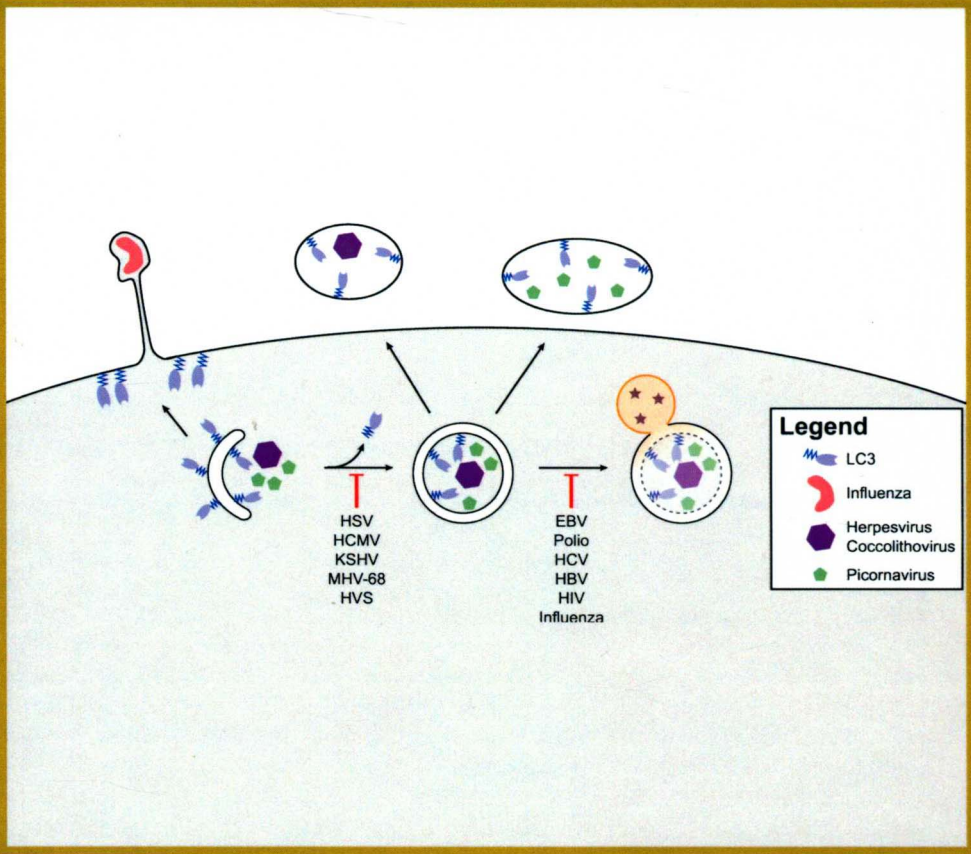
Advances in VIRUS RESEARCH



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ADVANCES IN VIRUS RESEARCH

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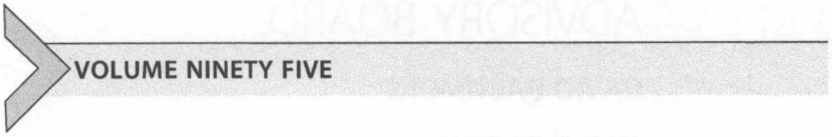

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CHAPTER ONE

Peste des Petits Ruminants Virus

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Abstract

Peste des petits ruminants virus (PPRV) causes a severe contagious disease of sheep and goats and has spread extensively through the developing world. Because of its disproportionately large impact on the livelihoods of low-income livestock keepers, and the availability of effective vaccines and good diagnostics, the virus is being targeted for global control and eventual eradication. In this review we examine the origin of the virus and its current distribution, and the factors that have led international organizations to conclude that it is eradicable. We also review recent progress in the molecular and cellular biology of the virus and consider areas where further research is required to support the efforts being made by national, regional, and international bodies to tackle this growing threat.

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Peste des petits ruminants (PPR) is a highly contagious viral disease of small ruminants that causes mortality rates that may be as high as 50–80% in naïve populations (Diallo and Libeau, 2014). The disease is caused by a morbillivirus, *Peste des petits ruminants virus* (PPRV), which is an enveloped ribonucleic acid (RNA) virus with a monosegmented genome of negative sense, belonging to the genus *Morbillivirus* in the family *Paramyxoviridae*. It is in the same group as, and causes similar clinical signs to, *Rinderpest virus* (RPV), which causes disease in large ruminants and was declared globally eradicated in 2011. The basic biology of PPRV has been extensively reviewed in a number of recent publications, in journals (Albina et al., 2013; Kumar et al., 2014; Parida et al., 2015), book chapters (Baron, 2011, 2014), and entire books (Munir, 2014). It is clearly unnecessary to cover all of that information in detail here, and our aim in this review is to highlight the more recent advances in research on this virus, setting them in the context of the emergence of this important disease. We also provide an up-to-date epidemiological status of the distribution and spread of PPRV and the control program being put in place by international organizations. We conclude by highlighting areas where research is needed to support those control programs, leading to the hoped-for eventual eradication of the disease (OIE, 2014; OIE and FAO, 2015) with the consequent economic benefits (FAO and OIE, 2015).

1. EMERGENCE OF PPRV

Currently, PPR is the fastest expanding and potentially the most economically important disease of sheep and goats in many regions of the developing world where these domestic animals play an integral and important role in sustainable agriculture and development. PPR has spread so alarmingly during the last two decades that it has become a matter of concern for the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE), which have now initiated efforts for its control and eradication (OIE, 2015).

One of the more interesting epidemiological questions that is yet to be answered is the origin of PPRV. This is important because our understanding of the risks of the emergence of new morbilliviruses depends on our understanding of the history of those of which we are already aware. The first report of PPR as a separate disease dates back to only 1942, following the observation of Gargadennec and Lalannene (1942) of a rinderpest-like disease that was afflicting goats in Côte d'Ivoire in 1940, while at the same

time in-contact cattle were healthy. They gave that disease the name "peste des petits ruminants" (plague of small ruminants). In the same period, a similar disease was reported in Dahomey (the former name of Benin), where it was termed "peste des espèces ovine et caprine" (plague of sheep and goat species) (Mornet et al., 1956). For some time, reports of PPR were confined to West Africa. It is only later that its recognized geographical distribution has steadily expanded through many African countries, the Middle and Near East, and Asian countries extending from West Asia to China (Banyard et al., 2010; Libeau et al., 2014). Today about 80% of the world's sheep and goat populations are threatened by PPR (Fig. 1).

This apparent rapid expansion of the geographical distribution of PPRV may be facilitated by an increase of livestock movements across countries and regions, but is mainly due to the development and availability of PPRV-specific diagnostic tests and, in a way, to the successful global eradication of rinderpest. While this latter disease may also affect small ruminants, it has only been proven to do so on rare occasions. However, it has similar clinical signs to PPR (apart from the respiratory syndrome that is one of the common clinical signs of the acute form of PPR) and may have been the diagnosis of choice until RPV itself became rare, and was not the automatic diagnosis. As pointed out by Taylor (1984), the "rinderpest" outbreaks

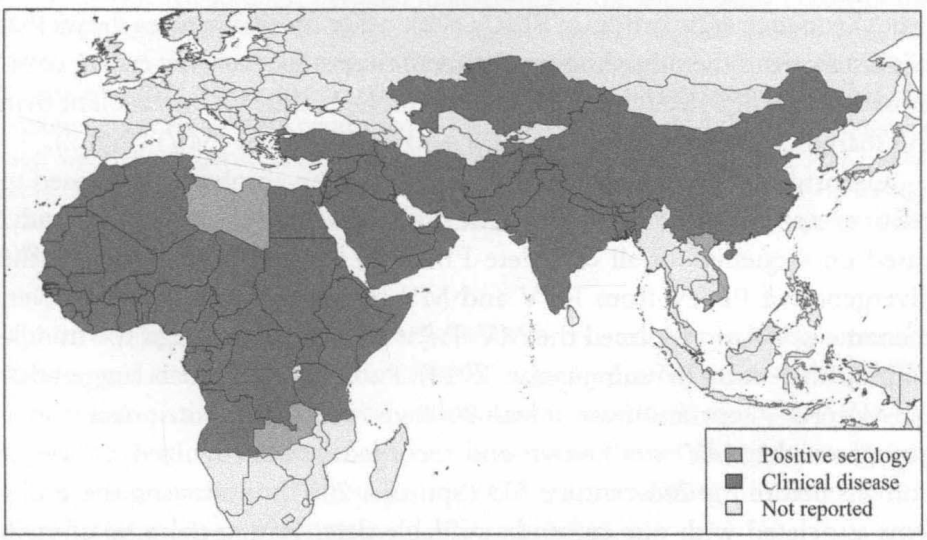

Fig. 1 Global PPR distribution map at the end of 2015 (clinical disease reported or virus identified (*dark orange* (*dark gray* in the print version)) or only serological information (*light orange* (*mid-gray* in the print version))). A country is entirely colored as infected even the event concerns only one locality. *Sources of information: OIE, FAO-EMPRES, and publications.*

in Senegal and French Guinea, in 1871 and 1927, respectively (Curasson, 1942), may have in fact been PPR. Similarly of interest is the case of PPR in Sudan, where an outbreak initially reported as rinderpest in small ruminants was shown to have been PPR after a reassessment 10 years later (El Hag Ali, 1973; El Hag Ali and Taylor, 1984). The same may be true for some "rinderpest" outbreaks that were reported in Asia in the past, such as the "rinderpest" affecting goats, but not in cohoused cattle, reported in India in the 1930s (Bawa, 1940). The disease was not recognized in Asia until the first verified PPR case report in 1987 in India (Shaila et al., 1989; Taylor et al., 2002). In addition to the psychological effect of the prevalence of RPV, there may also have been a direct effect of RPV on PPRV epidemiology. Subclinical infection of sheep/goats with RPV protects them from PPRV infection (Taylor, 1979), so PPRV may have had more limited possibilities of spread in countries where rinderpest was endemic, and only began to spread widely as rinderpest came under control.

The progressive control of rinderpest from the 1970s until its global eradication in 2011, coupled with the development of specific diagnostic tests, clearly demonstrated that PPRV was different from, but closely related to, RPV and that the two viruses displayed different epidemiological patterns (Diallo et al., 1995; Gibbs et al., 1979; Taylor, 1984). Molecular data support the suggestion that PPR has been present in small ruminant flocks for a long time. Sequence comparison of PPRV with other morbilliviruses shows that it is distant from the other known viruses in the genus; the most recent common ancestor of PPRV and RPV, for example, is clearly more ancient than the shared common ancestor of RPV and measles virus (MV) (Fig. 2).

Unfortunately, it is impossible as yet to place an absolute, as opposed to relative, age on these ancestors. The most comprehensive recent study, based on sequences of all complete PPRV genomes available, placed the divergence of PPRV from RPV and MV in the 17th century; however, the same calculations placed the MV/RPV divergence point in the middle of the 18th century (Muniraju et al., 2014). Purely historical data suggest that the MV/RPV separation was at least 2000 years ago, and quite possibly longer, given that MV was known and recorded as a recognized disease of humans before the 3rd century AD (Spinage, 2003), illustrating the problems associated with our currently available data. Dating the ages of virus lineages is very difficult, due to the effects of purifying selection (Duchene et al., 2014a; Wertheim and Kosakovsky Pond, 2011), and the absence of ancient isolates that would allow accurate calibration of the age of nodes (Duchene et al., 2014b). Given the age of the MV/RPV

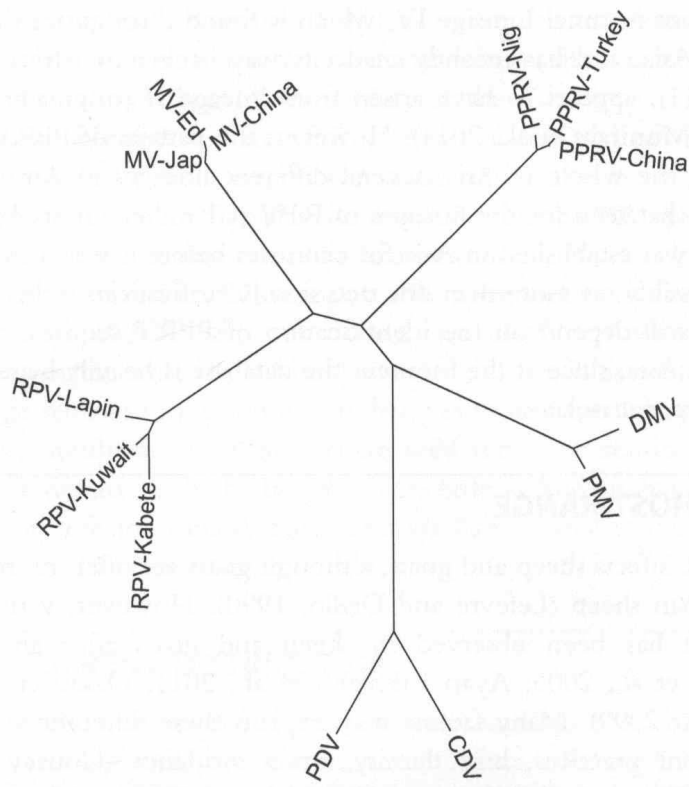

Fig. 2 Genetic relationships between morbilliviruses. The evolutionary history of the morbilliviruses was inferred using the Neighbor-Joining method (Saitou and Nei, 1987). The evolutionary distances were computed using the Tajima–Nei method (Tajima and Nei, 1984) and are in the units of the number of base substitutions per site. Evolutionary analyses were conducted in MEGA6 (Tamura et al., 2013). The sequences used were the N genes taken from: RPV-Kabete, X98291; RPV-Kuwait, Z34262; RPV-Lapin, AB547190; MV-Jap, S58435; MV-Ed, K01711; MV-China, EU435017; PPRV-Nig, X74443; PPRV-Turkey, AJ563705; PPRV-China, EU360596; DMV, NC_005283; PMV, AY949833; CDV, AF014953; PDV, X75717.

separation suggested by our knowledge of the history of measles as a human disease, and the observation that PPRV branched away from the morbillivirus common ancestor before that, it is likely that PPRV has been around as a separate virus for much longer and, as we have noted already, was simply not noticed because of the presence of RPV circulating in cattle, which dominated veterinary concerns in affected areas.

The geographic origin of PPRV is also not clear. Comparison of the sequences of viruses of the four established lineages suggested that lineages II and III arose independently and at about the same time (Muniraju et al., 2014), and that the virus therefore arose in both West and East Africa at a

similar point in time. Lineage IV, which is found throughout the Middle East and Asia, and has recently made its way back into Africa (Kwiatek et al., 2011), appears to have arisen from lineage II (originally found in Nigeria) (Muniraju et al., 2014). However, the pattern of PPRV lineages (one over the whole of Asia, several different lineages in Africa) is very similar to that seen for the lineages of RPV (Chamberlain et al., 1993), a virus that was established in Asia for centuries before it was introduced to Africa, possibly on more than one occasion. Clarification of the history of the virus will depend on the identification of PPRV sequences in older samples in Asia, since at the moment the database is heavily biased toward the most recent isolates.

2. HOST RANGE

PPR affects sheep and goats, although goats are often more severely affected than sheep (Lefevre and Diallo, 1990). However, variable seroprevalence has been observed in sheep and goats after an outbreak (Abraham et al., 2005; Ayari-Fakhfakh et al., 2011; Ozkul et al., 2002; Swai et al., 2009). Many factors may explain these differences: livestock management practices, host density, strain virulence (Couacy-Hymann et al., 2007a), as well as host species and breed (Diop et al., 2005). For instance, Sahelian goats are considered more resistant than Guinean dwarf goats, while Alpine goats are very sensitive after experimental infections (Hammouchi et al., 2012).

PPRV is not considered as pathogenic in cattle, domestic, and wild African buffaloes (*Syncerus caffer*) although 10% or more of these species may seroconvert when exposed to PPRV in enzootic regions (Abraham et al., 2005; Couacy-Hymann et al., 2005; Ozkul et al., 2002). In a nationwide serological survey recently implemented in Senegal (2015), seroprevalence rates as high as 80% were observed in regions where both cattle and small ruminants were abundant, without any reported clinical sign in cattle (Seck, I., Directorate of Veterinary Services; Diop, M., National Veterinary Laboratory—ISRA-LNERV, personal communication). Conversely, high case fatality rates (96%) were reported in India in domestic buffaloes (*Bubalus bubalis*) and the disease was experimentally reproduced in these animals (Govindarajan et al., 1997). Additionally, PPR has been suggested to occur as a disease in camelids; a respiratory syndrome was the main sign in Ethiopia and Sudan (Khalafalla et al., 2010; Roger et al., 2000). However, attempts to reproduce the disease in camels have not been successful (Wernery, 2011).

Whether PPRV-infected and sick buffaloes and camels are a source of infection for small ruminants remains unclear and deserves more attention. Other wild ruminants, including representatives of the *Gazellinae*, *Tragelaphinae*, and *Caprinae* subfamilies, may show a serious illness and mortality when infected with PPRV from neighboring small ruminant populations. In specific conditions, wildlife may play an important role in PPR epidemiology, as was seen in the Arabian Peninsula (Kinne et al., 2010), but it remains to be determined whether wildlife is primarily a sentinel victim rather than a reservoir for PPRV, as was found for RPV (Anderson, 1995; Couacy-Hymann et al., 2005; Mahapatra et al., 2015). This is an area where knowledge remains scarce and which deserves more attention, since PPR is progressing southward in Africa where wild ruminant density, as well as sheep/goat density, is high. In particular, little is known regarding virus excretion in infected camels, cattle, and wildlife, as well as the persistence of infectious PPRV in urine and feces.

3. CURRENT DISTRIBUTION

In recent years, field data and laboratory findings have confirmed the dramatic spread of PPR toward the south of Africa, affecting Gabon, Democratic Republic of Congo, Somalia, Kenya, and Tanzania (Swai et al., 2009). In northern Zambia, serological evidence of PPRV infection was reported to the OIE by the Veterinary Services in Jul. 2015. Moreover, in Oct. 2012, PPR was reported for the first time in Angola (OIE notification). The risk of PPR introduction is now high for neighboring countries with major sheep/goat populations, such as Republic of South Africa and Mozambique.

Apart from Egypt, which has been infected at least since 1989 (Ismail and House, 1990), the Moroccan outbreak in 2008 was the first reported PPRV incursion into North Africa. However, the infection was already present in Tunisia in 2006 (Ayari-Fakhfakh et al., 2011). PPRV has now been identified in Tunisia (Sghaier et al., 2014) and Algeria (De Nardi et al., 2012; Kardjadj et al., 2015a,b). Although it had been eradicated following several years of nationwide mass vaccination campaigns following the 2008 outbreak (Ettair, 2012), PPRV has reemerged in Morocco in 2015 (OIE notification). Illegal cross-border trade and intense sheep movements associated with the generalized practice of sheep fattening lots are probably the cause of this reemergence. The Moroccan experience has highlighted the need for regional PPR control strategies to support sustainable PPRV eradication at the national level.

In addition to the spread in Africa, many Asian countries are now infected, including China. After an initial identification in Tibet in 2007 (Wang et al., 2009), this country experienced a major PPR epizootic in 2013–14 and implemented mass vaccination campaigns (Wu et al., 2015). Interestingly, the circulating viruses in 2013–14 were genetically closer to viruses identified in Pakistan or Tajikistan than to those isolated in Tibet during the earlier outbreak (Bao et al., 2014).

4. VIRUS TRANSMISSION AND SPREAD

Infected animals (mostly domestic ruminants) are the only source of PPRV. At an early stage of infection, virus excretion is massive in the exhaled air. By analogy with RPV, this probably allows noncontact transmission over at least a few meters (Idnani, 1944). Nasal and ocular discharges, saliva, and feces also contain large amounts of viral antigen (Abubakar et al., 2012). In goats, PPRV-RNA or antigen is excreted in the feces during at least 2 months after a natural infection (Abubakar et al., 2012; Ezeibe et al., 2008), though it is not known if this is infectious virus. Since PPRV is quickly inactivated in the environment, its transmission most often occurs by direct contact between infected and healthy animals. However, indirect transmission through recently (within hours) contaminated material cannot be excluded and should be considered in epidemiological models and risk-based control measures.

Because of its rapid spread in immunologically naïve flocks, a common belief is that PPRV can only persist in large populations and only if new susceptible hosts (newborn, migrating, or purchased animals) are available (Anderson, 1995). This is the case for sheep/goat populations which have high turnover (commonly at least 30%/year, compared to the 10%/year normal in cattle). However, even in this epidemiologically simple situation, well-established transmission parameters for PPRV are missing, such as the basic reproduction number R_0, the expected number of cases generated by the introduction of a single infectious individual to a fully susceptible and immunologically naïve population. One of the most important uses of R_0 is the estimation of the postvaccination immunity rate T needed to stop virus transmission: in a homogeneous host population $T=1-1/R_0$ (Heesterbeek and Roberts, 2007). Available estimates of R_0 range from 4.0 to 6.8 (EFSA Panel on Animal Health and Welfare, 2015), implying that vaccination efforts must hit levels from 75% to 85% of the small ruminant population to stop PPRV transmission. However, these empirical estimates were

obtained in field situations with many uncertainties. Much more data are needed before reliable estimates can be provided to animal-health managers to inform decision making. Moreover, more complexity in PPRV transmission and persistence arises in actual field situations where small ruminant populations are heterogeneous in genetics, space, and time. Indeed, several species and breeds often coexist, each with its own susceptibility to both PPRV infection and pathogenesis. These small ruminant populations are further segregated by village or ecosystem, thus constituting a complex meta-population, with elementary host populations connected by a dense mobility network (local and regional trade, and transhumance). In such a situation, virus transmission is highly variable, and PPRV might persist much longer than in a simple, homogeneous host population (Grenfell and Harwood, 1997). For instance, in a study of PPR transmission in a small region of Senegal (Sine-Saloum), in the absence of vaccination, we were able to find the virus in goat flocks from neighboring villages during several consecutive years (Salami, 2015), though the average seroprevalence rate was 86% (95% confidence interval: 79–94, $n=23$ herds and 207 goats).

In that example, we quantified and mapped the intensity of local and regional small ruminant trade with specific field surveys implemented in collaboration with Senegalese and Mauritanian Veterinary Services (Fig. 3). The dots on the map represent small ruminant market places, and the links between the *dots* represent small ruminant trade movements. Dot size is proportional to the number of traded livestock, and the red (gray in the print version) intensity is proportional to the so-called betweenness of market places, ie, a measure of market centrality in the livestock trade network. A market with a large centrality has a large influence on the transfer of items by the commercial network of markets—including pathogens borne by animals (Ortiz-Pelaez et al., 2006). The largest and most central market in the network was Kaolack, the regional capital of Sine-Saloum, where we found intense PPRV circulation.

Indeed, livestock trade is the most likely route of PPRV introduction into new territories. Europe is relatively well shielded from such introduction thanks to strict control measures at its outer borders, together with generally adequate preparedness of its member states for early reaction in the case of PPR introduction. At the time of writing (early 2016), Bulgaria and Greece are at the highest risk of introduction from Turkey. The risk of introduction from northern Africa into southern Europe is considered as very low (EFSA Panel on Animal Health and Welfare, 2015). The situation in central Asia should quickly improve with the implementation of