woo et al. (2014) |
| ACoV-00-1381 | Alpaca | 1998  | USA | DQ915164 | Neonatal diarrhoea | Jin et al. (2007) |
| CA08-1/2008 | Alpaca | 2008  | USA | JQ410000 | Respiratory disease | Crossley et al. (2012) |
| US/OH-WD470/1994 | White-tailed deer | 1994  | USA | FJ425187 | Sporadic diarrhoea | Alekseev et al. (2008) |
| US/OH-WD388/1994 | Samber deer | 1994  | USA | FJ425189 | Winter dysentery | Alekseev et al. (2008) |
| US/OH-WD388-TC/1994 | Samber deer | 1994  | USA | FJ425188 | TC adapted | Alekseev et al. (2008) |
| US/OH-WD388-Gnc/1994 | Samber deer | 1994  | USA | FJ425190 | Calf passaged | Alekseev et al. (2008) |
| Wisent/2010 | Wisent | 2010  | South Korea | HM573326 | Winter dysentery | Chung et al. (2011) |
| US/OH/2003 | Giraffe | 2003  | USA | EF424623 | Sporadic diarrhoea | Hasoksuz et al. (2007) |
| US/OH/2006 | Giraffe | 2006  | USA | EF424624 | Calf passaged | Hasoksuz et al. (2007) |
| US/OH-TC/2006 | Giraffe | 2006  | USA | EF424622 | TC adapted | Hasoksuz et al. (2007) |
| Himalyan Tahr1-10/01 | Himalyan tahr | 2010  | South Korea | HM573327 | Winter dysentery | Chung et al. (2011) |
| Himalyan Tahr2-10/01 | Himalyan tahr | 2010  | South Korea | HM573328 | Winter dysentery | Chung et al. (2011) |
| Nyala 10/01 | Nyala | 2010  | South Korea | HM573330 | Winter dysentery | Chung et al. (2011) |
| Sitatunga 10/01 | Sitatunga | 2010  | South Korea | HM573329 | Winter dysentery | Chung et al. (2011) |
| US/OH/1/2003 | Water buck | 2003  | USA | EF424621 | Winter dysentery | Alekseev et al. (2008) |
| US/WD358/1994 | Water buck | 1994  | USA | FJ425186 | Winter dysentery | Alekseev et al. (2008) |
| BCoV Mebus | Cattle | 1972  | USA | U00735 | Calf diarrhoea | Stair et al. (1972) |
| BCoV ENT | Cattle | 1998  | USA | NC_003045 | Shipping fever | Storz et al. (2000) |
| BCoV LUN | Cattle | 1998  | USA | AF391542 | Shipping fever | Storz et al. (2000) |
| BCoV DB2 | Cattle | 1983  | USA | DQ811784 | Calf diarrhoea | Tsunemitsu et al. (1991) |
| BCoV LY-381 | Cattle | 1965  | USA | AF058942 | Calf diarrhoea | Doughri et al. (1976) |
| BCoV Quebec | Cattle | 1972  | Canada | AF220295 | Calf diarrhoea | Dea et al. (1980) |
| BCoV LSU-94LSS-051-2 | Cattle | 1994  | USA | AF058943 | Respiratory disease | Chouljenko et al. (1998) |
| BCoV 0501/2005 | Cattle | 2005  | South Korea | EU686689 | Winter dysentery | Park et al. (2006) |
| BCoV 0502/2005 | Cattle | 2005  | South Korea | EU401986 | Winter dysentery | Park et al. (2006) |
| BCoV Kakegawa | Cattle | 1979  | Japan | AB354579 | Winter dysentery | Akashi et al. (1981) |
| BCoV OK-0514-03 | Cattle | 2003  | USA | AF058944 | Respiratory disease | Chouljenko et al. (1998) |
| HCoV 229E | Human | NA | Germany | AF304460 | Respiratory disease | – |
Recently, three species of CoVs were identified in DCs in Saudi Arabia during a surveillance study that included 1309 nasal and rectal swab samples collected between May 2014 and April 2015 (Sabir et al., 2016). These CoVs included two Betacoronaviruses: MERS-CoV (group C) and camel HKU23-CoVs (group A), and one Alphacoronavirus (similar to human CoV 229E). All CoV-positive samples except three were nasal swabs, which indicates that the respiratory tract is the major shedding portal for

Fig. 1. Phylogenetic analysis of bovine-like coronaviruses based on the sequence of (a) nucleocapsid gene and (b) spike gene. Reference bovine coronaviruses were included for comparison purposes. Sequences were downloaded from GenBank (Table 3) and aligned together using Clustal W algorithm of MegAlign program, Lasergene software, version 3.18 (DNASTar, Madison, WI). Phylogenograms were constructed by MEGA 7.0 software using the maximum likelihood method. The strength of the tree was evaluated by bootstrapping of 1000 replicates. Bootstrap values are shown at the branch nodes of the tree. Bovine-like coronaviruses are grouped according to the type of animal(s), state or country of origin, and year of identification as indicated in the brackets at the right side. The scale bar at the bottom indicates the number of nucleotide changes per site.
CoVs in DCs. Regardless of MERS-CoV that has been detected in DCs in many countries worldwide, the HKU-23-CoV was detected in DCs in Dubai short time earlier (Woo et al., 2014) and a closely related camelid Alphacoronavirus was isolated from alpacas in the USA in 2007 (Crossley et al., 2010; Crossley et al., 2012). The high prevalence of CoVs in the collected samples, the frequent co-infections and the lack of symptoms in most CoV-positive cases propose that these CoVs are enzootic in DCs, at least in Saudi Arabia, and that they may play an important role in CoV ecology.

**New world camелиds**

CoV infection of llamas and alpacas was first recognized during an outbreak of severe diarrhoea in Oregon, USA in 1998. Among 39 pathogens detected, CoV was identified as the primary cause of the diarrhoeal complex in juvenile animals (crias) with a variable degrees of severity and frequent deaths (Cebra et al., 2003; Cebra, 2007). A single alpaca CoV (designated ACoV-00-1381) was isolated from the diarrhoeic samples by propagation in HRT-18 G cells. Sequence and phylogenetic analysis of the complete ACoV-00-1381 genome revealed close homology (≥99.5%) with two BCoV strains involved in shipping fever pneumonia and enteritis in feedlot calves: LUN and ENT, respectively (Storz et al., 2001; Fig. 1). A common ancestral origin of alpaca CoV and both strains of BCoV was proposed (Jin et al., 2007).

Bovine-like CoV was also acknowledged as a potential cause of neonatal diarrhoea in alpacas in two separate studies conducted in Casco in southern Peruvian highlands. In the first, CoVs have been detected in three out of 14 (23%) of the alpaca crias using immunochromatography (López et al., 2011). While in the second, the virus was detected in 20 out of 50 (40%) of the crias during an episode of diarrhoea in January and February 2010 using RT-PCR (Rojas et al., 2016). All the cases in the second study showed co-infection with other (up to three) enteric pathogens including *Eimeria* spp., *Cryptosporidium* spp., *E. coli* and rotavirus. However, the exact role of CoV in disease development and progression was unclear.

CoV-associated diarrhoea in adult alpacas is generally a rare event and is supported mostly by anecdotal evidence. A single report has documented the identification of a CoV in faecal specimen collected from 4-year-old hembra (female alpaca) in Stillwater, Oklahoma (Genova et al., 2008). The virus was classified as a member of antigenic group 2 CoVs (later termed as Betacoronaviruses) as a result of its cross-reactivity with MAb specific for N protein of antigenic group 2 CoVs in IHC.

In contrast to all previous reports that correlate CoVs in alpaca with gastroenteritis, a novel CoV was retrieved from the lung tissue of a clinical case with alpaca respiratory syndrome (ARS) in California on October 2007. The CoV was isolated with the CRFK cell line and its identity was confirmed by transmission EM, sequence analysis of a short conserved fragment within the polymerase gene (Crossley et al., 2010), and later by full-genome sequencing (Crossley et al., 2012). The widespread nature of respiratory CoV in alpacas was verified through testing 40 sera samples taken from animals with a history of ARS and 167 sera samples randomly selected from alpacas with unknown disease history. The majority of samples with ARS history (60%) has shown antibody titres ≥1:16 in VN assay using the plaque-purified respiratory alpaca CoV. However, only 3% of the samples collected from animals with unknown history showed similar titres (Crossley et al., 2010).

No consequent outbreaks of the respiratory alpaca CoV was recorded in the USA or elsewhere, which raised questions about the origin and circulation of the virus in the alpaca population. Genome sequencing of the respiratory alpaca CoV revealed close homology with the Alphacoronaviruses (particularly with HCoV-229E; 92.2%), unlike the enteric alpaca CoVs that were routinely identified as Betacoronaviruses. Comparison of S gene sequences from the respiratory alpaca CoV and a range of HCoV-229 isolates recovered from 1962 to 2003 showed close genetic homology with HCoV-229 strains isolated from the 1960s until the early 1980s. It was concluded that a common ancestor of HCoV-229E and respiratory alpaca CoV may have existed either in people or alpacas before 1960, and crossed the interspecies barrier to establish infection in the other species thereafter (Crossley et al., 2012). The virus may have circulated among alpacas at low levels for decades before suddenly appearing during the 2007 outbreak. Explanation of the absence of further disease outbreaks in the subsequent years needs further investigation.

**Bovine-like CoVs in captive and free-range wild ruminants**

**Deer (Cervidae)**

Deer are one of the most widely distributed ruminant animals on the Earth. They constitute a natural component of the biological communities in all continents except Australia and Antarctica. All deer species are included in the family Cervidae with two subclasses: (1) old world deer (subfamily Cervinae), which contains 33 deer species including elk (wapiti), muntjac, chital, sika deer and sambar deer, (2) new world deer (subfamily Capreolinae), which comprises 21 deer species including reindeer (caribou), pudu and European elk (moose) (Bertin, 2017). Breeding of deer (particularly in game farms) is currently a growing interest for venison production, which is characterized by high-protein content and low-cholesterol level (Smits, 1991). To date, bovine-like CoVs were demonstrated in only six deer species, which are caribou/reindeer (*Rangifer tarandus caribou*) (Elazhary et al., 1981), elk/wapiti (*Cervus elephus*) (Smits, 1992; Majhdi et al., 1997; Daginakatte et al., 1999), sambar deer (*Cervus unicolor*), white-tailed deer (*Odocoileus virginianus*) (Tsunemitsu et al., 1995; Alekseev et al., 2008), sika deer (*Cervus nippon yesoensis*) (Yokoi et al., 2009) and water deer (Kim et al., 2018).

**Cariboo/reindeer**

The evidence of bovine-like CoVs in Cariboo was demonstrated through a surveillance study that investigated the prevalence of antibodies to five bovine respiratory and enteric viruses in two caribou herds in Northern Quebec, Canada. While bovine viral diarrhoea virus was the most prevalent in both years, bovine-like CoV was the least prevalent (bovine parainfluenza 3 virus was absent from all samples). Among 30 samples collected in 1978 and 28 samples in 1979, CoV-specific antibodies were detected in four (13.3%) and zero (0%) samples in both years, respectively. The source of bovine-like CoV infection was unclear because both caribou herds had no direct contact with domestic ruminants for at least 25 years (Elazhary et al., 1981).

**Elk/wapiti**

CoVs have been frequently linked to enteritis and scouring in neonatal elk. The virus was isolated as the only pathogen in five
out of 11 calves with diarrhoea (45.5%) in western North America (Smits, 1991; Smits, 1992). In a subsequent study, two CoV isolates were retrieved from faecal samples collected from 10-month-old captive elk calves with diarrhoea in the USA (Majhdi et al., 1997). The virus isolates in the latter study (designated WY-28 and WY-29) showed a high degree of antigenic and genetic relation to BCoV, based on several observations: (1) comparable protein profiles as determined by SDS-PAGE, (2) similar transcriptional patterns in Northern blot analysis, (3) significant sequence homology (99%) between N gene sequence of both viruses, (4) cross-reactivity with MAb specific for S protein of BCoV in WB, and (5) ability of four MABs specific for N protein of elk CoV, to detect BCoV in intestinal tissues by IHC (Majhdi et al., 1997; Daginakatte et al., 1999).

**Samber and white-tailed deer**

Infection of sambar deer with bovine-like CoVs was only recorded during an outbreak of diarrhoea that occurred in a wild animal park in southern Ohio, USA in the winter season of 1993/1994. Affected animals showed severe symptoms of bloody diarrhoea, which resembled WD in adult cattle, with a mortality rate of 30%. In another wild animal park in north central Ohio, episodes of watery diarrhoea in white-tailed deer were also monitored throughout 1994. CoV particles were identified in faecal samples collected from three sambar deer and one white-tailed deer using immunocytochemistry and antigen detection ELISA. Two CoV isolates (KI-D2 from sambar deer and WTD from white-tailed deer) were recovered in the Cariboo HRT-18 cell line. Both isolates demonstrated close relationship with several BCoV strains causing CD and WD based on similar biologic (haemagglutination and receptor-depressing activities) and antigenic reactivity in HI, VN, IF and WB tests (Tsunemitsu et al., 1995). Analysis of the full genome sequence of both isolates (either cell culture-adapted or gnotobiotic calf-passaged) confirmed the marked similarity with BCoVs, particularly LUN and ENT strains isolated in 1998 (Fig. 1b), with no specific genetic markers that can discriminate KI-D2 and WTD from BCoV strains (Alekseev et al., 2008). Additionally, 30 sera samples were acquired from free-range healthy white-tailed deer located in a third wild animal park in Ohio. Two samples (6.6%) were seropositive against both isolates and several BCoV strains in IF assay (Tsunemitsu et al., 1995).

**Sika deer**

This type of deer is a native species in Hokkaido, Japan. A single observation of potential infection with bovine-like CoV was reported in a serosurveillance study that evaluated the prevalence of antibodies to eight bovine viruses in sika deer. Serum samples were collected from a farm of sika deer in eastern Hokkaido between June 2006 and September 2007 and from wild animals during the hunting season of 2000. Among 179 farmed deer, only two (1.1%) samples were reactive to BCoV in VN assay. Unfortunately, not all samples collected from wild sika deer (no = 97) were tested for BCoV (Yokoi et al., 2009).

**Water deer**

The evidence of water deer (Hydropotes inermis) infection with bovine-like CoVs was not demonstrated in captive animals during a study that extended between 2010 and 2012 in South Korea (Kim et al., 2014). However, in a recent study that involved 77 nasal swab samples, collected during 2016 and 2017 from non-captive water deer living in Chungnam Wild Animal Rescue Center, South Korea, three positive samples (3.9%) were obtained.

The phylogenetic analysis, based on a partial sequence of the polymerase gene, indicated close relationship of the three water deer CoVs with BCoV (99.2%). Complete genome sequencing of a single water deer CoV strain (designated W17-18) revealed close relationship to BCoV and other bovine-like CoVs (homology >98%) with minor unique genetic characteristics of the non-structural protein 4.8 kDa. This report is the only one that proposes the implication of bovine-like CoVs in respiratory diseases of wild ruminants (Kim et al., 2018).

**Wild cattle**

Similar to domestic cattle, wild bovidae have also been associated with CoV-induced scourds in calves and WD in adults. During the winter season of 1979–1980, an outbreak of diarrhoea occurred among a group of musk oxen (Ovibos moschatus) in Whipsnade zoological park in Bedfordshire, UK. CoVs were identified in the faecal samples collected from diseased animals using EM. Unfortunately, virus strains were not isolated or characterized due to technical limitations (Chasey et al., 1984). CoVs are also among the common pathogens isolated from bison (Bison bison) calves with diarrhoea (Haigh et al., 2002). However, the actual prevalence of CoVs in bison is underestimated because bison mask the clinical signs of the disease syndrome (Berezowski, 2001). CoVs were also demonstrated in the faeces of adult wisent – European bison (Bison bonasus) suffering from severe diarrhoea in the National Zoo of South Korea. The outbreak started in a wisent, albeit no cattle were housed in the zoo and no cattle farms existed in the vicinity, and spread to other wild ruminants in the park. All identified CoVs were quite similar in terms of nucleotide and deduced amino acid sequence. They also showed high level of genetic relationship (99.4–99.5%) to BCoVs isolated in South Korea after 2004, particularly BCoV-0501 and BCoV-0502 strains (Fig. 1b). It was concluded that all bovine-like CoVs characterized in this study were replicates of a single strain that has no restricted host specificity. This strain may originate, via an unclear pathway, from the same ancestor of BCoV-0501 and BCoV-0502 strains of cattle (Chung et al., 2011). More recently, a serological study was conducted in a population of wood bison (B. bison athabascae) that were reintroduced in the wild in southwestern Youkon, Canada since 1988. Antibodies to BCoV were demonstrated in only two out of 31 (7%) of the animals tested (Harms et al., 2019).

**Antelopes**

The antelope is a deer-like mammal that belongs to the family Bovidae but is not cattle, buffalo, sheep or goat. Antelope is not a taxonomic name rather than a common term that collects a variety of grazing ruminants characterized by long legs and permanent horns. These old world animals are indigenous to Africa and Euroasia and may be found in parts of the Americas (Estes, 2017). To date, the role of bovine-like CoVs in CD and WD was only described in four species of antelopes including waterbuck (Kobus ellipsiprymnus) (Chasey et al., 1984; Tsunemitsu et al., 1995), sitatunga (Tragelaphus speki) (Chasey et al., 1984; Chung et al., 2011), nyala (Tragelaphus angasii) (Chung et al., 2011) and sable antelope (Hippotragus niger) (Hasokusz et al., 2007).

**Waterbuck**

In the beginning of 1982, an outbreak of watery diarrhoea was suddenly erupted in a herd of nine waterbucks in the Cotswold wildlife
park in Oxfordshire, England. Four animals (two adults and two calves) were lost and bovine-like CoVs were identified in the faeces of affected animals using EM and ELISA. Attempts to propagate these viruses in HRT-18 cell culture were unsuccessful. Additionally, experimental infection of gnotobiotic calf calves with the faecal materials of dead waterbucks did not reveal clinical reproduction of the disease. The inoculated calves did not shed the virus in their faeces, did not develop antibody responses and were not immune against experimental challenge with BCoV field strain (Chasey et al., 1984). Infection of waterbuck with bovine-like CoVs was further confirmed in another epizootic outbreak of diarrhoea that occurred in Ohio wild animal park in 1993 and 1994. The aetiologic virus (designated KI-WB) has been isolated in cell culture and has close biologic and antigenic relation to BCoVs (Tsunemitsu et al., 1995). Unlike the virus detected in the UK in 1982, the gnotobiotic and Colostrum-deprived calves experimentally infected with KI-WB strain developed signs of acute diarrhoea and excreted the virus in their faeces and nasal secretions.

**Sitatunga**

CoVs were identified in faecal samples collected from sitatunga on two different occasions. The first was during an outbreak of diarrhoea in Whipsnade Zoological Park in the winter season of 1979/1980 (and again in February 1984) using EM and ELISA (Chasey et al., 1984). The second occurred during an outbreak that affected four animal species, including sitatunga, in the National Zoo of South Korea in 2010. Sitatunga was the only animal that showed both enteric and respiratory symptoms. Among 16 affected animals in the park, rectal swabs were taken from three adult sitatunga (older than 2 years) and all of these samples showed the characteristic CoV particles by EM (Chung et al., 2011).

**Nayla**

Two nayla animals were affected during the diarrhoea epidemic that occurred in the National Zoo of South Korea in 2010. The CoV particles detected in the faeces of affected animals were quite similar to those identified in wisent, sitatunga and Himalayan tahr, suggesting all of these are host-range variants of the same strain (Chung et al., 2011).

**Sable antelope**

An outbreak of diarrhoea occurred in several ruminant species in an Ohio wild animal park in 2003. The outbreak started in a sable antelope and spread 1–2 weeks later to giraffes that were housed in a separate barn 0.5 miles away. A single faecal sample was obtained from the sable antelope and was tested by immunocytchemistry using BCoV-specific antisera. CoV particles were detected in the faecal sample, but, unlike the giraffe isolates, the virus strain could not be adapted to cell culture or to induce productive infection in gnotobiotic calves (Hasoksuz et al., 2007). Genetic analysis revealed close relatedness with the giraffe isolates, several BCoVs, and to a lesser extent with KI-D2, WTD and KI-WB strains isolated from sambar deer, white-tailed deer and waterbuck, respectively (Alekseev et al., 2008; Fig. 1).

**Giraffe (Giraffa camelopardalis)**

Giraffes are the tallest animals and the largest ruminants on the Earth. They mostly inhabit Africa and are considered vulnerable to extinction, with an overall worldwide population of 97,000 animals (Milman, 2017). A single report described isolation and characterization of bovine-like CoVs from giraffes during the outbreak of diarrhoea in an Ohio wild animal park in 2003 (Hasoksuz et al., 2007). Bovine-like CoVs were identified in the faeces of three (two males and one female) giraffes by immunocytchemistry. The virus was successfully adapted and isolated from the faecal extract of a 24-year-old male giraffe with HRT-18 cell culture. The virus isolate (designated as GiCoV-OH3) revealed close biologic, antigenic and genetic relationship with different strains of BGoV, principally with the enteric strains ENT and DB2.

Although infection in giraffes was conclusive from the outbreak progression in the wild animal park, the definite source of this outbreak remains uncertain. The infection may have originated from wild animals in the park, which harbour the virus without clinical signs, or from a nearby cattle farm. The latter possibility was supported by the ability of GiCoV-OH3 strain to induce severe diarrhoea when orally administrated into a gnotobiotic calf, with virus shedding that lasts for 2–3 days. The risk of virus transmission between cattle and giraffes seems important, particularly in Africa where grazing regions of both animals overlap. This may allow virus evolution and potential spread of new CoV strains to remote regions upon change in pastures, game farming and transfer of wild animals to zoological parks.

**Himalayan tahr (Hemitragus jemlahicus)**

Tahr is a wild species of goat native to the Himalayan mountains in Central Asia. They are specially adapted to life on the mountain slopes and are now considered a near-threatened species (Bhatnagar and Lovari, 2008). During the epizootic outbreak of WD that affected several ruminant species in the National Zoo of South Korea in 2010, three Himalayan tahrs presented signs of weakness, depression, anorexia, bloody diarrhoea and dehydration. Bovine-like CoVs were demonstrated in the faeces of affected animals using EM and their genetic characteristics were analysed (Chung et al., 2011).

**Conclusion**

Bovine-like CoVs are widely distributed in domestic ruminants other than cattle and in captive and free-range wild ruminant species. The majority of bovine-like CoVs have confirmed close relationship with different BCoV strains that produce gastroenteritis in neonatal calves and lactating cows, and respiratory disease complex in growing and steer calves. It is generally accepted today that bovine-like CoVs are host-range variants of BCoV, which is crossing the interspecies barriers on a regular basis. Transmission of BCoV variants from cattle to other ruminants and vice versa allows persistence of the infection in nature, recurrent emergence of epidemics and continuous evolution of the virus. Wild ruminants, in particular, are not confined to discrete geographic regions and are always moving to seek new pastures, to escape from predators, and to find mates. Human activities, including – but not restricted to – deforestation, over-hunting and game farming, also force wild animals to change habitats. Continuous movement of wild animals promotes virus transmission to new terrestrial areas, and, importantly, provides a window for the virus to adapt to new hosts and to develop into novel strains.

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