

Review

Global distribution of peste des petits ruminants virus and prospects for improved diagnosis and control

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Viral diseases of farm animals, rather than being a diminishing problem across the world, are now appearing with regularity in areas where they have never been seen before. Across the developing world, viral pathogens such as peste des petits ruminants virus (PPRV) place a huge disease burden on agriculture, in particular affecting small ruminant production and in turn increasing poverty in some of the poorest parts of the world. PPRV is currently considered as one of the main animal transboundary diseases that constitutes a threat to livestock production in many developing countries, particularly in western Africa and south Asia. Infection of small ruminants with PPRV causes a devastating plague and as well as being endemic across much of the developing world, in recent years outbreaks of PPRV have occurred in the European part of Turkey. Indeed, the relevance of many once considered 'exotic' viruses is now also high across the European Union and may threaten further regions across the globe in the future. Here, we review the spread of PPRV across Africa, Asia and into Europe through submissions made to the OIE Regional Reference Laboratories. Further, we discuss current control methods and the development of further tools to aid both diagnosis of the disease and prevention.

Introduction

Peste des petits ruminants virus (PPRV) causes an increasingly important viral disease of livestock that predominantly infects small ruminants such as sheep and goats. It is classified in the order *Mononegavirales*, family *Paramyxoviridae*, subfamily *Paramyxovirinae*, genus *Morbillivirus* on account of its genetic similarity with other members of the genus *Morbillivirus* that includes measles virus (MeV), rinderpest virus (RPV), canine distemper virus (CDV) and a number of other viruses that infect aquatic mammals. The non-segmented, negative-strand genome encodes eight proteins: the nucleocapsid protein (N), the phosphoprotein (P), the matrix protein (M), the fusion protein (F), the haemagglutinin protein (H), the polymerase protein (L) and the two non-structural proteins, C and V (Fig. 1a). Structurally, the morbilliviruses are morphologically pleomorphic particles (400–500 nm) similar in appearance to other members of the family *Paramyxoviridae* being enveloped (cell membrane derived) with viral glycoproteins seen as peplomers protruding from the envelope. Under the electron microscope the negative-sense RNA genome in association with viral protein is also visible; this ribonucleoprotein (RNP) complex forms a helical structure and in appearance resembles a 'herring bone'

(Barrett *et al.*, 1993). For RPV, these complexes are visualized as distinct regions within the cytoplasm (Fig. 1b). However, the mechanisms of assembly, aggregation and interactions between viral RNP, viral proteins and host factors remains largely unknown (Fig. 1b).

PPRV has a widespread distribution spanning West and Central Africa, Arabia, the Middle East and southern Asia (Nanda *et al.*, 1996; Shaila *et al.*, 1996). This area encompasses much of the developing world that relies heavily on subsistence farming to supply food or goods for trade, and small ruminants provide an excellent supply of both. With its associated high morbidity and mortality, PPRV constitutes one of the major obstacles to subsistence farming; mortality from infection reaching 50–80% in a naive population (Kitching, 1988). In severe cases PPRV is characterized by pyrexia, mucopurulent ocular and nasal discharges, conjunctivitis and erosion of the mucosa (especially the pulmonary tract). In most fatal infections, death is caused by primary viral bronchopneumonia or severe dehydration caused by acute diarrhoea. Infection of pregnant animals with the virus has also, albeit rarely, been linked to abortion. The importance of this and the mechanisms by which it occurs are currently unknown

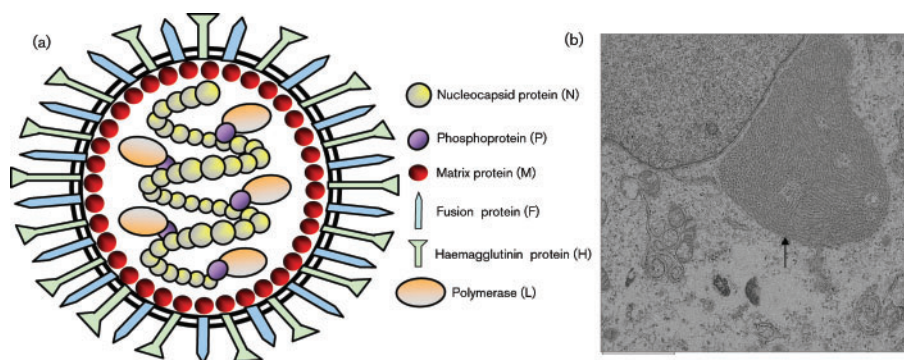


Fig. 1. Morbillivirus structure. (a) A schematic diagram of morbillivirus virion structure. (b) Electron micrograph of viral ribonucleoprotein (RNP) present within an RPV-infected cell. The RNP is clearly seen as a typical 'herring-bone' structure (arrow) and is known to contain viral RNA and proteins within the cytoplasm. Bar, 2000 nm.

(Abubakar *et al.*, 2008) although co-infection with both PPRV and pestiviruses in cases of abortion has been reported (Kul *et al.*, 2008). The virus is highly contagious and easily transmitted by direct contact between the secretions and/or excretions of infected animals and nearby healthy animals (Ezeibe *et al.*, 2008). Virulence appears to vary from strain to strain, although there is only one serotype, and disease symptoms are often confused with, and exacerbated by, secondary infections making PPRV a difficult disease to characterize, diagnose and treat (Couacy-Hymann *et al.*, 2005) with differential diagnosis including pasteurellosis, contagious ecthyma, contagious caprine pleuropneumonia (CCPP), bluetongue (BTV), heartwater, coccidiosis, mineral poisoning and foot-and-mouth disease. PPRV is sometimes referred to as a more serious disease of goats than sheep, however, reports detailing an increased susceptibility of sheep populations, goat populations and outbreaks affecting sheep and goat populations have been equally reported (Chauhan *et al.*, 2009; Roeder *et al.*, 1994; Singh *et al.*, 2004; Taylor & Abegunde, 1979; Taylor *et al.*, 2002; Wang *et al.*, 2009). In fact in some outbreaks goats appear not to be affected, while sheep succumb with high rates of mortality and morbidity (Yesilbag *et al.*, 2005). The reason for this variability is unclear but both virus sequence and host species are thought to be of importance. Different strains of PPRV have been shown to exhibit varied virulence when experimentally infected into the same breed of goat (Couacy-Hymann *et al.*, 2007), and different breeds of goat have been shown to respond differently to infection with the same virus (Diop *et al.*, 2005). Asymptomatic infections are also known to occur in some species (Bidjeh *et al.*, 1995) although how the virus circulates in the absence of clinical disease is not understood.

Virus identification and host range

Historically, PPRV has often been confused with the closely related Rinderpest virus (RPV), the history of which dates

back as far as the late fourth century AD (Curasson, 1932; Henning, 1956). RPV is predominantly a disease of large ruminants and is linked historically with devastating epidemics often with very high mortality rates. In contrast to the extensive historical data available on RPV the first recorded description of PPRV dates back to 1942 when Gargadennec and Lalanne, identified a disease closely related to RPV in the Ivory Coast. Early observations suggested that the disease was not transmissible from small ruminants to in-contact cattle and this led them to assume it was a novel virus distinct from RPV (Gargadennec & Lalanne, 1942).

PPRV primarily infects sheep and goats, although both cattle and pigs are susceptible to infection, but do not contribute to the epidemiology as they are unable to excrete virus. The existence of sylvatic reservoirs for PPRV has been reported with infections and deaths in captive wild ungulates from several species having been described previously (Abu-Elzein *et al.*, 2004; Furley *et al.*, 1987; Kinne *et al.*, 2010; Ogunsanmi *et al.*, 2003). These outbreaks of disease, often described in wildlife collections living in semi-free-range conditions, have shown that many species are susceptible (Table 1). Interestingly, within the species reported by Kinne *et al.* (2010) no oral lesions were observed in any of the infected animals, which in turn may have implications for transmissibility. Genetic characterization of the virus responsible for these deaths suggested that it was more closely related to Chinese strains of PPRV recently isolated than Arabian viruses (Kinne *et al.*, 2010). Whilst it is clear that a number of wildlife species are susceptible to infection, the role of wildlife in the epizootiology and epidemiology of PPRV remains an enigma.

It has been proposed that PPRV may circulate silently, occasionally causing sporadic epidemics when the host population's immunity levels drop. The spread of PPRV is affected by both host density and birth rate and animals that survive infection are protected for life. Where

Table 1. Detection of PPRV in wildlife species

| Species | Latin name | Reference |
|---------------------------|------------------------------------|------------------------------------|
| Laristan sheep | <i>Ovis gmelini laristanica</i> | Furley <i>et al.</i> (1987) |
| Gemsbok | <i>Oryx gazella</i> | Furley <i>et al.</i> (1987) |
| Dorcas gazelles | <i>Gazella dorcas</i> | Furley <i>et al.</i> (1987) |
| Thompson's gazelle | <i>Eudorcas thomsonii</i> | Abu-Elzein <i>et al.</i> (2004) |
| Nubian Ibex | <i>Capra nubiana</i> | Furley <i>et al.</i> (1987) |
| Indian buffalo | <i>Bubalus bubalus</i> | Govindarajan <i>et al.</i> (1997) |
| African Grey dukier | <i>Sylvicapra gramma</i> | Ogunsanmi <i>et al.</i> (2003) |
| Arabian oryx | <i>Oryx leukoryx</i> | Frölich <i>et al.</i> (2005) |
| Bubal hartebeests | <i>Alcelaphus buselaphus</i> | Couacy-Hymann <i>et al.</i> (2005) |
| Buffaloes | <i>Syncerus caffer</i> | Couacy-Hymann <i>et al.</i> (2005) |
| Defassa waterbuck | <i>Kobus defassa</i> | Couacy-Hymann <i>et al.</i> (2005) |
| Kobs | <i>Kobus kob</i> | Couacy-Hymann <i>et al.</i> (2005) |
| Arabian mountain gazelles | <i>Gazella gazella cora</i> | Kinne <i>et al.</i> (2010) |
| Springbuck | <i>Antidorcas marsupialis</i> | Kinne <i>et al.</i> (2010) |
| Arabian gazelles | <i>Gazella gazella</i> | Kinne <i>et al.</i> (2010) |
| Barbary sheep | <i>Ammotragus lervia</i> | Kinne <i>et al.</i> (2010) |
| Bushbucks | <i>Tragelaphus scriptus</i> | Kinne <i>et al.</i> (2010) |
| Impala | <i>Aepyceros melampus</i> | Kinne <i>et al.</i> (2010) |
| Rheem gazelles | <i>Gazella subgutturosa marica</i> | Kinne <i>et al.</i> (2010) |
| Afghan Markhor goat | <i>Capra falconeri</i> | Kinne <i>et al.</i> (2010) |

particularly virulent isolates are involved and a naïve population is exposed to the virus, the mortality rate is often very high. Herd animals that are in constant contact with each other, like sheep and goats, are therefore very susceptible to serious outbreaks (Anderson, 1995).

Historical distribution

PPRV has been identified as the cause of several serious epidemics in small ruminant populations over the last three decades and, since 1993, the Arabian Peninsula, the Middle East and major parts of the Indian subcontinent have reported major outbreaks and the virus is now considered endemic across this region (Dhar *et al.*, 2002). Lineage differentiation is determined by the sequence comparison of a small region of the F gene (Forsyth & Barrett, 1995) or N gene (Couacy-Hymann *et al.*, 2002), depending on the reaction components used by the testing laboratory. Historically, African isolates of PPRV were numbered lineage I–III according to the proposed spread of the virus from West Africa to East Africa. Following this nomenclature, the N gene primer sets (Couacy-Hymann *et al.*, 2002) typed West African viruses from Senegal, Guinea, Guinea-Bissau, Ivory Coast and Burkina Faso as belonging to lineage I. The isolates derived from Ghana, Mali and Nigeria then formed lineage II and those detected in Ethiopia and Sudan were from lineage III. Data derived from the F gene material reversed the classification of lineage I and II isolates and historically this difference has been maintained (Shaila *et al.*, 1996). The current molecular characterization of PPRV virus isolates divides them into four genetically distinct lineages: lineage I being represented mainly by Western African isolates from the

1970s and recent isolates from Central Africa; lineage II by West African isolates from the Ivory Coast, Guinea and Burkina Faso; lineage III by isolates from Eastern Africa, the Sudan, Yemen and Oman; lineage IV includes all viruses isolated from recent outbreaks across the Arabian Peninsula, the Middle East, southern Asia and recently across several African territories. Data generated by PCR and sequencing is routinely used to construct phylogenetic trees for PPRV and ascribe different isolates to the different lineages (Dhar *et al.*, 2002; Ozkul *et al.*, 2002; Shaila *et al.*, 1996). It is unclear whether this lineage assortment has any relationship to pathogenicity or is just a result of geographical speciation. The current classification of characterized PPRV isolates from data generated from both the nucleocapsid (N) gene and the fusion (F) gene are detailed in Fig. 2(a, b), respectively. Recent studies with very closely related lineage IV isolates have suggested that the N gene is more divergent and therefore more suitable for phylogenetic distinction between closely related circulating viruses (Kwiatk *et al.*, 2007).

Current distribution of PPRV

Africa

West Africa. PPRV was first identified in West Africa in Nigeria in 1942. It is currently believed to be endemic across much of West Africa (Fig. 3). However, virus outbreaks are often poorly characterized due to the lack of reporting systems and facilities within which to conduct molecular tests. West Africa includes 16 countries distributed over an area of approximately 5 million square km. A number of these countries have experienced significant outbreaks of PPRV. In recent years, material submitted to Regional



Fig. 2. Phylogenetic trees for sequenced isolates of PPRV. (a) Genetic characterization using PCR based on the N gene at CIRAD-EMVT (Couacy-Hymann *et al.*, 2002). The tree was constructed using a weighted neighbour-joining method. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. Phylogenetic analyses were conducted using the Darwin package. (b) Phylogenetic characterization of genetic material derived from the F gene PCR at IAH (Forsyth & Barrett, 1995). The evolutionary history was inferred using the neighbour-joining method with evolutionary distances being computed using the Kimura two-parameter method. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. Phylogenetic analyses were conducted in MEGA4.

Reference Laboratories (RRLs) has confirmed the presence of the either antibodies to the virus or the detection of viral nucleic acid in samples from Burkina Faso (2008), Ghana (2010), Nigeria (2007) and Senegal (2010) (Fig. 3). PPRV strains from both lineages I and II are currently circulating across West Africa although undoubtedly many outbreaks are not characterized at the molecular level. Other cases of PPRV in sheep, goat and camel populations have also recently been described in Nigeria (El-Yuguda *et al.*, 2010; Ibu *et al.*, 2008) and a further Nigerian study used haemagglutinin tests with faecal matter to detect PPRV

excretion and suggested that healthy animals may serve as carriers for PPRV (Obidike *et al.*, 2006). In Burkina Faso, antibody prevalence to PPRV of 28.5% has been reported in the north (Sow *et al.*, 2008).

East Africa. East Africa is generally used to specifically refer to the area now comprising the countries of Kenya, Tanzania and Uganda but often includes Somalia, Djibouti, Ethiopia and Eritrea. PPRV is endemic across the majority of these countries with genetic typing of the virus in 1996 determining a virus circulating in Ethiopia as belonging to

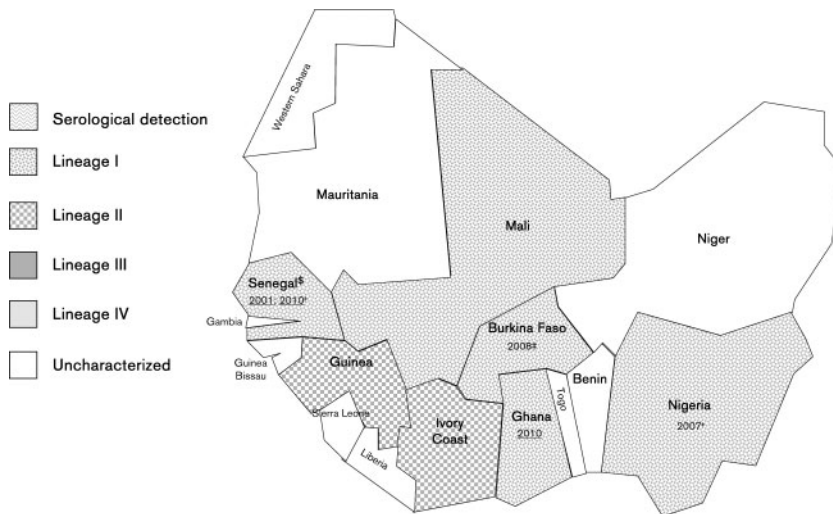


Fig. 3. Distribution of PPRV across West Africa (2000–2010). Countries that have reported disease between 2000 and 2010 are detailed. Historical detection of PPRV prior to 2000 is detailed in the text. All samples submitted to RRLs are shown with the following key: XXXX, serological detection by IAH; XXXX[±], serological detection by CIRAD; XXXX, RT-PCR detection by IAH; XXXX[±], RT-PCR detection by CIRAD. Samples taken from wildlife species are marked *. Where characterized, lineage differentiation and serological positivity are shaded according to the key next to the map. \$, Historically both lineages I and II have been detected in Senegal.

lineage III (Fig. 2a, b). Previous isolations of viruses that group in lineage III include two isolates from wildlife in Oman (1983) and the United Arab Emirates (1986), a Sudanese isolate (1972) and an unexpected virus isolate from sheep in southern India from 1992 (discussed in further detail below). More recently, confirmation of endemicity of PPRV across East Africa has been shown through the detection of antibodies to PPRV in Kenya (1999 and 2009) and Uganda (2005 and 2007). Molecular tools have characterized, where appropriate samples were available, some of these viruses as belonging to lineage III with isolates being characterized in Sudan (2000), Uganda (2007), and most recently in Tanzania (2008 and 2010) (Fig. 4). Lineage IV viruses have also been isolated from the Sudan in 2000, 2004, 2008 and 2009 (Khalafalla *et al.*, 2010) (Fig. 2a). Clearly both lineages III and IV are circulating in the Sudan and further serological reports from the country have confirmed outbreaks of PPRV in Sudan (Osman *et al.*, 2009; Saeed *et al.*, 2010). Swai *et al.* (2009) recently confirmed natural transmission of PPRV and circulation of virus within herds in Tanzania. In this study, serological detection methods were used to evaluate seroconversion among sheep and goat herds from seven different geographical regions in northern Tanzania. A high overall seroprevalence of antibodies to PPRV in sheep and goats (45.8%) was seen with seropositivity of goats (49.5%) being significantly higher than that seen in sheep (39.8%) (Swai *et al.*, 2009).

PPRV was recently detected in Kenya in 2006 in the Turkana district. The disease rapidly spread to 16 districts, including several where it has been associated with severe socioeconomic consequences for food security and has impacted on the livelihoods of the local population. Mortality rates varied according to age with 100% mortality in kids, 40% in young animals and 10% in adult animals. Between 2006 and 2008 it is estimated that more than 5 million animals were affected across the 16 Kenyan districts with more than half of the infected animals succumbing to

disease. The annual loss attributed to PPRV in Kenya is currently thought to be in excess of 1 billion Kenyan shillings (US\$15 million; UK 10.5 million). Vaccination and quarantine have been used to stop the continued spread of PPRV in Kenya. However, inadequate funding, limited stocks of available vaccine, shortage of trained staff to coordinate vaccination programmes, tribal clashes, drought and the mobility of the pastoral communities

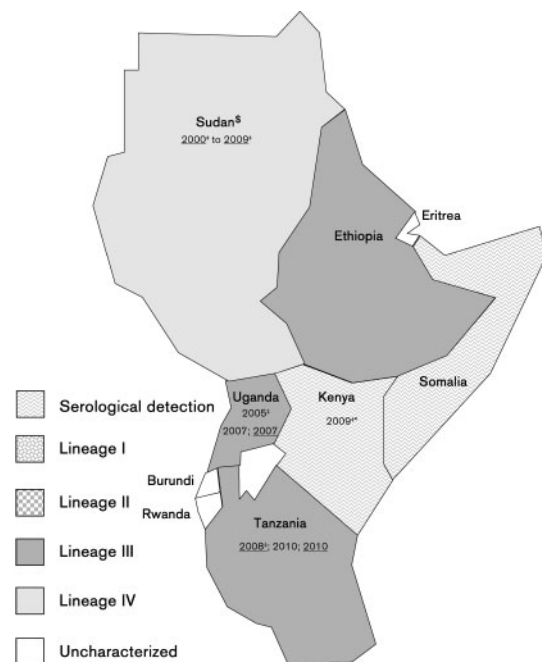


Fig. 4. Distribution of PPRV across East Africa (2000–2010). For key see Fig. 3. \$, Sudan currently has both lineages III and IV circulating although from 2000 to 2009 lineage IV has also been predominantly detected.

involved have made the task more problematic (Anonymous, 2008).

Somalia was also affected by PPRV in 2006 with the central regions being most seriously affected. Fortunately, the geological topology of Somalia prevented the spread of disease across the entire country. Nevertheless, ring vaccination was implemented in 2009 in Somalia to prevent further spread (Nyamweya *et al.*, 2009). Whilst not confirmed by laboratory diagnosis, PPRV was also seen in Ethiopia in 2008 and 2009 and vaccination was carried out alongside CCPP vaccination programmes (Nyamweya *et al.*, 2009). Despite the absence of molecular typing for the recent Kenyan and Somalian outbreaks it is likely that the virus circulating in these areas is lineage III.

Central Africa. Central Africa includes a core region of the African continent: namely Burundi, the Central African Republic (CAR), Angola, Cameroon, Chad, Gabon, the Democratic Republic of the Congo (DRC) and Rwanda. Historically, as with West and East Africa, serological techniques have identified PPRV in a number of regions. These include CAR (1999, 2005 and 2006), Congo (2006), Chad (1999 and 2006), Cameroon (2009) (Awa *et al.*, 2000) and Gabon (2007). Phylogenetic analysis has shown that lineage IV viruses are circulating across Central Africa (Fig. 5).

North Africa. North Africa is the northernmost region of the African continent, linked by the Sahara to sub-Saharan Africa. Geopolitically, northern Africa includes seven countries or territories: Algeria, Egypt, Libya, Morocco, Sudan, Tunisia and Western Sahara. Algeria, Morocco, Tunisia, Mauritania and Libya together are sometimes referred to as the Maghreb (or Maghrib), while Egypt is a *trans*-continental country by virtue of the Sinai Peninsula, which is in Asia. Historically, it is hypothesized that PPRV spread into North and East Africa from West Africa, moving up through trade routes through Sudan and Egypt and into the Middle East. The *trans*-continental classification of Egypt makes categorization of it into a defined region difficult. Historically, PPRV has been detected in 1987 and 1990 in Egypt (Ismail & House, 1990), whilst more recently an outbreak in Aswan province again highlighted the ability for infected goats to occasionally be asymptomatic, whilst others develop severe clinical disease (El-Hakim, 2006). Molecular typing has characterized a recent discovery of PPRV in Egypt as lineage IV (Fig. 6).

With the *trans*-continental status of Egypt it is suggested that the remainder of North Africa was totally free from PPRV until recently when an extensive outbreak occurred in Morocco. During 2008, local veterinary services reported 257 outbreaks across 36 of Morocco's 61 provinces. Despite low mortality and morbidity rates this outbreak was of great significance due to commercial trade between Morocco and both Algeria and Spain. This factor heightened interest in the Moroccan cases enabling rapid

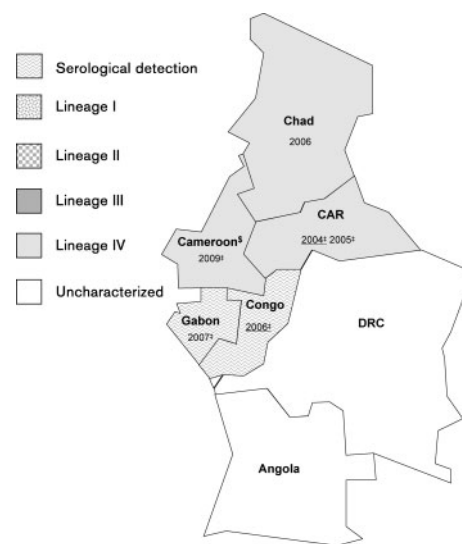


Fig. 5. Distribution of PPRV across Central Africa (2000–2010). For key see Fig. 3.

vaccination programmes to be implemented with approximately 20.6 million of Morocco's sheep and goat population being vaccinated. Genetic characterization of the Moroccan virus classified it as a lineage IV virus (FAO, 2009; Khalafalla *et al.*, 2010). The origin of the Moroccan outbreak remains unknown although studies have recently presented serological evidence for PPRV infection in Tunisia (Ayari-Fakhfakh *et al.*, 2010) so the virus may well be present across other, as yet unknown, regions of North Africa. The current distribution of PPRV across North Africa is detailed in Fig. 6.

Asia

The Arabian Peninsula and the Middle East. In 2000, the presence of PPRV was analysed in Saudi Arabia and it was concluded that the disease was not circulating in the country (Al-Naeem *et al.*, 2000). However, by April 2002 an outbreak with a case mortality rate of 100% was reported in sheep and goats (Housawi *et al.*, 2004) and since then further serological surveys and outbreaks have been reported

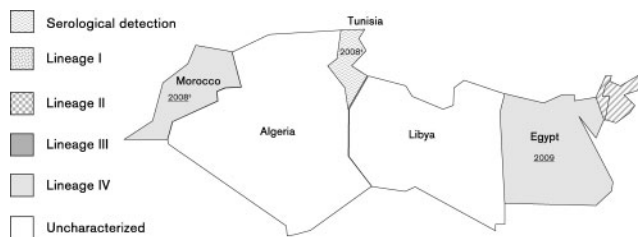


Fig. 6. Distribution of PPRV across North Africa (2000–2010). For key see Fig. 3.

(Al-Dubaib, 2008, 2009; Abu-Elzein *et al.*, 2004; El-Rahim *et al.*, 2005). A possible role of camels in the dissemination of PPRV to goats has also been suggested (El-Hakim, 2006) as in Ethiopia in 1995 (Roger *et al.*, 2001) although more recent surveys in Sudan have suggested this route of dissemination as being unlikely (Khalafalla *et al.*, 2010). Seroprevalence of both sheep and goats has also been reported in North Jordan (Al-Majali *et al.*, 2008) and in the Lebanon with seroprevalence of up to 48.6% being reported (Attieh, 2007).

On the remainder of the Arabian Peninsula, lineage IV virus has been detected in a game reserve in the United Arab Emirates (Kinne *et al.*, 2010) as well as in Qatar (2010). Interestingly, in Qatar both lineages III and IV are circulating with both lineages being isolated from goats in 2010. The situation in Qatar is further complicated by the recent detection of PPRV in wild deer populations. However, the role of sylvatic PPRV and potential transmission to domestic species remains unknown (C. Oura, personal communication). Within Yemen, the most southerly region of the peninsula, lineage III virus continues to circulate with no introduction of lineage IV having been reported in Yemen or Oman (Fig. 7).

Pakistan. PPRV has been reported in Pakistan since 1991 with initial epidemics in the Punjab region being characterized by using PCR in 1994 (Amjad *et al.*, 1996). Since then both the spread of the virus and an increase in reporting has meant that PPRV has been documented on several occasions. Serum samples from healthy animals in a goat flock following a suspected outbreak in 2005 were seropositive for PPRV antibodies (Ahmad *et al.*, 2005) with further reports in the north of the country (Abubakar *et al.*, 2008; Mehmood *et al.*, 2009), north, south and central

Punjab (Durrani *et al.*, 2010), Lahore (Rashid *et al.*, 2008) and in Islamabad where an outbreak in Afghan sheep (*Bulkhi*) occurred (Zahur *et al.*, 2009). Currently, only lineage IV virus has been identified in Pakistan (Fig. 7).

India. PPRV is endemic across much of India and an improvement in veterinary services, reporting networks and diagnostic capabilities across India has led to an increase in awareness of the disease. The virus was first reported in southern India in 1987 (Shaila *et al.*, 1989) where it seemed to remain for several years before spreading across the entire country and surrounding regions. Molecular characterization of virus isolates from India show that virtually all isolates analysed belong to lineage IV, which until recently had been thought to be restricted to the Arabian Peninsula, Middle East and India. One exception to this is a virus detected in the Tamil Nadu region of India in 1992. This Indian isolate is the only case of a lineage III virus being present in India and no further lineage III viruses have been detected in India since its discovery. It is thought that the introduction of the Tamil Nadu isolate was an importation through trade in small ruminants and that the virus was unable to spread and establish itself in the area. Alternatively, it may have been replaced by lineage IV virus that swept across the Arabian peninsula, the Middle East and the Indian subcontinent between 1993 and 1995 (Dhar *et al.*, 2002).

More recent epidemiological studies of PPRV in India have characterized a number of closely related lineage IV viruses being present (Dhar *et al.*, 2002). The virus continues to be reported periodically across India with recent reports documenting presence of PPRV in Rajasthan in the north (Kataria *et al.*, 2007), the Kolkata region in the east (Saha

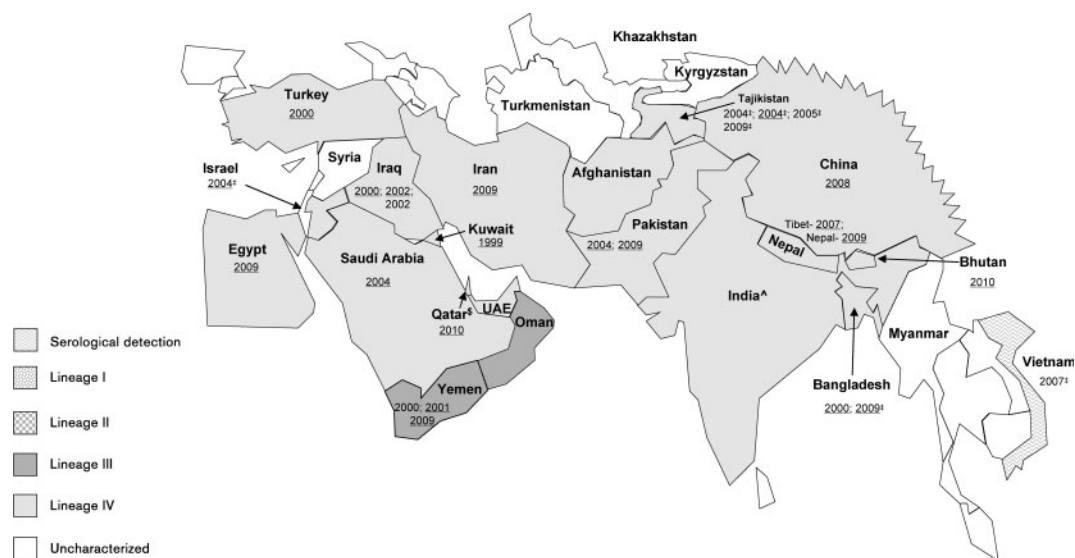


Fig. 7. Distribution of PPRV across Asia (2000–2010). For legend see Fig. 3. ^, Numerous reports of PPRV in published material – all lineage IV; \$, both lineages III and IV currently circulate in Qatar. *, PPRV also detected in wildlife species.

et al., 2005), Karnataka and Maharashtra in the south-west (Chavran *et al.*, 2009; Santhosh *et al.*, 2009) and across the southern peninsula (Raghavendra *et al.*, 2008). These reports reflect the endemicity of the disease across the entire country.

In those areas affected by the disease, PPRV is considered to be a major limiting factor in the development of the small ruminant industry. This is especially evident in a country like India where sheep and goats play an integral role in sustainable agriculture and employment. India is estimated to have 126 million goats and 58.2 million sheep, with the husbandry of these animals often being the responsibility of landless labourers and small farms. As a result, the impact of PPRV on the poorer section of society is disproportionate, reflecting an intrinsic dependence on sheep and goat farming. For example, in 2004, estimates of the economic cost of PPRV in India was thought to be 1800 million Indian rupees (US\$ 39 million, UK 21 million) per year (Singh *et al.*, 2004).

Iraq, Iran and Afghanistan. The presence of PPRV is poorly characterized across great stretches of the Middle East with outbreaks in Iraq most frequently being reported. Historically, detection of PPRV in Iraq dates back to 2000 where a virus causing high morbidity and low mortality rates was characterized (Barhoom *et al.*, 2000). However, retrospective seroanalysis has shown that the virus was previously circulating in 1994 (Shubber *et al.*, 2004). Iran has also had PPRV circulating for many years with initial detection back in 1995, leading to extensive spread of the virus across the country at a huge economic cost (Bazarghani *et al.*, 2006). Further episodes of PPRV disease in Iran are reviewed by Abdollahpour *et al.* (2006). More recently in 2009, virus from Iran has been characterized at the genetic level, being grouped with lineage IV viruses (Fig. 7).

The Near East. The recent detection of PPRV in areas of the Near East has highlighted the potential for spread of PPRV into areas that have never previously been documented. Tajikistan borders Afghanistan where PPRV is believed to be present and was previously reported in association with RPV outbreaks (Kwiatak *et al.*, 2007). PPRV is also believed to be present in Kazakhstan although only very few seropositive animals have been identified (Lundervold *et al.*, 2004). The recent detection of PPRV in China was officially reported in the Ngari region of western Tibet in July 2007 (Wang *et al.*, 2009). Previously, PPRV infection has been recognized in several countries bordering the south-western region of China, including India, Nepal (2009), Bangladesh (2000 and 2009), Pakistan (2004 and 2009) and Afghanistan (Fig. 7). All recent virus strains detected in south-west Asia and the Middle East belong to lineage IV and the Tibetan isolate is of the same lineage and is closely related to isolates from both India and Tajikistan. The terrain of western and south-western Ngari permits uncontrolled animal movement, and a small ruminant trade exists between Tibet and bordering nations such as India and Nepal. These factors suggest that

animals from a neighbouring country in south-west Asia are the most likely source of PPRV in Tibet (Wang *et al.*, 2009). Serological detection of antibodies to PPRV have also been detected in samples from Vietnam (Maillard *et al.*, 2008) and samples submitted to RRLs from Bhutan have recently been typed as lineage IV virus (Fig. 7). These findings suggest that the virus may be present across a greater area than currently thought. It is possible that PPRV has spread into many other bordering countries, but the unfamiliarity of local human populations with the disease means that it may remain either unnoticed or be misdiagnosed as a different disease with similar clinical manifestations.

PPRV and the threat to Europe

Recent reports of PPRV in areas close to European borders have increased its profile both scientifically and in the media. Whilst this devastating disease of small ruminants has continued to plague agriculture across Africa and Asia for many years, the threat of spread into the developed world has greatly renewed interest in the virus. The detection of PPRV in European Turkey in 1996 raised initial awareness of the virus and questioned the potential for PPRV to spread across the rest of Europe (Ozkul *et al.*, 2002). Indeed, there have been numerous reports of PPRV in Turkey having now also been reported in Western Turkey, Bursa province (Yesilbag *et al.*, 2005) and Mugla and Aydin provinces (Toplu, 2004) in the Aegean district. Throughout 2005, 78 separate outbreaks of PPRV were recorded across Turkey with quarantine and vaccination being used to prevent further spread of the disease (Tufan, 2006). In 2007, the first outbreak of fatal PPRV was reported in Kirikkale Province, Central Anatolia (Kul *et al.*, 2007), suggesting spread of the virus into the central belt of the country and in 2009 infection of sheep in the Middle and Eastern Black sea region of Turkey was reported (Albayrak & Alkan, 2009). These reports suggest that PPRV is present across much of Turkey and diagnostic samples received by RRLs have confirmed Turkish PPRV isolates as belonging to lineage IV (Fig. 7).

The Moroccan outbreak and the potential existence of as-yet-unidentified foci of PPRV infection across other territories in northern Africa also increases the threat of movement of infected animals into southern Europe. Historical exchanges exist between Morocco and Spain where both ovine and caprine populations are important. An increase in human population and in turn the small ruminant population across such areas no doubt increases the risk of further emergence of PPRV across North Africa. It is therefore essential that Europe maintains surveillance of the disease in order to successfully contain the disease should it be imported (Minet *et al.*, 2009).

PPRV: diagnosis, prevention and future control

The methods for detection, prevention and control of PPRV vary widely depending on local facilities, techniques

adopted and the provision of veterinary services and vaccine, respectively. Detection of antibodies to PPRV is generally carried out using ELISA techniques. Currently, the OIE recommend the use of the competitive PPRV-specific anti-H monoclonal based ELISA (cH-ELISA) (Anderson & McKay, 1994) and virus neutralization tests (FAO, 1996). However, several alternatives exist (Choi *et al.*, 2005; Libeau *et al.*, 1995) including the indirect N ELISA (Ismail *et al.*, 1995), immunofiltration (Dhinakar Raj *et al.*, 2008), a novel sandwich ELISA (Saravanan *et al.*, 2008), haemagglutination tests (Dhinakar Raj *et al.*, 2000; Ezeibe *et al.*, 2008) and latex agglutination tests (Keerti *et al.*, 2009).

Detection of PPRV antigens can be performed using a variety of tools including immunocapture ELISA (ICE; Libeau *et al.*, 1994), counter immunoelectrophoresis (CIEP) or agar gel immunodiffusion (AGID) (FAO, 1996). CIEP and ICE can distinguish PPRV from RPV, but the AGID test cannot differentiate these two viruses. AGID is also relatively insensitive, and may not be able to detect small quantities of viral antigens in milder forms of PPRV. Immunofluorescence and immunochemistry can also be used on conjunctival smears and tissue samples collected at necropsy.

Virus isolation in cell culture can also be attempted with several different cell lines, although recovery of virus is not always successful. Previously, a marmoset-derived cell line (B95a) was primarily used (Sreenivasa *et al.*, 2006) although primary lamb kidney or African green monkey kidney (Vero) cell cultures have also been successful (Mahapatra *et al.*, 2006). However, morbilliviruses are now recovered and grown in Vero/SLAM cells (Ono *et al.*, 2001; Seki *et al.* 2003). Generally, cultures are examined for cytopathic effect in the days following infection of a monolayer with suspect material; the identity of the virus can be confirmed by virus neutralization or molecular techniques (Singh *et al.*, 2009).

For molecular detection, standard RT-PCR (Couacy-Hymann *et al.* 2002; Forsyth & Barrett, 1995) has been superseded by real-time RT-PCR assays specific for PPRV (Bao *et al.*, 2008; Kwiatek *et al.*, 2010) and loop-mediated isothermal amplification techniques (Wei *et al.*, 2009). The generation of a standard RT-PCR product is, however, necessary in order to perform sequence analysis and subsequent phylogenetic characterization of novel virus isolates. Extensive validation of these diagnostic techniques is required before they can be accepted as approved OIE methods.

Control strategies that have been successful in ensuring the eradication of RPV are also valid for PPRV (Barrett *et al.*, 1993) although small ruminant population structures differ greatly to that of cattle. In endemic areas, the virus is currently controlled either through administration of a live-attenuated PPRV vaccine such as the Nigeria 75/1 strain (Nig 75/1) (Diallo, 2003). In India three live-attenuated vaccines are currently licensed for use: Sungri 96, Arasur 87 and Coimbatore 97 (Saravanan *et al.*, 2010).

Historically, live-attenuated rinderpest vaccine was also used to protect small ruminants against PPRV due to the antigenic cross-reactivity between the two viruses (Taylor, 1979). However, use of the latter was halted to avoid false-positive detection of RPV during the final stages of the eradication campaign and to enable a country to seek OIE recognition for freedom from rinderpest (FAO, 2007). In areas where PPRV is not endemic, outbreaks are controlled most efficiently through a number of methods including: slaughter of infected herds, good sanitation, import controls, movement restrictions and quarantine. However, a lack of suitable facilities, including the provision of veterinary services, often preclude effective outbreak management. Regardless of the level of viral presence within an area seromonitoring through surveillance initiatives, as used successfully during the different RPV eradication programmes, remains a critical tool in combating PPRV infection and preventing further spread. A number of factors can be used in order to gain an understanding of the epidemiological picture of PPRV infection within a region; antibody prevalence (Abraham *et al.*, 2005; Singh *et al.*, 2004); the presence of viral antigen in tissues from naturally infected animals (Yener *et al.*, 2004); the role of colostral antibody dynamics in protection levels (Awa *et al.*, 2002) and haemagglutination test results (Odo, 2003) are all considered to be of great use.

Several studies have involved the development of a new generation of marker vaccines that will enable the differentiation of infection in vaccinated animals (DIVA). For RPV, a DIVA vaccine was successfully generated through reverse genetic manipulation of the RPV vaccine by swapping the RPV N gene with the N gene of PPRV (Parida *et al.*, 2007). This DIVA vaccine, however, was not utilized during the RPV eradication campaign as vaccination had ceased and countries were undertaking extensive serosurveillance activities to confirm absence from infection. Further, development of a novel rinderpest based chimeric vaccine against PPRV has been attempted by swapping the glycoprotein genes (F and H) between PPRV and RPV. This RPV-PPRV FH recombinant virus grew poorly in cell culture (Das *et al.*, 2000). To improve potential for virus growth using the above system the M, F and H genes of RPV were replaced with those from PPRV and a higher virus yield was obtained with the resulting chimera. In pilot studies, this chimeric virus protected goats from challenge with a virulent strain of PPRV (Mahapatra *et al.*, 2006) and it was possible to differentiate between vaccinated and infected animals using the competitive cH-ELISA (Anderson & McKay, 1994) and cN-ELISA test (Libeau *et al.*, 1995). Unfortunately, the mAb based RPV and PPRV N competitive ELISAs cross-react thus limiting the use of this type of genetically marked vaccine. This problem has now been overcome by the development of a more specific test using the carboxy-terminal variable region of the rinderpest N protein (Parida *et al.*, 2007) although the test requires further validation. This chimeric MFH PPRV marker vaccine may be of use to

control PPRV, but field trials have never been conducted due to the ongoing rinderpest eradication campaign.

There is a clear need for a PPRV marker vaccine and a companion diagnostic test. Further development of a multivalent vaccine is essential in countries where political and economic infrastructures are unable to support concerted vaccination programmes. Development of novel bi- or trivalent vaccines that are able to protect small ruminants against common viral pathogens would greatly enhance poverty alleviation in areas where multiple viral pathogens of small ruminants exist. With PPRV, sheepox, goatpox and BTV being endemic across much of Africa and India these viruses would seem an obvious choice for the development of novel multivalent vaccines. Indeed co-infection of goats with PPRV and BTV has been reported in India (Mondal *et al.*, 2009). Multivalent vaccines are currently being developed that may both protect vaccinated animals against several viral pathogens and enable vaccinated and infected animals to be distinguished using DIVA tests. Currently, vaccines exist based on the incorporation of PPRV immunogens into vectors such as sheep and goat pox (Berhe *et al.*, 2003; Chaudhary *et al.*, 2009; Chen *et al.* 2010; Diallo *et al.*, 2002) and attempts are also being made to develop new vaccines based on recombinant DNA technology (Diallo *et al.*, 2007).

Unfortunately, political instability continues across much of Africa. The cost of vaccines and their administration and the nature of sheep and goat farming make regional vaccination campaigns problematic and a worldwide vaccination campaign for PPRV very unlikely. The next generation of novel PPRV vaccines and DIVA tests may prove of great benefit in future control programmes.

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