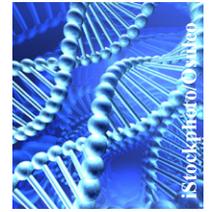


Evolutionary genetics underlying the spread of peste des petits ruminants virus



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Implications

- Peste des petits ruminants (PPR) constitutes one of the major hurdles to the improvement of small-ruminant production in countries where it is endemic, directly affecting the poor, the main keepers of those species. Despite the existence of highly effective vaccines for more than 25 years, this disease remains a worrying and emerging cause of morbidity and mortality in endemic and high-risk regions of Africa, the Middle East, and Asia.
- Evolutionary biology of peste des petits ruminants virus (PPRV), the causative agent of PPR, has taught us much in the last 10 years, most notably about its recent evolutionary history and the extent of genetic diversity that lead to the four viral lineages known. Emergence of PPR, an ongoing issue, is disclosed through tracing back viruses belonging to these lineages.
- It is likely that viral infections are manifested by a variation of clinical patterns, including strains with altered virulence or epidemiological potential and that the virus may eventually emerge in other species. However, there are still major gaps in our knowledge, most notably, the extent and causes of genetic diversity behind the disease dynamics and the evolution/variation in the disease severity.
- Thus, special attention is to be paid to evolutionary and epidemiological factors underlying PPRV emergence, maintenance and spread, geographic distribution, and disease patterns. Integrated knowledge will provide decision-making tools for better guidance of control efforts against PPR.

Key words: epidemiology, evolution, food security, peste des petits ruminants virus, phylogeny

Biology and Epidemiology of PPR

Peste des petits ruminants (PPR) is one of the most widespread and devastating infectious disease of domestic and wild small ruminants. Since its first description in Côte d'Ivoire in 1942, the disease has steadily progressed over time across Africa, the Middle East, and Asia. When the infection results in overt and acute disease, the most common outcome is death with case fatality rates that may exceed 90% in naïve

populations. As well as imposing a major disease burden, the economic impact of PPR is considerable, with effects on food security and animal products. It is in the list of animal diseases, which on identification, has to be notified to the World Organization for Animal Health (OIE).

The causative agent of this disease, peste des petits ruminants virus (PPRV), is an enveloped, single-stranded negative-sense RNA virus belonging to the genus *Morbillivirus* within the family *Paramyxoviridae* where it groups together with measles (MV), canine distemper (CDV), and rinderpest (RPV) viruses (Gibbs et al., 1979). A description of the PPRV genome and encoded proteins is presented in Figure 1.

Small ruminants are the main natural hosts of PPRV although some other artiodactyls including camels and small-ruminant wildlife species are susceptible. The wildlife, by sharing same grazing areas and water points with domestic animals, may potentially be part of the epidemiology of the disease. However, for the moment, their role remains unclear (Banyard et al., 2010).

The virus generally causes an acute disease in small ruminants, although sheep are often less severely affected than goats (Lefèvre and Diallo, 1990). The disease is characterized by high fever, oral lesions, pneumonia, and diarrhea with severe dehydration often leading to death. In naïve populations, mortality approaches 90%, 5 to 10 days post-infection. Viremia initiates 2 to 3 days after infection, preceded by 1 or 2 days of symptom onset, and continues on several days afterward. In the case of virulent strains, high virus excretion may be expected in the expired air. Large quantities of virus are also found in nasal and ocular discharges, saliva, and feces of infected animals. Therefore, transmission can occur through the oral route by ingestion of contaminated feed and water in addition to the respiratory mucosal route. On field clinical assessments, moderately and minimally virulent isolates were described, allowing the recovery of infected sheep and goats, which were subsequently fully protected (Hamdy et al., 1976). Wild species are clinically affected by PPRV in a similar manner to domestic sheep and goats; the virus will hence have little trouble spreading into this population should the opportunity arise.

Reasons for disease spread, more obviously in domestic ruminants, are not well understood. To date, small-ruminant populations at risk to PPR are estimated to be 63% by the Food and Agriculture Organization (FAO, 2009) especially those from southern Africa, central Asia, Southeast Asia, China, Turkey, and southern Europe. Despite the existence of a highly effective vaccine since 1989 (Diallo et al., 1989), failure to sustain control programs has probably resulted in PPRV emerging in other regions and other animal species such as camels. Several other reasons might be invoked: 1) long-time negligence or inattentiveness

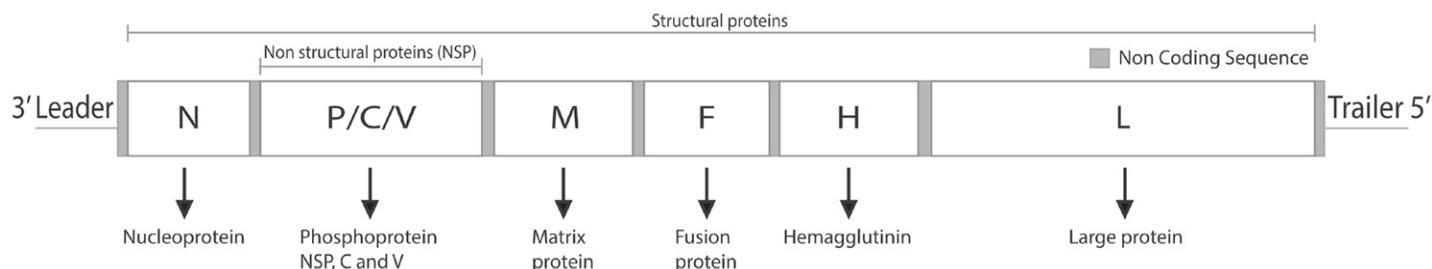


Figure 1. Peste des petits ruminants virus genome organization. The PPRV genome is a single-strand negative-sense RNA of 15,948 nucleotides. The genes encoding the structural proteins are present in six transcription units separated by non-coding sequences (NCS). The gene order has been established as 3'-N-P/C/V-M-F-H-L-5' flanked by 3'-Leader and 5'-Trailer responsible of the synthesis of positive and negative sense RNA. P gene encodes for two non-structural proteins, C and V, via alternative open reading frames and RNA editing. Source: Barrett et al. (1991).

to the small-ruminant health sector in all the countries now enzootic for the disease, leading to a lack of performing diagnostic tests; 2) increasing size and mobility of small-ruminant populations; 3) cessation of rinderpest circulation, which is generally mild in small ruminants and which the cross-reactive antibodies allowed for an additional gain in protection.

Regular epizootic activity across the Sahara-Sahel Belt in Africa resulted in spread of the disease into new uninfected areas in this continent, particularly from 2004 to 2013 as reported to the OIE (2013). Peste des petits ruminants virus first stretched northwards reaching Tunisia in 2006 (Ayari-Fakhfakh et al., 2011), Morocco in 2008 (Kwiatk et al., 2011) and Algeria in 2011. The virus simultaneously went southwards when it entered into the United Republic of Tanzania in 2008 and in 2012, in the Democratic Republic of Congo, Angola and the Comoros. This also holds true for the Asiatic continent. Virus from the enzootic areas in the Middle East spread towards the edge of European Union, with sporadic outbreaks that occurred in both the Anatolia (Asian Turkey) and Thrace (European Turkey) in 2004 (Yesilbağ et al., 2005). In southwest Asia, it spread to China (Tibet Autonomous Region) in 2007 (Bao et al., 2008), the Maldives in 2009, and Bhutan in 2010. In Asia, the impact of PPR has increased in the last decade to such a point that regular epizootic activities resulted in spillovers in the wild population and large die-offs among different wild species, some of them being endangered, notably bharal in Tibet (Bao et al., 2011, 2012), ibex in Pakistan (Abubakar et al., 2011), and wild goats in Kurdistan (Hoffmann et al., 2012). All events were related to PPR-infected livestock. Currently, there is a risk of transmission to more than one billion sheep and goats. The huge impact on small-ruminant production has resulted in PPRV emerging as an essential global animal health concern. Hence, PPR has been proposed as the next animal disease to be eradicated after rinderpest (FAO, 2013).

Origin of PPRV

Although antigenic studies have long shown that PPRV should be classified as a morbillivirus, it has required molecular typing methods to improve our understanding of the virus. Phylogenetic analysis performed on different genes showed MV and RPV to be the closest viruses within morbilliviruses (Diallo et al., 1994; Minet et al., 2009). However to shed light on the evolutionary history of morbilliviruses, Bayesian coalescence approaches have been used to estimate the phylogenetic split that occurred among the ancestral viruses of MV and RPV (Pomeroy

et al., 2008; Furuse et al., 2010) and to put a new perspective on PPRV modern evolution as reported in a recent analysis by Muniraju et al. (2013).

To date, insight into the history of MV and RPV was obtained by reconstruction of the molecular timescale of their evolution. It was shown that the earliest phylogenetic split between the two viruses is remarkably recent, occurring around 11th and 12th centuries. The archaeovirus capable of infecting both human and cattle should approximately correspond to the first rinderpest or measles-like disease (Furuse et al., 2010). In addition, most of the genetic diversity currently observed among lineages of PPR is a quite contemporary story; it was acquired from the mid-19th century as recently demonstrated by Muniraju et al. (2013). In addition, this study suggests that lineage III (see below), currently present in East Africa and in the south of the Arabian Peninsula, may be the most ancient virus. Evolutionary history leading to the diversity now shown for PPR was a relative fast phenomenon. As a comparison, the diversity of the MV may have emerged in humans within the last 70 years, an even more recent episode (Pomeroy et al., 2008).

Thus, until this recent study, there was no consensus on the original source of all four lineages currently described (see below). With new light on the topic, significant differences arise with the speculations that prevailed. Several reasons accounted for this situation. First, this is largely because PPR symptoms, when discovered, were not easily diagnosed and also confused with rinderpest, a disease affecting small ruminants that is currently eradicated but was present at that time. Second, the first well-documented case of what came to be known as PPR and as a separate entity from rinderpest took place in Côte d'Ivoire and Benin in 1942 (Gargadennec and Lalanne, 1942), ensuring the link of PPR to West Africa. Lastly, the spread of the disease in all countries of central and western Africa and the apparent movement from west to east in Africa, the Middle East, and Asia has not made the link among lineages any easier to sort out (Scott, 1981; Kwiatek et al., 2007; Banyard et al., 2010).

Nevertheless, the above-mentioned estimates for genetic diversity establishment among PPR viruses are in line with the first descriptions of the disease. The earliest report suggests the presence of a disease bearing a strong resemblance to rinderpest that caused epidemics in small ruminants in 1871 and 1927, in Senegal and French Guinea (Diallo, 1988). The disease was certainly widespread in West Africa by the late 19th and early 20th century long before its first description by the French veterinarians in Côte d'Ivoire. The subsequent pattern of epidemics in Africa suggests introductions in West Africa and East Africa

from the south of the Arabian Peninsula via ships that traded animals between these regions. The high prevalence of rinderpest certainly masked the disease resulting in delayed PPR identification, as exemplified in 1987 in India (Shaila et al., 1989; Taylor et al., 2002). However, clinical rinderpest or rinderpest-like disease in sheep and goats was diagnosed in the past in central and East Africa more specifically in Kenya (Libeau and Scott, 1960; Rossiter and Jessett, 1982), in Nigeria (Beaton, 1955; Johnson, 1958), and in Uganda (Scott and Brown, 1961). Some of these infections were probably PPR.

However even with these advanced analyses, some aspects of the history of PPR are still missing and require further data analysis, for example when the PPRV separated from ancestral viruses and when PPRV first appeared in small-ruminant populations. Indeed, despite its historical importance and current status of emerging disease, there are still relatively few PPRV sequences available: at the time of the writing of this article, there are only 639 PPRV nucleic sequences in GenBank, of which only 11 are complete genomes. Consequently, the actual scope of PPRV genetic diversity is limited to unravel its evolutionary path, particularly since data from some geographic regions and individual countries are under-represented.

Evolution and Phylogeny

Like all RNA viruses, PPRV presents the genetic variability characteristics that comes from the inherently high mutation rate associated with RNA-dependent RNA polymerase (Drake and Holland, 1999). This genetic variability is evidenced, using comparative gene sequence analysis, by the subdivision of PPRV strains into four lineages. The landmark analysis of intra-PPRV population variation was conducted by Shaila et al. (1996). Phylogenetic constructs based on the partial fusion (F) protein gene of nineteen PPRV isolates from African, the Middle East, and Asian countries defined four geographically distinct PPRV lineages. Three separate lineages were found in Africa, lineages I (isolates from the early 1970s in Central Africa), lineage II (isolates from the 1980s in West Africa), lineage III (isolates from southern India over a 20 year period including viruses from Sudan, Oman). Only one, lineage IV, grouped the most recently collected viruses across Middle East (Israel and Saudi Arabia) and Asia (Pakistan, Bangladesh, Nepal, and India). This pattern of apparent geographic genetic stability and clustering according to region was supported by subsequent studies on the F gene using additional viruses from India (Dhār et al., 2002) and Turkey (Ozkul et al., 2002).

These results were further confirmed by the phylogeny study based on a 255 fragment located on the 3' terminus of the nucleoprotein (N) gene of the virus (Kwiatk et al., 2007). In this study, PPRV sequences were derived from strains isolated over a period of roughly 30 years. They consisted of "historical" strains from the late 1960s (Senegal) and 1970s (Nigeria and Ghana) as well as strains collected from the 1980s to 2005 in West, Central, and East Africa; the Middle East; and Asia. The live-attenuated Nigeria 75/1 vaccine strain currently in use and derived from a Nigerian isolate is thus clustering accordingly with the wild strain and fall in lineage II. Nomenclature used for the F and N gene was slightly different, inducing a reversed classification of lineage I and II isolates. Lineages described according to the N gene were called I–III according to the apparent spread of the virus as described above. Apart from this difference, genetic clustering behaves the same, and phylog-

enies also showed the same branching order among the four viral lineages whether derived from the F or N gene (Banyard et al., 2010). The further description of lineages in the article is followed according to the phylogenetic study based on the partial N gene of PPRV.

All phylogenetic analyses undertaken to date reveal four distinct lineages of PPRV with strong bootstrap support for the critical nodes using adequate small variable sequences. Branching in four lineages was also observed with the complete open reading frame of major structural protein genes, notably from the N, the matrix protein M, the F, the hemagglutinin H (Balamurugan et al., 2010), and from the large protein L (Minet et al., 2009), suggesting a constant evolutionary rate across the genome. Thus, resolution of PPRV clustering in lineages does not require the analysis of complete genome sequences, and most studies now rely on the N gene sequence (255 nucleotides) as a phylogenetic marker (Figure 2). Aside from this, there is no evidence to support recombination as a factor of evolution in PPRV in nature and in vitro.

Thus, the most striking feature of PPRV from the early phylogenetic studies was the genetic stability within regions and the strong geographic clustering between and within continents as described by Kwiatek et al. (2007), a characteristic that seemed to indicate an evolution of the virus in isolation in particular geographic and specific conditions. Thus, although sub-Saharan Africa, the Middle East, and Asia experienced severe epidemics, the genetic variation of PPR viruses suggested that outbreaks observed, at least until late 1990, were seeded locally within each of the four specific geographic basins where PPR was settled for a long time. An exception was noted in the Middle East where a virus belonging to lineage III was isolated within wide circulation of lineage IV viruses, certainly a result of an importation from East Africa into this region where this lineage was widespread. Coexistence of viruses of these two PPRV lineages in the region importing animals from both East Africa, (lineage III), and many Asian countries (lineage IV), is expected. Besides lineage III, one of the salient aspects presented from the start by lineage IV and differing from the other lineages, was the wide geographical coverage and cosmopolitan behavior but still confined to Asia as seen in the pioneering studies on lineages.

The prominence and strong capacity of expansion of Asian lineage IV is supported by recent studies (Figure 3). Constant increase of disease incidence has been associated with this lineage, particularly that which occurred in North and East Africa and in Asia, from 2004 to 2013, this suggesting an increase in virulence (Kwiatk et al., 2011). In addition, countries otherwise known to have regular epizootic activity such as Sudan, Central African Republic and Cameroun, proved to harbor the Asiatic lineage. Indeed, analysis of pathological samples collected during different PPR outbreaks in Africa since the mid-2000s has disclosed the spread of this Asian PPRV lineage in Central Africa, North Africa (Morocco, Algeria, and Tunisia), and northern part of East Africa (East Sudan and Eritrea) affecting domestic species (including camels). However, this was surprising, since at the date of sampling, in 1997 for Cameroon and in 2004 for Central Africa Republic (Kwiatk et al., 2007; Banyard et al., 2010), there is no know history of animal movement from Asia in these countries. Currently, in a large zone encompassing Sudan, Ethiopia, Somalia and Kenya, lineage IV is slowly replacing PPRV lineage III (Khalafalla et al., 2010; Kwiatek et al., 2011; Cosseddu et al., 2013; Maganga et al., 2013). In West Africa, a similar scenario has occurred with lineage II. Indeed all PPRV detected in that region after 2005 belong to lineage II instead of lineage I that was the dominant, if

not the unique, lineage found there (Banyard et al., 2010; Munir et al., 2012).

Thus, a key question is whether geographical distribution and expansion observed for PPRV lineage IV and II may be attributed to some natural selection providing viruses with more epidemiologic potential, or whether they are a result of intensified animal movement and trade. In this regard, would it be correct to believe that viral strains from lineages with cosmopolitan behavior are subject to stronger positive selection pressure as they infect many different species and breeds of small ruminants and also camels according to the region? Can we also expect that replaced strains have seemingly a different fitness? On the pattern of extinction replacement, no formal explanation is given, however, to be a matter of any process. Greater sequence variation has been shown to correlate with greater dispersal in the case of MV (El Mubarak et al., 2002). This may be the case of PPRV as well (Kwiatk et al., 2011). However, although these studies tentatively imply that viruses may differ in fitness, no virulence determinants have been described until now. Increased mobility of small ruminants by transhumance and trade, as a potential amplifier of viral spread and the constant increase of disease incidence, should not be neglected as well. This is an area that deserves especial consideration and further investigation, in as much as it may allow preventing spread of those viral strains affecting and threatening an increasing number of small-ruminant and livestock keepers.

Evolution, Host Interaction, and Clinical Outcome

Little attention has been paid over the past decades to viral strain diversity and its capacity to cause variable clinical outcomes (Couacy-Hymann et al., 2007). Peste des petits ruminants virus induces an acute systemic viral infection with a wide spectrum of disease manifestations, ranging from sub-clinical infection to severe and fatal disease. From these observations, infection outcome is suspected to depend in part on specific interactions between host and pathogen genotypes. Discovery of specific pathogen-receptor interactions have attested in the recent years of the specific evolution and adaptation of host and pathogen genomes (Tatsuo et al., 2001; Birch et al., 2013).

From the host perspective, previous studies have pointed out that, while manifestation of the disease is comparable to that induced by rinderpest, unlike RPV strains, distinct classes of virulence cannot be described for PPRV strains. Experimental infections hardly allow reproducing the pathogenicity initially recognized in the field. Factors unrelated to the virus may modulate the clinical expression, and it seems, in many ways, that the pathogenesis depends on the host. Thus, host

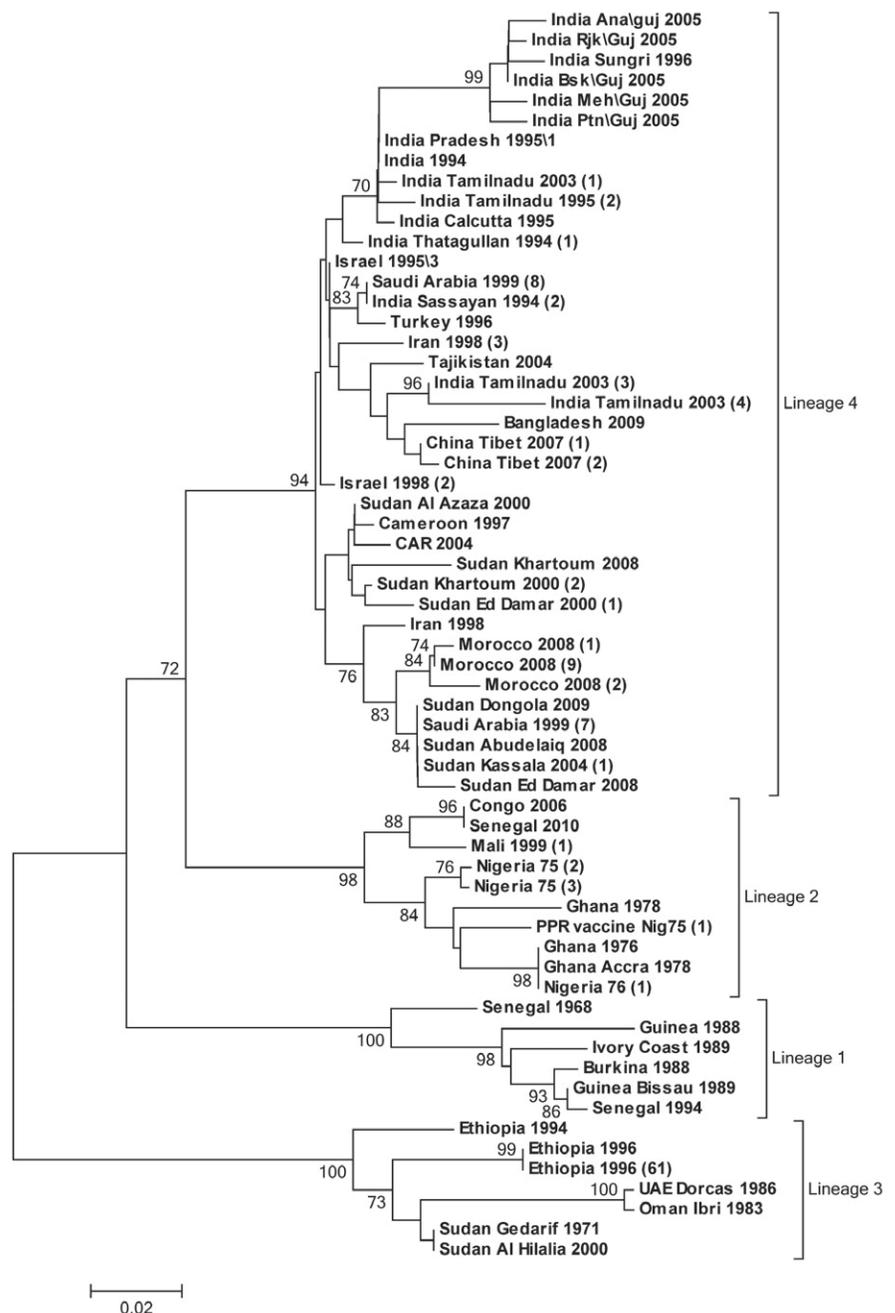


Figure 2. Phylogenetic tree representing the genetic diversity in peste des petits ruminants virus (PPRV). The tree is constructed on the basis of 255-nucleotide sequences of the PPRV nucleoprotein gene. Analysis was performed using a weighted neighbor-joining method. The scale bar indicates nucleotide substitutions per site. Bootstrap support values > 70 are shown at nodes (1,000 replicates).

susceptibility is considered of great importance in the manifestation of the disease. An example is the PPR outbreak reported by Diop et al. (2005) describing very severe symptoms in animals of West African Dwarf breeds while those of the West African Long-Legged breed were showing mild symptoms. However, the indication that different breeds/species equal different clinical outcomes is too simple of an approach and obviously requires further examination.

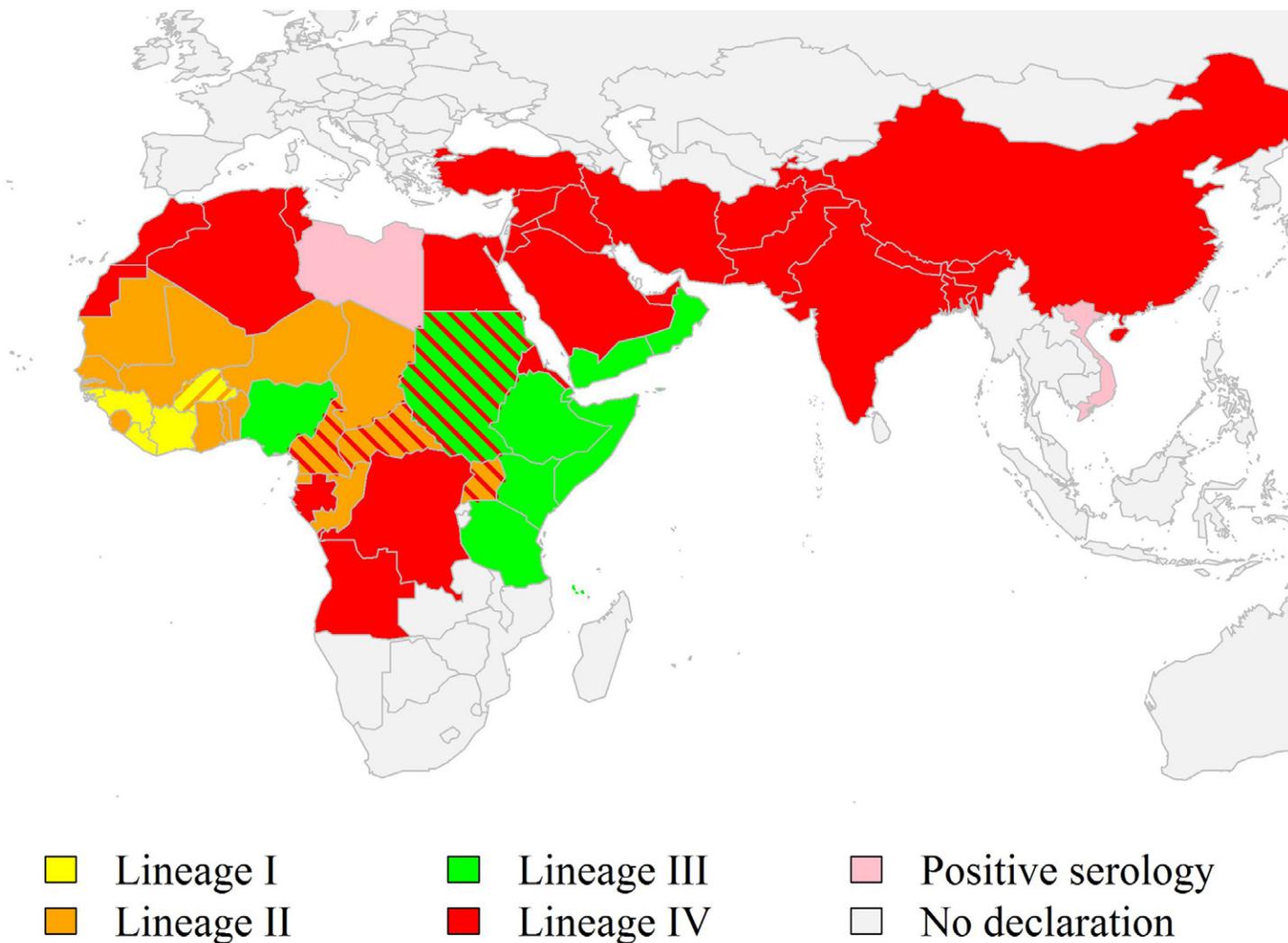


Figure 3. Map depicting the worldwide cumulative distribution of the four peste des petits ruminants virus (PPRV) lineages. Countries reporting at least one PPRV lineage are colored according to the identified lineages. Background color and colored bars represent the last identified lineages in the country. Adapted from Albina et al. (2013).

Partial- and whole-genome sequencing of the PPRV isolated from susceptible hosts with clinical data has been initiated on a large scale. The consensus sequences that have been analyzed bear witness to genetic diversity of PPRV, but are far from representing the whole genetic polymorphism. Indeed, during the short-term and acute infection, PPRV as an RNA virus is notoriously prone to mutation, meaning that the population within an infected individual may be polymorphic. Continuous generation of mutants and selection pressure leads to a dynamic population structure, known as “quasi-species” (Domingo and Holland, 1997). Individual populations may thus contain viruses that differ in their virulence and transmissibility. While this expectation has not been confirmed yet for PPRV through natural or experimental infections, genetic diversity may lead to association with other host types. PPRV in dromedaries is now recognized as an emerging disease (Roger et al., 2000; Khalafalla et al., 2010). If true, this observation obviously has a major bearing on host diversification capacity of this virus. The role played by strains with differences in virulence, including transmission potential, need long-term prospective studies to be performed in areas where PPRV is enzootic. To meet the challenges, high-throughput analy-

sis pipelines are now able to achieve alignment and mapping of viral genomes generated by next generation sequencing. This information will allow the proposing of a comprehensive data bank documented by all the viral genetic polymorphisms. An in-depth characterization of the phylogeny of PPRV and the correlation between genetic mutations and virulence can now be considered more serenely. While initial studies have looked at these animal–virus interactions on a broad scale, integrated genomic data from the host and the pathogen can now be foreseen for in-depth characterization of the infection even on an individual basis. Not only will such information be important in the development of future intervention strategies, but it also has a major bearing on the evolution of virulence in PPRV, a subject that has received little attention so far.

Discussion and Future Prospects

The continued spread of PPR has become an essential animal health concern in endemic countries despite the existence of an effective vaccine. Re-emergence of PPR through different lineages has been dis-

closed in recent years with high losses of livestock, and the threat is now heightened for PPR-free countries at the border of the current endemic areas. Currently, the rapid spread of the disease in small-ruminant populations is attributed to the highly contagious nature of the disease and a combination of factors, including exponential population growth, globalization of travel and exchanges, and lack of proper control. Such a dramatic extension of the disease has resulted in increased recognition by the international community and definition of needs and commitments for organizing global control and foreseeing, as for rinderpest, a possible eradication. The prospect of achieving global eradication of PPR relies on several technical factors. This requires a coordination of the private and public actors of animal health management and the implementation of joint regional campaigns with sustained international commitment and financial support. Corollary activities such as evaluation of the effectiveness of vaccination and development of new vaccines are to be encouraged and funded to help sustain the gains achieved.

In addition, the key elements to better and efficiently control PPR should be based on a thorough understanding of the dynamics of the target disease. Thus, to meet the threat of PPR, a better understanding is needed of the underlying drivers of spread listed above and other epidemiological factors which influence its dynamics. Thus, it is essential to elucidate the role of evolutionary factors critical on the emergence, virulence, and adaptation to novel hosts. Success of control should rely on all innovations made in the field of virus identification and epidemiology investigation and modeling. The integration of molecular epidemiology and quantitative knowledge is a key element to understand the bio-ecological processes and enable dynamic mapping of health risks. To this end, a greater resolution of sampling of host populations and of genome sequencing must be foreseen throughout the geographic range of the virus. This work will allow grasping the genetic diversity of PPRV and evolutionary forces acting on genomic diversity. This information as well as relevant epidemiological data related to sampled animals (e.g., relevant species and animal mobility) is needed to establish the diversity of strains in the field, trace the spatiotemporal origin of a virus, and estimate the basis of its introduction into the herd. The plasticity of the virus in samples of diseased hosts (goats, sheep, and camels) will also lead to better understanding of the epidemiology of PPRV circuits. This information in particular will assist in our understanding of the mechanism of replacement or extinction or of the coexistence of viruses in some areas and not in others to produce predictive models and how they may be influenced by factors such as vaccination, migration, and transhumance. The results of these studies will be interesting aids to support decision making in an optimized approach of PPR control.

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