Future research to underpin successful peste des petits ruminants virus (PPRV) eradication

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Abstract
Peste des petits ruminants virus (PPRV) is a significant pathogen of small ruminants and is prevalent in much of Africa, the Near and Middle East and Asia. Despite the availability of an efficacious and cheap live-attenuated vaccine, the virus has continued to spread, with its range stretching from Morocco in the west to China and Mongolia in the east. Some of the world’s poorest communities rely on small ruminant farming for subsistence and the continued endemicity of PPRV is a constant threat to their livelihoods. Moreover, PPRV’s effects on the world’s population are felt broadly across many economic, agricultural and social situations. This far-reaching impact has prompted the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) to develop a global strategy for the eradication of this virus and its disease. PPRV is a morbillivirus and, given the experience of these organizations in eradicating the related rinderpest virus, the eradication of PPRV should be feasible. However, there are many critical areas where basic and applied virological research concerning PPRV is lacking. The purpose of this review is to highlight areas where new research could be performed in order to guide and facilitate the eradication programme. These areas include studies on disease transmission and epidemiology, the existence of wildlife reservoirs and the development of next-generation vaccines and diagnostics. With the support of the international virology community, the successful eradication of PPRV can be achieved.

INTRODUCTION
Peste des petits ruminants (PPR) represents one of the most important challenges to sustainable small-scale agriculture, particularly sheep and goat farming, in the developing world [1]. High mortality epidemics of PPR, combined with long-term endemicity, threaten the livelihoods of subsistence farmers and undermine the fragile economies that this industry supports [2, 3]. In a worrying trend, the last 15 years have seen PPR virus (PPRV) broaden its distribution, with epidemics as far apart as Morocco and China [4], including recent (2016) outbreaks in Georgia and Mongolia. PPRV has now spread to over 70 countries in Africa, the Near and Middle East, and Asia, and is currently threatening more than 1.7 billion sheep and goats (80% of the global population) [4] (Fig. 1). Within this area, 300 million low-income families rely on small ruminants for food and for trade; demand for small ruminant meat/milk is predicted to increase by 177% by 2030 [5]. PPR has therefore been highlighted as a significant disease in need of immediate global control [4]. The impact of PPR is perhaps best illustrated from an economic perspective, as it is estimated to cause $1.45–$2.1 billion (USD) worth of losses per year [4, 6].

As a result of the clear economic, social and health impacts of PPR on human populations, the international community, in particular the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), is now targeting PPR for eradication [4]. This campaign is justified by the benefits that would accrue from PPR control, and builds upon the successful eradication of rinderpest virus, the closely related morbillivirus of large ruminants. The international community’s success in eradicating rinderpest was based on the readily available, cheap and effective live attenuated Plowright vaccine, as well as collaboration on a global scale. These features are central also to the eradication strategy for PPR, which comprises a multi-stage process involving status assessment followed by disease control (vaccination) leading to PPRV-free status (full details can be obtained on the FAO and OIE websites (www.fao.org/ppr/en/ and www.oie.int/animal-health-in-the-world/ppr-portal/). As was the case with the rinderpest eradication...
programme, there are effective vaccines against PPRV [7, 8] and good laboratory diagnostic tests [9]. However, much of our understanding of the virus is based on an assumed similarity to rinderpest virus (RPV) [10]. While certain correlations are likely to be valid, particularly in areas relating to the physical properties of the virus, the pathogenesis and transmission may differ significantly, while the breadth of host species susceptible to infection with PPRV has not been well characterized, as was the case for RPV. The purpose of this review is to summarize current and future research that can support the PPRV eradication campaign, through basic and applied studies in molecular biology, epidemiology and vaccinology. While there exists a good basis of support for the control programmes being set up, more research is required to ensure the ultimate success of the eradication campaign.

PPRV VIROLOGY AND EPIDEMIOLOGY: IMPROVING OUR FUNDAMENTAL UNDERSTANDING

An effective live attenuated vaccine strain (Nigeria 75/1; lineage II) was derived in the 1980s [13]. This vaccine is known to give protection for at least 3 years [8, 10] and has been used throughout Africa, the Middle East and many countries in Asia. The major exception is India, where several similar vaccine strains, e.g. Sungri 96 (lineage IV), have been developed and are in widespread use in that country [7, 14]. However, since PPRV is mono-serotypic there is no evidence that the original vaccine strain would not be effective in India, or that the Indian vaccine strains would not be effective in Africa, the Middle East or other parts of Asia.

Sequence-based phylogenetic analyses have been used to divide the known isolates of PPRV into four distinct lineages [15]. There is no evidence that these lineages vary in their pathogenicity – rather they are a reflection of the distinct geographical origins of the viruses (allopatricity) and allow limited conclusions to be drawn as to the origin of new outbreaks, e.g. it was clear that the virus that caused the first outbreaks in Africa north of the Sahara was lineage IV, and so must have come from Turkey or the Middle East, since only lineages I, II and III were circulating in sub-Saharan Africa at that time [16, 17].

PPRV VIROLOGY AND EPIDEMIOLOGY: IMPROVING OUR FUNDAMENTAL UNDERSTANDING

There have been many advances in morbillivirus research in the last 10–15 years, e.g. identification of two receptors
CD150/SLAMF1 and Nectin-4 [18, 19], as well as a better understanding of pathogenesis (reviewed here: [20]). However, PPRV-specific knowledge still lags behind that of MeV and RPV. In particular, features such as host-susceptibility, transmission and field epidemiology remain poorly characterized.

Examining small ruminant susceptibility

Previous reports have suggested that goats may be more severely affected than sheep by PPRV infection [21–23]. However, variation in disease severity has also been observed between different species of goats [24, 25], and detailed research is required to define this susceptibility and whether the variation extends to specific features such as the duration of viral shedding in infected animals, which will contribute to the dynamics of PPR transmission. If within-species genetic variation in host susceptibility to disease is found, as has been shown for other ruminant pathogens, such as the sheep lentiviruses that cause ovine progressive pneumonia [26], the identification of naturally PPRV-resistant breeds could provide opportunities for selective breeding. An extensive sheep and goat breed genome database is available, which was used to show, for example, that variation in the PPRV epithelial receptor, nectin-4, does not confer differential susceptibility [27], and this is a promising area for continued research. However, while completely resistant breeds serve as an important tool in endemic areas to complement ongoing eradication, the impact of such animals on PPRV epidemiology (e.g. the possibility of subclinical spread of the virus) should be considered carefully.

The role of other species in PPRV epidemiology

There are numerous reports of PPRV infection in animals other than domestic sheep and goats. Infection of wild sheep/goats [28–30] and other wild and domestic ruminants (cattle, buffalo, gazelle and wildebeest) have been reported [31–34], as well as camels [35] and recently even dogs [36]. If confirmed and shown to be relevant from a transmission perspective, such observations would be very important due to the continued existence of transhumance and pastoralism amongst sheep and goat herders. However, few of these reports discriminate between (i) species that can be infected subclinically, seroconvert but do not shed virus (spill-over or dead-end infections); (ii) species that develop disease and which actively secrete infectious virus; and (iii) species in which infection is clinically inapparent but the animal remains infectious, shedding virus. Even where a specific pathogenesis has been related to isolated PPRV, as was the case with camels [37], follow-up investigations in which the isolated virus has been reintroduced into naïve camels have not been performed. It is important that such observations should be extended robustly to correlate pathogenesis, antibody responses and virus excretion. The level of virus excretion is the most difficult to determine; however, without this information it is very difficult to address adequately the associated risk to the PPR control and eradication campaign. The presence of the disease in wildlife is another area where additional research is needed. In December 2016, the disease was diagnosed in several wildlife populations in eastern Mongolia, e.g. saiga antelope (Saiga tatarica mongolica), ibex (Capra ibex) and goitred gazelle (Gazella subgutturosa), with more than 5000 deaths (World Animal Health Information Database; WAHIS interface). An important first step in this area is to ensure that the currently available tests for sero-diagnosis of PPRV are validated in serum samples from these animal species, e.g. camels, saiga deer and ibex. With specific reference to the PPRV eradication campaign, the significance of these infections as a whole
should be carefully evaluated, as they may not significantly affect the ultimate success of the programme.

**Characterizing PPRV transmission**

Some basic parameters of the transmission of PPRV remain to be established. Early studies on RPV established the period during which live virus was excreted from infected animals and the level of virus in various excretions, such as milk, urine and faeces [38]. These studies have never been carried out on PPRV and, while it is tempting to assume a similar pattern for related viruses, there are clear differences between the two diseases which may have significant effects on the transmission dynamics, notably that PPRV shows extensive lung pathology in infected sheep/goats, which was not seen in RPV-infected cattle. Quantitative data should therefore be acquired to improve our understanding of the key differences between PPRV and RPV.

Similarly, little is also known about the stability of PPRV in the environment [10]. In order to provide the required supporting data to the eradication campaign, research must be conducted on the stability of PPRV in relevant contexts, e.g. the role of contaminated bedding and fomites in PPRV transmission by animal movement, or its stability in products such as milk and meat. An important characteristic of morbillivirus infections is their systemic infection, with the virus being found in various excretions and bodily fluids [39], and this pathogenic feature cannot be overlooked in modelling the transmission of the virus.

**Factors affecting herd immunity and determining vaccination policy**

The success of the PPR eradication strategy could depend on our ability to model virus transmission and epidemiology correctly. While it is clear that the entirety of a naïve herd can rapidly become infected by PPRV, our understanding at a farm-by-farm level, with varying herd-immunities, is much weaker. Further field studies on PPRV transmission are therefore required to define the basic reproduction number ($R_0$) and effective reproductive number ($R_e$) (in the context of herd immunity) of PPRV and to analyse how different environments, farming intensity, animal replacement rates and pastoral systems influence these values. Knowledge of $R_0$ and $R_e$ is required to establish the level of herd immunity required to prevent transmission; in the absence of specific data, the target immunity levels may only be estimated. Currently, herd immunity levels of anything from 70 to 90% are widely quoted as being required to successfully prevent PPR transmission, figures which are rooted in the rinderpest eradication campaign begins [40, 41, 45, 46]. The causes of this irregularity are considered to be linked to exogenous factors, particularly altering birth rates during vaccination [45]. It will therefore be important for field epidemiologists to monitor the effects of the eradication campaign on small ruminant birth rate, which may increase in relation to herd immunity. Independently, there is also a requirement for well-controlled transmission studies to facilitate this discussion, although it is already known that within herdmortality rates of 50–90% [4, 47].

From a broader perspective, a more detailed understanding of the trade in small ruminants might also improve our understanding of PPR transmission. Research in this area can be used to guide targeted vaccination strategies and may also help to define the true nature of endemicity from a virology, epidemiology and pathogenesis perspective. These resources and research will be particularly important in the later stages of an eradication campaign, when movement controls are a critical tool in preventing the spread and re-emergence of the disease.

**PPRV VACCINATION: CURRENT SITUATION AND FUTURE TRENDS**

**Implementing thermostable vaccines**

One of the key issues in effective implementation of the existing live PPRV vaccines is their limited thermotolerance, which requires the maintenance of a cold-chain. For rinderpest virus this problem was overcome through use of specific lyophilized vaccine preparations with high thermotolerance [48]. Freeze-drying using lactalbumin hydrolysate and sucrose stabilizers increased the robustness of the vaccine preparation, allowing short-term storage at temperatures up to 37°C or even 45°C. Similar technologies have been applied to PPR vaccines [49] and the process appears to provide good stabilization, e.g. several months at 37°C [50]. Research in this area must focus on optimizing these approaches to provide technology that can be directly applied by commercial producers of the vaccine.

**Development and application of PPRV vaccines**

There have been repeated calls for the development of a new generation of PPR vaccines, specifically vaccines capable of distinguishing vaccinated from infected animals (DIVA) [7, 51]. Some of the most promising DIVA candidates are recombinant viruses expressing viral surface glycoproteins to elicit a protective immune response. Since a natural PPRV infection also elicits an anti-nucleoprotein response in animals, these DIVA vaccines theoretically make the serological response in vaccinated animals distinguishable from naturally infected animals. This is especially useful in situations where surveillance is being
implemented at the same time as vaccination. In recent years several such vaccines have been successfully developed, particularly using adenovirus [52–55] and goat/sheep pox vectors [56–58], and some have been tested for efficacy in conventional PPR challenge studies; however, their capacity for long-term protection (up to 2 years) has yet to be determined. For vectored vaccines, the presence of pre-existing immunity against the vector, i.e. in the case of capripox combination vaccines [59], has also not been thoroughly examined in the field. In all these cases, further research is required to convert their clear potential into applicable field vaccines. Besides trans-expression of viral glycoproteins, there have also been approaches taken to generate recombinant PPRV-based DIVA vaccines, e.g. negatively marking dominant epitopes in H commonly detected during sero-surveillance [60]. Two systems for making recombinant PPRV have been published [61, 62], offering a promising route for the production of such novel marker, DIVA or heterologous vaccines. However, it remains to be seen how effective this approach could be for PPRV, and how stable these mutations are during live-vaccine production. Importantly, all of these vaccines constitute ‘genetically modified organisms’ (GMOs), and therefore adequate planning must be taken before they can be legally implemented in the field.

Separately, it is also worth considering the age at which vaccination can be performed efficaciously. Sheep and goats have short gestation periods (c. 150 days) and can breed twice a year. This, combined with their short economic life-spans in the developing world (c. 3–5 years), means that populations are highly dynamic, complicating the development of the robust herd immunity levels required for eradication. Younger animals will therefore be a primary target for vaccination; however, few detailed research data are available to indicate the age at which they can be vaccinated. In addition, the duration of protective maternal immunity provided by an immunized or naturally infected dam is also unclear, as well as the degree to which this immunity can prevent effective vaccination. These are clearly areas where specific research needs to be performed to provide data to support vaccination, and ultimately eradication.

**PPRV co-morbidities and the control of other diseases of small ruminants**

Co-morbidities are a frequent problem in small ruminant farming, e.g. in one study in Turkey, PPRV, bluetongue virus and sheep/goat pox virus were all identified in the same flock of sheep and goats [63]. There is also evidence for co-circulation of PPRV with other pathogens such as *B. anthracis* and foot and mouth disease virus (FMDV) [64] or *Brucella* spp [65]. Another concern is that viruses such as Rift Valley fever virus (RVFV) or Nairobi sheep disease virus (NSDV) may replicate preferentially in PPRV-affected animals. MeV infection has been shown to cause profound immune suppression as a result of lymphopenia, cytokine imbalances and deficient expansion of PBMCs [66]. Immune suppression was also seen in RVFV-infected animals, even those exposed only to the vaccine [67]. Research is therefore required to examine whether PPRV similarly causes long-term immune suppression and whether the vaccine strains have any such effect, even if transient, which may impact on the efficacy of co-administered vaccines.

Nevertheless, a well-orchestrated PPR eradication campaign could provide an excellent platform for the control of other small ruminant diseases. The major cost of any vaccination campaign is normally that of vaccine delivery. Significant benefits and cost improvements could be achieved through simultaneous vaccination against several small ruminant diseases. This could be addressed either by recombinant vaccines such as the capripox/PPRV vaccine [59] or by combined vaccination against PPR and sheep goat pox, which has already been shown to be effective [58]. Integrated control campaigns of this kind are already being implemented in some countries, e.g. in Morocco for PPR and sheep pox [68]. However, as mentioned above, this approach raises concerns about the possible interactions between co-administered vaccines. For this type of approach to be generally implemented in the PPR vaccination or eradication strategy, further research is needed to determine the safety and efficacy of different combinations of these vaccines.

**DIAGNOSTICS – EVERYDAY APPLICATION AND FUTURE INNOVATION**

The existing diagnostic platforms to support PPR eradication range from commercially available ELISAs and RT-PCRs to gold-standard VNTs. These assays serve to detect either the virus directly (either through isolation of infectious virus or via detection of viral antigen or genome) or to detect the animal’s response to infection (primarily through virus-specific antibody responses). Although robust tools exist, there is still a need for research to improve and adapt existing tests to match various situations that may arise during the implementation of the eradication campaign.

**Novel tools in the pipeline**

Recent developments include a lateral flow device (pen-side test) for rapid-detection of PPRV in the field [69]. This test is proving particularly useful in field situations where there is poor access to laboratory diagnostics, either through geographical restrictions or political instability, and allows more rapid decisions about the implementation of control measures. The recently established viral-pseudotype system for PPRV, which permits detection of virus-specific antibodies without the need for live virus, is also a noteworthy development [70]. This alternative to classical VNT assays could prove particularly useful during an eradication campaign for those diagnostic laboratories that do not have the facilities to handle high-containment pathogens such as PPRV. The development of the pseudotype-based assay for neutralizing antibodies highlights a hitherto unexplored aspect of ‘gold-standard’ live virus-based VNTs. Morbillivirus infections may induce cross-neutralizing antibodies, and hence the detection of a neutralizing antibody titre in cattle...
against PPRV by live virus-based VNT is not conclusive evidence of PPRV infection; the animal may have been exposed to PPRV, RPV or CDV, all of which may induce anti-PPRV neutralizing or cross-neutralizing antibodies [70, 71]. The recent development of a helper cell-dependent recombinant PPRV has also yielded a promising, yet bio-safe, source of viral antigen for future diagnostics, since this system produces replication-incompetent virus [72].

**Future perspectives on monitoring the virus in the field**

Sequencing and molecular epidemiology will play an effective role in PPR control and eradication. Existing phylogenetic analysis of PPRV focuses on relatively short regions in the N and F genes; however, it is possible that these may prove insufficiently variable in the future, should one lineage, e.g. lineage IV, predominate. Future research should therefore focus on insuring against such an eventuality. One option is to concentrate analysis on the ectodomain region of the H ORF, as is the case for MeV [73], since these data can also be translated into functional information on receptor binding [74] or antigenicity [75], while still providing sufficient data to cluster the viruses phylogenetically along similar lines to the existing N- and F-based systems (Fig. 3). Logically, however, it may be beneficial to plan strategically for entire genome sequencing, to allow detailed monitoring of any ongoing PPRV epidemic. This genome-wide approach was shown recently to be essential for identifying the origin of a measles outbreak at the 2010 Vancouver Winter Olympic Games [76]; furthermore, full PPRV genome sequences, including vaccine sequences, are already available to support this effort [79, 80] (Table 1 and Fig. 2). It is also possible that a PPRV eradication campaign could drive an evolutionary reduction in viral pathogenesis in the field, complicating surveillance and detection mechanisms and undermining the success of the strategy. This has been suggested as a potential explanation for the ‘mild’ rinderpest strains reported in East Africa towards the end of that eradication campaign [81]. Future research in this area must complement both *in vivo* experimentation and transmission studies with ongoing molecular epidemiology and genome-wide sequencing endeavours in order to adequately address these risks.

Separately, in countries where PPR is endemic, there is a need to develop low-cost diagnostic tests or simple tests that can be applied in the field or in low-technology situations. If the global PPR strategy recommends combining PPR control with control of other diseases of small ruminants, a cost-effective, multi-disease diagnostic test would be very useful for simultaneous surveillance for all the target diseases. These multi-disease diagnostic tests may also be necessary during the final stages of the eradication programme, when PPR-like disease symptoms must be investigated to rule out virus re-incursion and provide robust differential diagnostics.

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**Table 1. Currently available PPRV genome sequences ordered by genetic lineage and year of virus isolation**

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<th>Lineage</th>
<th>Year of isolation</th>
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*Denotes vaccine strain.

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**Fig. 3.** A phylogenetic tree comparing PPRV haemagglutinin amino acid sequences. Isolates from all four recognized genetic lineages (I–IV) of PPRV are represented and cluster accordingly. This pairwise tree was constructed using the AlignX package within Vector NTI, with Kimura’s correction. Genetic distances from the branch are provided in parentheses; please refer to Table 1 for Genbank accession numbers.
SOCIO-ECONOMIC IMPACT

Socio-economic studies into the impact of PPRV on small ruminant production and livelihoods should not be overlooked, as these studies will assist in advocating for investment in the PPR Global Eradication Programme. Despite increased attention and laboratory research on PPRV in the last 10–15 years, we neither fully understand nor publicize the impact of this disease on the livelihoods of small ruminant keepers and national economies across the world. In order to leverage funding for the research detailed in this review, we must highlight the role and importance of goats and sheep within agriculture, e.g. by examining the multiple uses and services they provide as well as the roles they play in different farming systems. A better appreciation of the impact of socio-economic factors on PPRV vaccination is also needed, e.g. the incentives and disincentives associated with small ruminant production and how they influence participation in eradication campaigns. At present an in-depth understanding of this balance is lacking from both the service providers’ and livestock owners’ perspective, especially in areas directly affected by PPRV. Developing better analytical approaches to estimate and compare all products and services, and how these are affected by PPRV, will help to highlight the true worth of small ruminants and the importance of research that supports the eradication campaign.

EXAMINING THE POTENTIAL FOR INTER-SPECIES (AND ZOONOtic) TRANSMISSION OF MORBILLIVIRUSES

There is one additional point for consideration across the research community, the consequences and impact of which may lie downstream of PPRV’s eradication. Immune responses to morbilliviruses show significant levels of cross-protection against infection with other species of morbilliviruses [13, 82]. Accordingly, the eradication of one species of morbillivirus and the subsequent cessation of vaccination may have long-term consequences on host immunity to zoonotic infections with other morbilliviruses. It has been suggested that rinderpest eradication and the cessation of vaccination may have played a role in the ongoing spread of PPR [3, 47]. Future studies should investigate whether there is indeed a causal link, for example by examining the effect of removing cross-protective antibodies from host populations. The recent spread of PPR may be due to other factors such as better surveillance, a shift in veterinary focus to sustainable small ruminant production, increased trade in ruminants over larger distances, or increased regional political instability. There are fears that other morbilliviruses (known or emerging) may colonize newly available ‘vacated niches’ [83]. Post-PPRV eradication, the world’s cattle, sheep and goat populations would lack cross-protective immunity to morbillivirus infection. Canine distemper virus (CDV), a virus with an almost global distribution, is capable of causing significant disease in a broad range of hosts, including non-human primates [84, 85]. CDV can rapidly adapt to use the human form of the morbillivirus receptor (SLAMF1) in vitro [86], raising concerns about the ease with which these viruses can effectively jump hosts. Indeed, serological responses to CDV were described recently in Tanzanian cattle [71]. In addition, a new spectrum of previously uncharacterized morbilliviruses has been identified in global bat and rodent populations [87], as well as a specific new morbillivirus in domestic cats [88]. There is therefore a critical requirement to develop novel approaches for assessing the risk of such transmission events taking place, for example by defining the capacity for animal morbilliviruses to interact with receptors from target species and by assessing the degree of cross-protection afforded by neutralizing antibodies. By extension, this work would inform our approach to protecting human health following the global eradication of measles.

SUMMARY AND CONCLUSIONS

There are compelling animal health, economic and social reasons to support the FAO/OIE-led PPR Global Eradication Programme. Alleviating the effect of PPR will have a considerable impact on the sustainability of small ruminant agriculture in many low-income countries whilst simultaneously addressing the ubiquitous need for an increased and reliable source of animal protein. To facilitate the delivery and success of the eradication programme there are many areas, including those described above and highlighted in Box 1, where applied and basic research can provide support. It is important to note that little of this work requires the development of new technologies, or even the application of the very latest technologies, but rather the careful application of classical virology and epidemiology to provide quantitative data to support those coordinating the eradication of this important livestock disease.
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Conflicts of interest
The authors declare that there are no conflicts of interest.

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