

Eradication of peste des petits ruminants: Application of new research to guide and facilitate the global elimination of the disease

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Summary

Peste des petits ruminants (PPR) is a highly contagious viral disease of domestic and wild small ruminants caused by the peste des petits ruminants virus (PPRV), which belongs to the genus *Morbilivirus* in the family *Paramyxoviridae*. The PPRV causes disease in goats and sheep, as well as in wild ruminants, such as gazelle, deer, antelope, Nubian ibex, gemsbok and others. PPR was first recorded in early 1942 in Ivory Coast, West Africa, and spread to around 70 countries in Africa, the Middle East and Asia – regions that are home to over 80% of the world's sheep and goats. Until 2018, PPR had never been detected in Europe. On 24th June 2018, however, the Bulgarian authorities reported cases of PPR in sheep in the village of Voden, Bolyarovo municipality of Yambol region, on the border with the Thrace region of Turkey. It was the first occurrence of PPR in Bulgaria and in the European Union (EU). The control and eventual eradication of PPR is now one of the top priorities for the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE). In 2015, the international community agreed on a global strategy for PPR eradication, setting 2030 as a target date for elimination of the disease. The aim of this paper was to highlight future research that could be performed to guide and facilitate the PPR eradication programme. Such research includes studies on PPR transmission and epidemiology, as well as the development and application of new-generation PPR vaccines capable of differentiating infected from vaccinated animals (DIVA). Moreover, there is a need for research to improve and adapt existing diagnostic techniques as well as to develop novel PPRV recognition methods, such as a lateral flow device for in-field use, that accelerate decisions about the implementation of control measures.

Keywords: peste des petits ruminants (PPR), eradication, virological research, epidemiology and transmission, vaccines and diagnostics

Peste des petits ruminants (PPR) is a highly contagious acute viral disease that affects primarily domestic small ruminants and is associated with high mortality and heavy socio-economic costs (42). The impact of PPR on the productivity of small ruminants includes mortality, loss of milk, meat, fibers, and hides, weight loss, impaired growth, and abortion. The causal agent of PPR is peste des petits ruminants virus (PPRV), which belongs to the genus *Morbilivirus* of the family *Paramyxoviridae* (9). PPRV exists as a single serotype, but is divided into four distinct lineages at the genetic level. The molecular epidemiology of PPRV, based on the sequence comparison of a small region of either the N or the F gene, has revealed the existence of four distinct lineages (I-IV) of the virus (31). These short

regions in N and F genes may prove insufficiently variable in the future, should one lineage, e.g. lineage IV, predominate. Historically, the four lineages follow the geographic distribution, in which lineages I and II are found in western and central Africa, lineage II in eastern Africa and the southern part of the Middle East, and lineage IV in the Middle East and southern Asia (5). Identification of the lineage of PPRV is essential for understanding its epidemiology and for the control of PPR.

PPR was first recorded in early 1942 in Ivory Coast, West Africa (27). In the following years, the disease spread to other parts of the world and now circulates throughout Northern, Eastern and West Africa, as well as Asia – in particular China, Central Asia and

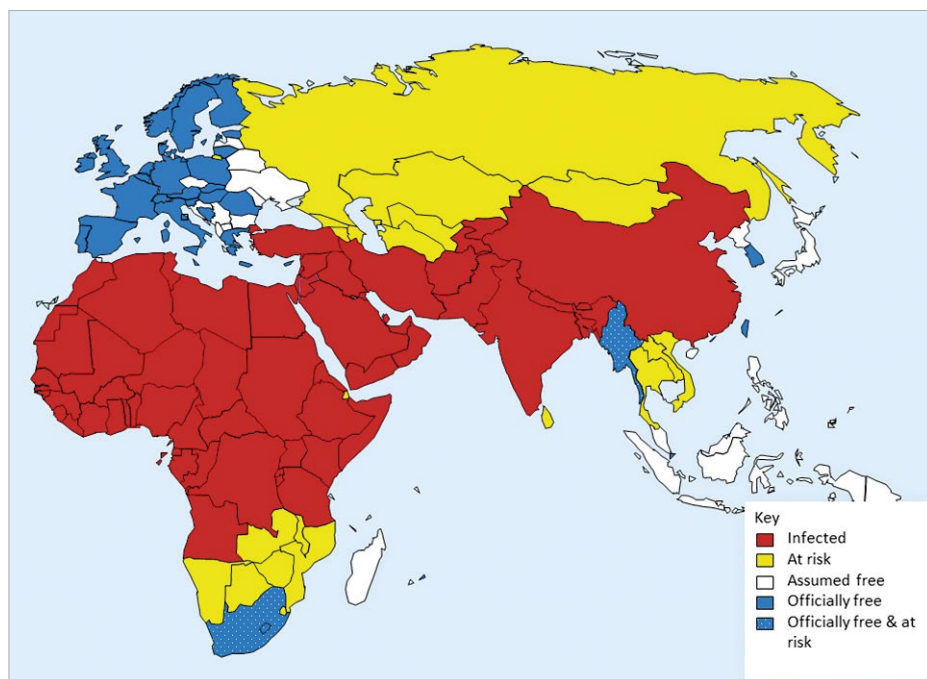


Fig. 1. The occurrence of peste des petits ruminants (PPR) in the world (modified, according to Jones et al. (26))

Eurasia, the Indian subcontinent and the Middle East (26) (Fig. 1). PPRV has spread to over 70 countries in different regions of the world and is currently threatening more than 80% of the global population of sheep and goats (19). More than one billion sheep and goats worldwide are at risk. Until June 2018, PPR had never been detected in Europe, with the exception of the European part of Turkish Thrace. However, on 24th June 2018 the Bulgarian authorities reported a case of PPR in sheep in the village of Voden, Bolyarovo municipality of Yambol region, on the border with the Thrace region of Turkey. It was the first occurrence of PPR in Bulgaria and in the EU (http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/WI). Management of disease eradication programmes is an adaptive and dynamic process that builds on existing knowledge, new learning, and new technologies. As was the case with the rinderpest (RP) eradication programme, there are effective vaccines against PPRV and laboratory diagnostic tests (16, 46). Rinderpest virus (RPV) and PPRV have a number of similar physical properties, but 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 specific epidemiological features of PPR and the related socio-economic considerations will have to be taken into account, and a sustained internationally coordinated and funded strategy based on a regional approach to PPR control will be the guarantee of success. Considering the wide distribution of PPRV and its multiple highly mobile target host species, the eradication can be a long process that cannot rely exclusively on mass vaccination (5). The aim of this paper is to present current

and future research that can support the PPRV eradication campaign through basic and applied studies in epidemiology, vaccinology and molecular biology. These studies could be very useful for ensuring the ultimate success of the eradication campaign.

The features of PPRV, such as host-susceptibility, field epidemiology and transmission, have not been adequately characterized and require further research. In its acute form, PPR causes severe disease, with fever, respiratory symptoms, congestion and necrosis of mucous membranes, diarrhoea, abortion and immunosuppression. Although the primary hosts for the virus are goats and sheep, goats seem to be more susceptible than sheep. Alpine goats are reported to be highly susceptible to PPRV, with mortality rates ap-

proaching 100%, unlike local breeds of sheep, which appear to be less susceptible to the disease (20). Other studies evaluated the tissue tropism and pathogenesis of PPR following experimental infection of sheep and goats. Upon infection with a virulent strain of PPRV, both sheep and goats developed clinical signs and lesions typical of PPR, but sheep displayed milder clinical disease compared to goats (49). However, variation in disease severity has also been observed between different species of goats (15). If within-species genetic variation in host susceptibility to disease is found, 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, permits PPRV to replicate efficiently and does not confer differential susceptibility (10). PPRV can also affect wild sheep and goats and other wild and domestic ruminants (cattle, buffalo, gazelle and wildebeest) as well as camels and even dogs (2, 39, 44, 50). 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 herds. In December 2016, the disease was diagnosed in several wildlife populations in eastern Mongolia, e.g. saiga antelope (*Saiga tatarica mongolica*), ibex (*Capra sibirica*) and goitre gazelle (*Gazella subgutturosa*), with more than 5000 deaths (4). It is important to ensure that the currently commercially available tests for PPRV serology are validated in serum samples from these wild animal species. With specific reference to the PPRV eradication programme, the significance of these infections as a whole should

be carefully evaluated, as they may significantly affect the ultimate success of the programme. The exact role of wildlife in the epidemiology of PPR is not clear. A recent serosurveillance at the interface of wildlife and domestic small ruminants in Tanzania revealed a spill-over of virus from domestic infected ruminants to wildlife, which needs further investigation (36). Future studies in this area must be complemented by both *in vivo* experimentation and transmission studies with ongoing molecular epidemiology and genome-wide sequencing in order to adequately address these risks.

PPRV is transmitted to close in-contact susceptible animals through exhaled aerosols, particularly during coughing, or through clinical excretions (lachrymal, nasal, saliva and faeces) (1). The virus can be spread over large distances through the movement of infected animals for trade or during migration, particularly animals incubating the disease without clinical signs. 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 (33). Such studies have never been carried out on PPRV, and, although 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 transmission dynamics. Notably, PPRV causes extensive lung pathology in infected animals, which has not been seen in RPV-infected cattle. Therefore, the major differences between PPRV and RPV should be thoroughly determined. The stability of PPRV in the environment should also be better explained. Research must be performed on the stability of PPRV in relevant contexts, e.g. the role of contaminated bedding and fomites in virus transmission by animal movement, or its stability in products such as milk and meat. The success of a PPR eradication strategy could depend on our ability to model virus transmission and epidemiology correctly. It is also possible that a PPRV eradication campaign could drive an evolutionary reduction in viral pathogenesis in the field, complicating surveillance and undermining the success of the strategy. It is well proven that the entirety of a naive herd can rapidly become infected by PPRV, but our knowledge at the farm-by-farm level, with varying herd immunities, is more limited. Detailed studies on PPRV transmission are required to define the basic reproduction number (R_0) and effective reproductive number (R_t) 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_t is required to establish the level of herd immunity required to prevent transmission, and in the absence of specific data, the target immunity levels may not be estimated. Currently, herd immunity levels from

70% to 90% are widely believed to be required to successfully prevent PPR transmission (45). Studies in Tanzania and Pakistan estimated R_t at 4.0 and R_0 at 6.9 (27, 51). Other factors, such as the short economic lifespan of small ruminants, pastoralism, agricultural production systems, population density and extensive international trade, are also probably important in PPRV transmission, and it is likely that PPRV epidemics will become irregular and unpredictable after the eradication campaign begins (18, 43). The causes of this irregularity are believed to be linked to exogenous factors, particularly to altering birth rates during vaccination (18). It will therefore be important to monitor the effects of the eradication campaign on the birth rate of small ruminants, which may increase in relation to herd immunity. A more detailed knowledge of trade in small ruminants might also improve our understanding of PPR transmission. Studies on this issue can be used to guide targeted vaccination strategies and may also help define the true nature of endemicity from the perspective of virology, epidemiology and pathogenesis.

PPR control is achieved mostly through the use of clinical or laboratory-based diagnosis coupled with vaccination and/or slaughter. Vaccination is a core component of the eradication strategy. The existing PPR vaccines are among the most effective vaccines available for any disease. Currently, three excellent PPR vaccines have been fully tested and used in the field. They are recognised by OIE and are available commercially for use in PPR eradication programmes (5). All these PPR vaccines are live attenuated strains of PPR (17, 47), the two most commonly used being derived from PPRV/Nigeria/75/1 (17) or PPRV/India/Sungri/96 (48). These live attenuated vaccines are safe and highly efficacious against all known isolates of PPRV, but are incapable of differentiating infected from vaccinated animals (DIVA) (16). To overcome these limitations, some recombinant vaccines have been developed. Some of the most promising DIVA candidates are recombinant viruses expressing viral surface glycoproteins to elicit a protective immune response (28). 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 useful especially in situations where surveillance is being implemented at the same time as vaccination. Recently, several such vaccines have successfully been developed, particularly using adenovirus (21, 23) and goat or sheep pox vectors (12, 14). Some of these have been tested for efficacy in PPR challenge studies, and their usefulness as DIVA vaccines for PPR was evaluated. For vectored vaccines, that is, capripox combination vaccines (13), the presence of pre-existing immunity against the vector has also been thoroughly examined in the field. However, in the case of vectored vac-

cines, further studies are required to convert their clear potential into applicable field vaccines. Two systems for making recombinant PPRV have been described, offering a promising route for the production of such novel marker, DIVA or heterologous vaccines (25, 40). It remains to be seen, however, how effective this approach could be for PPRV, and how stable these mutations are during the production of live vaccines. PPRV can co-circulate with other morbilliviruses. Pathogens such as bluetongue virus (BTV) and sheep pox virus (SPV) or goat pox virus (GPV) were all identified in the same flock of sheep and goats (41). Co-circulation of PPRV with *Bacillus anthracis*, foot and mouth disease virus (FMDV) and *Brucella* spp. has also been shown (38). Therefore, detailed studies are required to examine whether PPRV similarly causes long-term immune suppression and whether the vaccine strains have any such effect, which, even if transient, may limit the efficacy of co-administered vaccines. However, a well-planned PPR eradication campaign could provide an excellent programme for the control of other small ruminant diseases. It would be beneficial to carry out a simultaneous vaccination against several small ruminant diseases. This could be addressed either by recombinant vaccines, such as the capripox/PPRV vaccine (13), or by combined vaccination against PPR and sheep pox (24).

Since the clinical signs of PPR are not disease-specific and clinical disease is not reliable, it should be confirmed by laboratory testing. Currently, a PPR diagnostic capacity test is available to confirm clinical diagnosis of PPR, to measure the serological response to PPR infection both in individuals and in populations, to differentiate PPR from other similar diseases of small ruminants, and finally to genetically characterize the PPRV as an aid for describing the flows of virus through populations. Virus isolation is a sensitive, but time-consuming and cumbersome method. Moreover, the preservation of samples collected under field conditions is not always adequate for successful laboratory results. African green monkey kidney cells (Vero) have long been the cells of choice for the isolation and propagation of PPRV. However, some isolates may not grow well in these cells. Recently, transformed monkey cells expressing sheep/goat signalling lymphocytic activation molecules (SLAM or CD150), the virus cellular receptors, have been shown to possess increased sensitivity. The most common, rapid, specific and sensitive laboratory PPR recognition techniques are immunocapture enzyme-linked immunosorbent assay (ELISA) for PPR antigen detection and real-time polymerase chain reaction (PCR) for detection of viral RNA (6, 30). In the eradication program, the ability to determine the immune status of a subpopulation is a crucial step that underpins decision-making about whether to vaccinate that subpopulation or adopt alternative epidemiologically based approaches, such as

movement restrictions. The most reliable and rapid test for antibody detection is a competition ELISA based on a monoclonal antibody directed against the virus nucleoprotein (32). The virus neutralization test (VNT) is also an OIE-prescribed reference method. Because VNT necessitates cell and virus cultures, and thus takes several days before result outcome, it is not used as a routine test. It is used mostly in reference laboratories to confirm unclear results. The effectiveness of PPR laboratory diagnosis can be greatly influenced by the integrity of the sample received, often affected by the conditions of its collection and transportation. Recently, an immunochromatographic lateral flow device has been developed and validated under field conditions (pen-side test) using a monoclonal antibody specific to the virus H protein (8). This test is very sensitive and specific and is particularly useful under field conditions with poor access to laboratory diagnostics, either through geographical restrictions or political instability. Thus it can lead to more rapid decisions about the implementation of control measures. In particular, 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. Recently, a viral-pseudotype system for PPRV, capable of detecting virus-specific antibodies without the need for the live virus, has also been developed (35). This alternative to classical VNT assays could be particularly useful during an eradication campaign for those laboratories that do not have the facilities to handle high-containment pathogens, such as PPRV. Regarding the use of VNT, it is worth noting that morbillivirus infections may induce cross-neutralizing antibodies, and hence the detection of a neutralising antibody titre against PPRV in cattle by VNT is not conclusive evidence of PPR infection; the animal may have been exposed to PPR or RPV, and these pathogens may induce anti-PPRV neutralizing of cross-neutralizing antibodies (35). The recent development of a helper cell-dependent recombinant PPRV has also yielded a promising source of viral antigen for future diagnostics that is biologically safe because this system produces replication-incompetent virus (7). If the global PPR eradication 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 of all target diseases. These multi-disease diagnostic tests may also be necessary during the final stages of the PPR eradication programme, when PPR-like signs of disease must be investigated to rule out virus re-incursion and provide robust differential diagnostics.

Regarding the socioeconomic importance of PPR, it should be noted that, because of its clinical incidence and restrictions on animal movement, PPR is a disease of major economic importance? in areas that rely on

small ruminants. It affects the lives of about 300 million of the world's poorest people whose livelihoods depend on small ruminants. Many small holders in poor developing countries in Asia and Africa depend on goats and sheep for nutrition and livelihood. PPR has therefore been highlighted as a significant disease in need of immediate global control (19). Moreover, these animals are a source of regular income, acting as "mobile banks" to depend on in times of hardship and cash urgencies in poor households. PPR causes annual global losses estimated at US\$1.4 to US\$2.1 billion. Eradication of PPR is therefore highly relevant to poverty alleviation. That is why the control and eventual eradication of PPR is now one of the top priorities for the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE). After the successful eradication of RP – an equally devastating livestock disease – in 2011, the FAO and the OIE began mobilizing support for a similar effort aimed at complete elimination of PPR in the world. In 2015, the international community agreed on a global strategy for PPR eradication, setting 2030 as a target date for elimination of the disease (19). The costs of PPR eradication have recently been estimated, and the benefit-cost analysis has been conducted (37). The estimated overall undiscounted cost of eradication was estimated as US\$3.1 billion, and the benefit-cost ratio for the most likely scenario was estimated at 33.8. The strategy is to invest more in epidemiology, surveillance, and diagnostics (US\$1.409 billion) than in vaccinology (US\$1.010 billion). In order to increase funds for research on the impact of PPR on the livelihoods of keepers of small ruminants and national economies around the world, the role and importance of small ruminants in agriculture must be highlighted. A better appreciation of the impact of socio-economic factors on PPR vaccination is also essential, e.g. the incentives and disincentives associated with production of small ruminants and how they influence participation in eradication campaigns. Efforts for PPR eradication will involve an approach that combines strengthening national veterinary health services and systems for disease surveillance, vaccination campaigns and awareness raising initiatives. This will require support for many institutions, such as national veterinary services, research and development organizations and vaccine manufacturing companies.

It should also be emphasized that immune responses of morbilliviruses show significant levels of cross-protection against infection with other species of morbilliviruses (17, 22). Therefore, the eradication of one species of morbillivirus, e.g. RP, and a subsequent cessation of vaccination may have long-term consequences for host immunity to zoonotic infections with other morbilliviruses. It cannot be ruled out that the eradication of RP and the cessation of vaccination may have played a role in the ongoing spread of PPR (29).

That is why it should be investigated 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 also be due to other factors, such as better surveillance, a shift in veterinary focus to sustainable small ruminants production, increased trade in ruminants over large distances, or increased regional political instability. It is believed that other morbilliviruses may colonize newly available "vacated niches" (34). After the eradication of PPR, the world's cattle, sheep and goat populations would lack cross-protective immunity to morbillivirus infection. There is therefore a need to develop novel approaches for assessing the degree of cross-protection afforded by neutralization antibodies.

In conclusion, there are many areas of key research that should be undertaken to facilitate the delivery and success of an eradication programme for PPR, such as 1) determining the role of atypical hosts (other than sheep and goats) in PPR epidemiology, 2) characterizing the effective reproductive number (R_e) for PPRV in various environments, 3) ensuring the effective and broad implementation of thermostable vaccine technology, along with good manufacturing practice, 4) improving our knowledge of vaccination efficacy in young animals, 5) developing a DIVA vaccine with associated and validated differential diagnostic tests, 6) refining the targets for molecular epidemiology and developing validated partner technologies, 7) increasing the scope and application of in-field diagnostics, 8) understanding the socio-economic impact of PPR on the livelihoods of small ruminant keepers and national economies around the world, 9) examining the potential for inter-species morbillivirus transmission. It is important to mention that most of this research does not require the development of new technologies, but rather a careful application of classical virology and epidemiology to provide quantitative data to those who coordinate the eradication of this important livestock disease.

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