Rinderpest and Peste des petits ruminants: state of play in the disease eradication efforts

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Summary

Rinderpest (RP) virus and peste des petits ruminants (PPR) virus are highly pathogenic viruses causing disease primarily in, respectively, cattle and small ruminants. Although the post-eradication process for RP has been largely successful, there are still a few gaps in our preparedness for any future RP reappearance, and the virus is still held in some facilities that have not been registered or inspected, which poses a threat to the global community. The global eradication programme for PPR will have to overcome significant hurdles to reach a world free of the disease by 2030. Achieving this goal will be made easier if plans are based on the best research and tools available, with proper involvement of communities. Focusing research and development efforts on the important remaining gaps should increase the efficiency of the control and surveillance strategies designed, if research outputs are effectively transferred to decision makers. We should start building on the experience of RP to prepare for a post-PPR world. The animal health community should also be vigilant for other viruses, including those yet unknown, that could emerge as the niches of rinderpest virus and PPR become vacant.

Keywords


Introduction

Rinderpest (RP) and peste des petits ruminants (PPR) are highly pathogenic infectious diseases primarily affecting, respectively, cattle and small ruminants (sheep and goats).
Both diseases are caused by viruses of the genus *Morbillivirus*. Although recent, multiple changes in the taxonomy of this genus have caused confusion in the animal health community (including World Organisation for Animal Health [WOAH] [1]), the name of the two viruses remain rinderpest virus (RPV) and peste des petits ruminants virus (PPRV) [2]. WOAH and the Food and Agriculture Organization of the United Nations (FAO) officially declared the eradication of RP in 2011. Here we review the ongoing efforts to avoid its reappearance. PPR was identified as the target of a new global eradication campaign in 2015 [3], prompted by its similarities with RP [4]. However, the two viruses are different in other ways, with many gaps in our understanding of PPRV molecular biology and epidemiology, and of the socio-economic context of PPR transmission and control. The PPR Global Research and Expertise Network was formed under the lead of WOAH and the FAO to coordinate efforts in filling these gaps [5]. Here, we review the recent progress in different fields of research and highlight important questions that still need to be addressed to support the goal of PPR global eradication by 2030.

**Rinderpest**

**Safety and preparedness**

As the first (and so far only) livestock disease ever globally eradicated, RP has been a proving ground for how to manage the post-eradication world, not only how to minimise the risk of the virus ever reappearing in livestock, but also how to manage the response to a possible future reappearance. WOAH and FAO established the Joint Rinderpest-Secretariat and the Joint Advisory Committee on rinderpest to coordinate the post-eradication strategy. The most important risk minimisation has been the effort to identify all countries still holding live RPV and persuade them to either destroy their stocks or to register the holding laboratory with the WOAH/FAO as a designated Rinderpest Holding Facility (RHF), with an alternative of transferring their Rinderpest virus containing material (RVCM) to a RHF in another country for safe storage. The current state has been recently reviewed in detail [6]: while great progress was made in the early stages, with the total of 44 laboratories in 35 countries in 2011 reduced to 14 laboratories in 12 countries at the time of writing, unfortunately, at least seven WOAH member states continue to hold RVCM in facilities that have not been registered or inspected, which poses a threat to the global community [7].

Preparations for a possible reappearance of RP were significantly aided by the publication of the joint WOAH-FAO Global Rinderpest Action Plan (GRAP) in 2018 [8].
However, the GRAP highlighted three important gaps between our current state and full preparedness, gaps which arose from the decision to include established RPV vaccine strains in the materials that are strictly controlled post-eradication. Importantly, this meant that there has been no production of the most widely used ‘Plowright’ vaccine for more than 20 years, and the existing stocks are limited in quantity and out of date. To bridge this gap, new stocks will be made in 2024, notably for the African Union vaccine reserve at the African Union – Pan African Veterinary Vaccine Centre (AU-PANVAC), using the WOAH/FAO-approved vaccine seed prepared and characterised at the RHF of the French Agricultural Research Centre for International Development (CIRAD, Montpellier, France). In addition, there is a plan to increase stocks of the LA-AKO rinderpest vaccine developed in Japan [9]; that country has a (national) legal requirement to keep emergency stocks of vaccine, which will provide an additional resource in the event of a reappearance.

Secondly, the prohibition on keeping even vaccine strains meant that national diagnostic laboratories had no suitable positive control to validate diagnostic tests for RPV (primarily RT-PCR), removing the possibility of conducting their own tests on the occasional suspect cases, and thereby reducing the probability of rapid detection of a real case of rinderpest. A positive assay control based on a modified RNA phage, similar to that published for PPRV assays [10], has been developed but is not generally available.

The third gap was the requirement for any country which suffered a reappearance of RP, to conduct serosurveillance after eliminating the disease. However, the antibody ELISA that was used during the eradication campaign, and which is known not to cross-react with anti-PPRV antibodies [11], was dependent on antigen produced by growing the RPV vaccine in cell culture. A project will begin in 2024 to develop an alternative antigen that does not require infectious virus, but which can be recognised by the same highly specific monoclonal antibody, so that this ELISA can be available should there ever be a reappearance of RP.

Remaining research areas

Since the formal announcement of RP eradication, any activity involving RPV-containing materials has been strictly controlled, and there have been few such activities permitted. RHFs have been encouraged to sequence the genomes of their remaining stocks and then destroy the live RPV, a process which has been completed by one RHF so far, providing some interesting insights into RPV history and evolution [12]; hopefully other RHFs will also soon complete this process, simultaneously reducing the risk of virus
escaping from a laboratory and improving our knowledge of the evolution of the virus. The example provided by the sequencing of a measles virus (MV) from 1912 [13] has shown that important insights into the origins of viral diseases can be obtained from sequence data from historic isolates. The more we know of the evolution and spread of MV, RPV and PPRV, the better we can judge the risks of new morbilliviruses emerging that can fill the niches left by the eradication of RP and (soon) PPR.

**Peste des petits ruminants**

**Distribution and host range**

Since its launch, the PPR global eradication programme has had a substantial effect on the control of the disease, with 68 out of the 78 countries having developed a PPR National Strategic Plan [14], and a reduction in outbreak reports between 2015 and 2019 [15]. Some countries that never reported PPR have successfully applied for official freedom recognition. Despite these encouraging results, the geographic distribution of the disease has not been effectively reduced, with none of the countries affected by PPR having been able to free themselves of the disease (Figure 1). The recent outbreaks of PPR in countries that had not previously reported the disease, e.g. Georgia [16], Mongolia [17], Bulgaria [18], Burundi [19], Thailand [20], and Rwanda [21], illustrates the extent of the problem, and the constant vigilance required to avoid further PPR spread, notably through commercial animal trade. In some cases of emergence in new areas, the disease was rapidly contained (e.g. Georgia, Bulgaria, Thailand); however PPR has become more established in others, notably in Mongolia [22] and China (Figure 1).

The outbreak in Mongolia was particularly notable due to its unprecedented impact on wildlife, with mass mortality reported in Mongolian Saïga antelope and deaths in several other wildlife species [23]. Previous reports had already highlighted that many wild artiodactyls, camels, and suids are susceptible to PPR infection [24, 25, 26], but this was the first report of heavy mortality in such species in the field, along with a realisation of the potential impact of PPR on biodiversity, and it prompted the proposal of guidelines for the control of PPR in wildlife populations [27]. However, the full range of species susceptible to PPR is not yet defined, and probably depends on many factors including the health status of the animals, environmental factors, and the virulence of the PPRV strains (e.g. Eloiflin et al. [28]). In-depth studies of host immune responses to PPRV may help in identifying which species and breeds are most impacted by the disease, as well as which play a role in its transmission (e.g. Eloiflin et al. [29] and Baron et al. [30]). Good field data will also be required to characterise PPRV circulation in complex environments.
such as at the wildlife-livestock interface [31]. Careful risk assessments are needed to prioritize resources for PPR research and control to avoid the most devastating effects on both livestock and endangered wildlife populations [24].

Epidemiology of the disease

Important progress in understanding the epidemiology of PPR has been made in recent years through a wide range of approaches. Field data is key for designing vaccination strategies and evaluating their efficacy [32], and carefully planned field studies remain of primary importance in characterizing the distribution and prevalence of the virus in host populations. However, diagnostic tools need to be further developed and validated to study the role of wildlife in PPRV transmission [33, 34]. Although the survival of PPRV in the environment is being explored [35, 36], little is yet known about its stability in different media such as fomites, water, bedding or carcasses under different environmental conditions, restricting the accuracy of transmission models.

Affordable sequencing technologies have increased our capacity to study PPRV molecular epidemiology. The distribution of the four PPRV genetic lineages is now better understood, although we are still lacking recent genetic data from many countries affected by PPR (see Figure 1 for a review of data from the last 10 years). Importantly, lineage IV has been spreading in West Africa (reviewed in Dundon et al. [37]; Figure 1), where it appears to be supplanting other West African lineages, suggesting an increased capacity for replication and/or transmission that should be investigated as a priority, to evaluate the impact of these changes on control and surveillance strategies. Full genome sequencing can provide important information on the origin of outbreaks and PPRV evolution, notably possible adaptations to non-standard hosts (e.g. Benfield et al. [38]). However, PPRV sequencing efforts and bioinformatic analyses must follow strict quality control guidelines to be useful [39].

The importance of animal movement, notably from trade and pastoralism, in PPRV circulation is well documented, including evidence from sequencing data (e.g. Spiegel et al. [40] and Bataille et al. [41]). Field studies aiming at characterizing livestock mobility can provide valuable information for disease surveillance and control [42, 43]. In general, better identification of risk factors for PPRV transmission has improved the power of risk analyses to predict PPR occurrence (e.g. Ruget et al. [44]). Participatory epidemiology methods are increasingly used to collect information directly from communities and other field actors on disease occurrence, host populations, and other key factors in PPR transmission (e.g. Lysholm et al. [45]). Integration of communities’ knowledge of the
disease can improve our understanding of patterns of virus circulation and help identify possible transmission hotspots [46].

Developments in diagnostic and control tools

Many pathogens can cause symptoms in small ruminants similar to PPR and laboratory tests are critical to discriminate these. All the basic diagnostic tools and vaccines are already in place for global PPR eradication (reviewed in Kinimi et al. [47]). Well-characterised ELISA kits to detect anti-PPRV antibodies are available [48, 49], and these assays’ ability to deal with sera from wildlife and other nonstandard hosts is being characterised [34]. A number of novel assays for PPRV-specific antibodies have been developed (e.g. Berguido et al. [50] and Logan et al. [51]), but none so far that match ELISA for simplicity and capability of high throughput. The original gel-based RT-PCR assays for PPRV are being replaced with the more sensitive real-time PCR assays (RT-qPCR), of which a number have been published and are in use in different laboratories. Ring trials have shown that some RT-qPCR assays are less sensitive than others, highlighting the need to follow recommendations from the WOAH Reference Laboratory Network for PPR on best practice [52, 53].

Several laboratories have developed assays based on loop-mediated isothermal amplification (LAMP) technology, which is faster and cheaper than gel-based RT-PCR [54], and may have advantages over RT-qPCR for laboratories with low throughput requirements. An interesting possibility with LAMP assays is that they can be carried out without prior purification of RNA [55]. They may be carried out in the field using a suitable heating block run from the vehicle battery. Lateral flow tests with sensitivity similar to antigen ELISA assays are available [56, 57] for rapid confirmation of outbreaks in the field (e.g. Jones et al. [58]). However, field testing is unlikely to be used in normal practice, since few affected countries have the funds to equip and incentivise their field veterinarians to carry out specific assays, most countries relying on clinical observations for immediate diagnosis, with occasional transfer of samples to a testing laboratory for confirmation.

Extensive experience over more than 20 years has shown that the live attenuated PPRV vaccine based on PPRV/Nigeria/75/1 [59, 60] is safe and effective, and this vaccine has been used in most affected countries, with the major exception being India, which has developed its own vaccines (reviewed in Saravanan et al. [61]). It has been shown that the most widely used Indian vaccine strain (based on PPRV/Sungri/96) and the Nigeria/75 vaccine are equally effective against all genetic lineages of PPRV [62]. It
remains a matter of concern that some countries are still using poorly characterised and validated vaccines (e.g. Kwiatek et al. [63]).

One of the few practical issues with the PPRV vaccines has been their general thermolability even when lyophilised, requiring a cold chain for delivery to the field. This problem has received significant attention in the last 5-10 years, bringing together scientists and vaccine manufacturers to improve methods of preparation of the vaccine, with significant progress [64, 65]; in addition, new stabilised liquid formulations of the vaccine are appearing [66], which may provide another way of simplifying delivery of vaccines to the point of use. AU-PANVAC has set up quality control for thermostable PPR vaccine preparations, and it is expected that this will improve the quality of these vaccines and their availability to those countries which need them.

With these vaccines it is not possible to serologically distinguish vaccinated from infected-recovered animals, i.e. a so-called DIVA (Distinguishing Infected and Vaccinated Animals) test is not currently available. Although such a test is not essential for the eradication of PPR (rinderpest was eradicated without one), it would greatly simplify the closing stages of the eradication process in individual countries, and especially in the post-eradication situation. A number of potential DIVA vaccines have been developed, though more extensive testing on safety and duration of protection will be required before commercial production. One alternative is the genetic modification of the vaccine virus to alter its antibody profile [67], with a new test to identify the new, non-PPRV, antibodies. Most of the research, however, has focused on the use of viral vectors to express the PPRV H glycoprotein (reviewed in detail in Rojas et al. [68]). Vaccinated animals have anti-H antibodies, but not anti-N antibodies, so existing ELISA kits could provide a DIVA test.

Strategies for surveillance and control

Experience from the last decade shows that vaccination organised purely at the national level may have limited success in many regional contexts. The re-emergence of PPR in Morocco and China despite successful control campaigns are examples of the problem that countries may face as they apply mass vaccination, while still having difficulties in controlling transboundary animal movements [69, 70]. Socio-economic instability in many regions is also likely to make control of human and animal movements even more difficult, and thereby increase PPR risk [40]. Faced with this situation, the second phase of the PPR Global Eradication Programme proposes defining areas (which often cross country borders) that are part of the same network of PPRV circulation, and encouraging
countries to focus coordinated control efforts on such ‘episystems’ [14]. Identification of these episystems should be based on robust epidemiological and PPRV genetic data. This needs to be considered when designing governance and allocating resources to PPR control strategies.

When resources are limited, risk analyses are vital to predict PPR occurrence, develop vaccination strategies, and prioritize surveillance and vaccination efforts (e.g. Ruget et al. [44] and Nkamwesiga et al. [71]). The surveillance system used should be regularly evaluated to ensure that appropriate resources are allocated to passive and active surveillance [72]. Different tools and methods are available for the economic assessment of vaccination campaigns [73, 74]. Transmission models have also been shown to be efficient in evaluating different vaccination strategies [75, 76]. However, research outputs seem to be only rarely translated into strategies applied in the field, possibly because of poor communication between researchers and decision makers.

Involvement of local communities and other animal health actors is key to the success of PPR eradication [14]. An increasing amount of research shows the importance of taking into account knowledge, culture and perception of communities to improve our understanding of the local context of PPR circulation (e.g. Lhermie et al. [77] and Jones et al. [78]) and to adapt control strategies to these contexts [46, 79]. Improving communication and access to vaccine in communities, especially for women, drastically increases trust and vaccine uptake (e.g. Bikaako et al. [80] and Nuvey et al. [81]), even in systems where livestock owners have to pay for the vaccines [82, 83]. In areas that are difficult to reach for veterinary services, involvement of communities, notably as state-approved animal health actors, can play an important role for the last-mile vaccine delivery and for disease surveillance, if provided with good incentives and integrated into an efficient surveillance system.

**Conclusions**

The PPR global eradication programme entered its second phase, with significant hurdles to be overcome to reach a world free of the disease by 2030. Achieving this goal will be facilitated if plans are based on the most advanced research and tools available. Focusing research and development efforts on important remaining gaps (summarized in Table I) should also increase the efficiency of the control and surveillance strategies. Our experience with the eradication of RP shows that the effort won’t stop with the successful eradication of PPR from animal populations. We should start building on the experience of RP to prepare for a post-PPR world and have everything in place to limit
the risk of PPR reappearance. The animal health community should also be vigilant to other viruses currently circulating at low frequency that could emerge as the niches of RPV and PPRV become vacant. Such commitment is needed to ensure sustainable contribution to food and economic security, community resilience, and biodiversity conservation.

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References


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Table I
Research priorities on rinderpest and peste des petits ruminants

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<th>Disease/main theme</th>
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<td><strong>Rinderpest</strong></td>
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| Surveillance and preparedness | - Finish ‘Sequence and Destroy’ projects to remove RPV-containing material  
- Registration and inspection of unregistered facilities holding RPV-containing material |
| Diagnostic tools | - Availability of positive controls for PCR assays  
- Development of a highly specific ELISA assay for RPV antibody detection |
| **Peste des petits ruminants** | |
| PPR host range | - Identification of markers of PPRV virulence and of host susceptibility |
| PPR epidemiology | - Evaluation of the role of atypical hosts in PPR transmission  
- Assess the risk of PPR transmission from different materials (meat, water holes, fomites, etc.)  
- Systematic gathering of information on key transmission factors (animal movement, density, etc.), notably through participatory approaches, to produce risk maps of PPR occurrence and transmission  
- Investigation of rapid spread of African lineage IV |
| Diagnostic tools and vaccines | - Development and validation of serological and non-invasive methods adapted to atypical hosts (e.g. wildlife)  
- Integration of field diagnostic tests in surveillance activities  
- Confirming efficacy and safety of DIVA vaccines with validated differential diagnostic tests |
| Surveillance and control strategies | - Definition of episystems and development of coordinated strategies at the level of episystems  
- Development of control strategies based on epidemiological and socio-economic research outputs  
- Improving communities’ engagement in surveillance and control efforts |
| **All morbilliviruses** | |
| Evolution and risk of emergence | - Evaluating the risk of new morbillivirus emergence |

DIVA: distinguishing infected and vaccinated animals  
ELISA: enzyme-linked immunosorbent assay  
PCR: polymerase chain reaction  
PPR: peste des petits ruminants  
PPRV: peste des petits ruminants virus  
RPV: rinderpest virus
Figure 1

Global distribution of peste des petits ruminants

Countries are coloured in blue if PPR has been officially reported at least once within their borders. Information on presence of different PPR virus genetic lineages within a country is only provided for data collected after 2013 (i.e. less than 10 years before this publication). World administrative boundaries used in the map are based on shapefile accessible in https://public.opendatasoft.com (accessed in July 2023). This representation does not imply expression of any opinion on the part of the authors concerning the legal status of any country, territory, city or area, or concerning the delimitation of frontiers and boundaries.

PPR:  peste des petits ruminants
PPRV:  peste des petits ruminants virus