Artykuł przeglądowy *Review*

Progress in vaccines against peste des petits ruminants virus

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Summary

Peste des petits ruminants (PPR) is a highly contagious and economically important viral disease of both domestic (goats and sheep) and wild small ruminants. Due to the devastating effect of this disease on livestock and livelihoods, the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (WOAH) endorsed the Global Strategy for the Control and Eradication of PPR (PPR GCES) and launched the PPR Global Eradication Programme (PPR GEP) to eradicate PPRV by 2030. In order to achieve this goal, a potent, safe and efficacious live-attenuated PPR vaccine with long-lasting immunity is available for immunoprophylaxis. However, the live-attenuated PPR vaccines are thermolabile and require maintenance of an effective cold chain to deliver to the field. In addition, infected animals cannot be differentiated from vaccinated ones (DIVA). To overcome these limitations, some new generation PPR vaccines have been developed: poxvirus vaccine, positive and negative marker vaccine through reverse genetic approach, chimeric vaccine, anti-idiotypic vaccine, subunit vaccine, virus-like particles vaccine, edible vaccine and combined vaccines. Novel recombinant PPR DIVA vaccines were evaluated in goats for safety and efficacy, and all vaccinated animals were clinically protected against an intranasal PPRV challenge. Furthermore, newly developed ELISAs were capable of differentiating between infected and vaccinated animals. Therefore, these DIVA vaccines and the associated tests can facilitate the serological monitoring process and speed up global PPR eradication through vaccination.

Keywords: peste des petits ruminants, recombinant vaccines, differentiation of infected from vaccinated animals (DIVA), novel DIVA vaccines

Peste des petits ruminants (PPR) is a highly contagious and economically important viral disease of both domestic (goats and sheep) and wild small ruminants (22). It is caused by the PPR virus (PPRV), a member of the genus *Morbilivirus* of the family *Paramyxoviridae*, and is clinically and pathologically close to rinderpest (RP) and human measles (11). PPRV contains a single-stranded negative-sense RNA genome of about 16 kb, organised into six transcription units encoding six structural proteins (nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H) and large polymerase proteins (L) in the order 3'-N-P-M-F-H-L-5' Among these, the nucleocapsid (N) protein gene is the most abundantly transcribed gene in the host cells, and it is therefore a preferred target site for genomic detection of PPRV. In addition, two non-structural proteins C and V are translated from the P-gene open reading frame (ORF) (22).

PPR was first recorded in early 1942 in Ivory Coast, West Africa (18). In the following years, the disease extended its distribution to other parts of the world and is now endemic in Asia, in countries such as Afghanistan, Bangladesh, Nepal, Pakistan, in the Middle East: Turkey, Saudi Arabia, Yemen, Iraq, Israel, Oman and Kuwait, and throughout Africa, except for some countries in southern Africa, such as Botswana, Lesotho, Namibia, Zambia, Madagascar and the Republic of South Africa (https://wahis.oie.int/) (Fig. 1). In total, PPR affects 30 million animals across 70 countries around the world. Sixty percent of these countries are in the African continent, and the other 40% are in the Middle East and Asia. The disease causes annual economic losses of up to 2.1 billion USD. Looking beyond this figure, 300 million families who rely on small animals are at risk of losing their livelihoods, food security and employment opportunities (http://www.fao.org/emergencies/resources/documents/resources-detail/en/c/282370/).

After recent outbreaks of PPR reported from the European part of Turkey, North African countries and Bulgaria, there is now a major risk of the introduction of PPR to the European mainland (2, 22). Due to

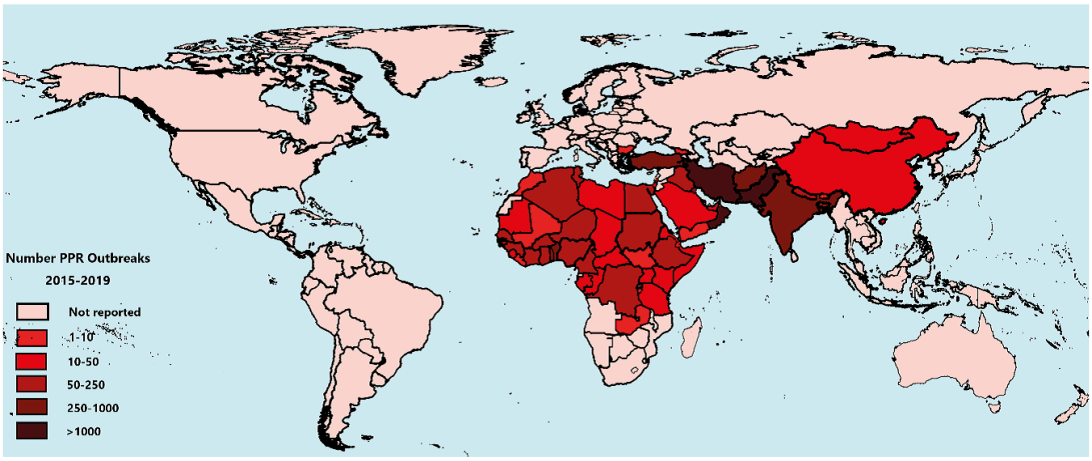

Fig. 1. Global distribution of the peste des petits ruminants (PPR) burden showing the total number of PPR outbreaks reported from 2015 to 2019. According to World Animal Health Information System (WAHIS)

the devastating effect of this disease on livestock and livelihoods, the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (WOAH) endorsed the Global Strategy for the Control and Eradication of PPR (PPR GCES) and launched the PPR Global Eradication Programme (PPR GEP) to eradicate PPRV by 2030 (www.oie.int./fileadmin/Home/eng/Health_standards/tahm/3.08.09_PPR.pdf). In order to achieve this goal, a potent, safe and efficacious live-attenuated PPR vaccine with long-lasting immunity is available for immunoprophylaxis. However, live-attenuated PPR vaccines are thermolabile and require maintenance of an effective cold chain to deliver to the field. In addition, infected animals cannot be differentiated from vaccinated ones (DIVA). This review provides a brief description of standard live-attenuated PPRV vaccines and the latest recombinant vaccines.

Live attenuated PPR vaccines

Currently, the PPR control and eradication strategy includes administration of two live attenuated vaccine strains (Nigeria/75/1 and Sungri/96), which provides lifelong immunity to all PPRV lineages as well as detectable antibodies after a single inoculation. However, much of vaccination does not provide sufficient levels of immunity to interrupt transmission. The most challenging practical issues are related to the delivery of vaccines to small ruminants at sufficient intensity to generate herd immunity levels capable of preventing the re-introduction of disease. Within the pastoral area, there is often a lack of harmonisation of vaccination campaigns at the epizoone level. This is also due to the lack of simultaneous funding for PPR eradication campaigns in neighbouring countries. PPRV could be cycling persistently at a low frequency among extensive rural small ruminant populations. Therefore there is a need for countries to define precise eradication strategies and implement them in a dynamic manner. Repeat pulses of extremely efficient vaccination separated by short time intervals could be used in specific areas. This technique could be further explored by epidemiological modelling with the hope that it can break virus transmission in endemic areas if supported by good clinical disease surveillance. It was found that integrating the supply chain of PPR vaccines with other veterinary or health commodities could reduce costs, as well as increase uptake (1). The maintenance of an effective cold chain for this vaccine alone has also proven difficult in subtropical countries.

Application of a thermotolerant (TT) live-attenuated conventional or recombinant vaccine may be the best way to avoid cold chain-associated problems in these areas. However, it must also be noted that, although the standard PPR vaccines are cheap and effective, there is a need, especially in developing countries, for vaccines that support broader sustainability in small ruminant production. To this end, there have been significant advances in designing multivalent small ruminant virus vaccines that can also contribute to PPR eradication. Additional field application of these multivalent vaccines to control common small ruminant pathogens, including PPR, would indeed help alleviate the problem. Whilst risk-based vaccination of sheep and goats in endemic countries might be a pragmatic approach to control PPR in the first phase of disease eradication, the development of a marker vaccine with a robust companion test may help with serological surveillance in the future. In conclusion, identifying and targeting high-risk populations through vaccination campaigns informed by the estimation of context-specific PPRV transmission levels would not only reduce the cost of PPR eradication, but also increase the likelihood of success by setting more achievable vaccination coverage. The thermostability of PPR vaccines has been improved by using new stabilizers and by employing improved freeze drying methods. Additionally, vaccines based on thermo-adapted (Ta) PPRV have been developed (4). One such vaccine was developed using the PPRV/India/2003/Jhansi strain. The virus was initially grown in Vero cells for 25 passages at 37°C, and then additional 25 passages were performed in Ta-Vero cells (at 40°C). The resultant attenuated virus (Ta PPRV) was found to be a safe, potent and efficacious vaccine candidate in sheep and goats, thus providing an alternative to the existing PPR vaccine. However, extensive clinical trials need to be carried out before using such a vaccine in the field. Over the

Tab. 1. PPR vaccination in some PPRV-infected countries from 2010 to 2018. The numbers show the percentage of the small ruminant population vaccinated. Modified according to Zhao et al. (33)

Country	Year								
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Eritrea						7.7			
Iraq		73.5	77.6	91.0	89.8		78.9	78.5	67.8
Kazakhstan						57.0			
Tajikistan	16.0	8.6	3.2	5.2	21.9	10.0			
Turkey	44.7		82.1	77.9	79.0	69.3			
South Sudan		1.2	0.8	0.9	1.5				
Sudan			15.5	12.8	39.7				
Uganda		10.5							

recent years, vaccination against PPR has been carried out in almost all PPRV-infected countries. Countries have adopted a range of approaches for vaccination depending on their epidemiological situation and the extent to which they have targeted their vaccination strategy according to the disease situation and their national strategic plans. An example of vaccination coverage reported by some PPRV-infected countries from 2010 to 2018 is presented in Table 1.

New generation PPR vaccines

The available live attenuated PPR vaccines provide long-lasting immunity following a single immunization. However these vaccines have two main drawbacks. First, the immune response is identical to natural infection, so it is not possible to perform a DIVA test. This is an important issue because serological surveys would lead to confusion in determining whether the virus has been eliminated by vaccination. Therefore, it is recommended that if a vaccine has been used for control of a disease, that region must prove that the susceptible animal population is free from infection by employing a DIVA test. Secondly, the vaccine is thermolabile, requiring a cold chain to deliver the vaccine to the hot and arid environmental of the PPR endemic regions, which makes it a costly and inconvenient affair. To overcome these limitations, some new generation recombinant PPR vaccines have been developed:

a) Poxvirus vectored PPR vaccines. The established vaccine strains of capripox viruses (the causative agent of sheep and goat pox) have been used to produce recombinant rinderpest (RP) and PPR vaccines. Capripox-vectored RP vaccine, due to the strong antigenic relationship within the genus morbillivirus, is capable of protecting goats and sheep against PPR (14). Capripox virus-vectored vaccines developed against PPR act as dual vaccines against both PPR and sheep and goat pox (8). Although the vaccine was found to be relatively thermostable, it did not elicit optimum antibody response, probably because of the pre-existing immunity against the vector. Since only a limited number of viral proteins (F and/or H) can be used as a recombinant antigen, the absence of PPRV N protein in the vaccine made it possible to identify infected animals serologically, and therefore made it a marker (DIVA) vaccine (14). However, such vaccines often require multiple doses and have a reduced efficacy compared to live attenuated vaccines. These vaccines have not moved forward beyond the experimental stage, because their licensing has been hampered by the controversy over the release of genetically manipulated organisms;

b) Positive and negative marker vaccines through reverse genetics approach. Reverse genetics, an approach to study the phenotypic effect of an engineered mutation in a gene, has made it possible to genetically alter the viral RNA genome through DNA copies (cDNA). After the development of a reverse genetics system for PPRV, two types of recombinant PPRV constructs have been developed: a positive marker PPRV construct by inserting enhanced green fluorescent protein (eGFP) between the P and M genes and a negative marker construct by deleting the C77 monoclonal antibody binding site on H protein (20). When such constructs were used as vaccines (using the PPRV/Nigeria/75/1 vaccine strain as a backbone), they resisted the challenge of a virulent PPRV and did not transmit the vaccine virus to susceptible in-contact animals. However, the C77 monoclonal antibody was not found to bind with a mutated form of the PPRV H protein, which makes it impossible to differentiate infected from vaccinated animals. A recombinant PPRV expressing the foot-and-mouth disease virus (FMDV) has also been generated (32). Insertion of FMDV VP1 into the PPR backbone neither impaired the replication of the recombinant virus *in vitro* nor did it affect immunogenicity in inducing a neutralizing antibody against PPRV in goats. Recombinant PPRV/VP1 also induced FMDV-neutralizing antibodies in goats and resisted challenge with virulent FMDV. Such a vaccine has potential to serves as a dual vectored vaccine against PPRV and FMDV (32);

c) Chimeric vaccine. Towards the end of the Global Rinderpest Eradication Programme (GREP), areas that had been declared free of RP could not use the RPV vaccine strain for vaccination against RP or PPR. Therefore alternative marker vaccines were produced by generating chimeric viruses with genes for immunogenic proteins derived from the related viruses i.e. PPRV and RPV. The H and F genes of RPV were replaced by the corresponding genes from PPRV, resulting in a chimeric RPV-PPRV recombinant virus vaccine (9). Virus-specific serological response in such vaccines can be identified by specific ELISAs, thus making it possible to discriminate between infected and vaccinated animals. Later on, an N protein-based chimeric RPV-PPRV marker vaccine was developed

which provided protection against challenge with virulent RPV in cattle (21);

d) Anti-idiotypic vaccine. An idiotype is a characteristic shared by groups of immunoglobulin or T cell receptor (TCR) molecules. An idiotype is located on variable regions of antibody molecules. Immune response can be regulated by a number of idiotypic determinants (Ids) and its counterpart, an anti-idiotypic antibody (anti-Id) or Ab2 (13). An internal image Ab2 against RPV and PPRV H/HN protein has also been shown to elicit a virus-specific antibody and cell-mediated immune response in the mouse model (28). Moreover, the DNA-encoding VH region of Ab2 has also been shown to elicit a long-lasting antibody and cell-mediated immune response in mice in the complete absence of the viral antigen (29). Such a DNA vaccine, which codes for the heavy chain variable region of an internal image anti-idiotypic antibody (that mimics a region of the HN protein of PPRV), was also found capable of eliciting an antibody and cell-mediated immune response in sheep in the complete absence of viral antigens (3). DNA-based vaccines are considered heat stable and generate immune response against a desired antigen (against PPRV HN protein in the above vaccine). Therefore they have potential to overcome both limitations (thermo-sensitivity and DIVA) of the current live-attenuated PPR vaccine used for mass immunization in the field;

e) Subunit vaccines. Baculovirus-expressed RPV "H" and "P" proteins were used as an antigen for subunit vaccines (31). They elicited a strong neutralizing antibody response, but did not provide protection against virulent RPV (5). However, when baculovirus-expressed H protein was incorporated into immuno-stimulating complexes (ISCOMs), a good level of protection was achieved on a virulent virus challenge. ISCOMs are known to induce cell-mediated immune response (10), so it appears that the cell-mediated immune response is a major factor in inducing protective immune response against morbilliviruses;

f) Virus-like particles (VLPs). Recombinant baculovirus has been constructed to co-express PPRV H, N and M proteins, which makes it possible to bud PPR virus-like particles (VLPs) from insect cell membranes. These VPLs were found to induce potent virus-specific neutralizing antibodies in mice, suggesting the potential of a VLP-based vaccine candidate against PPR (19);

g) Edible vaccine. Administering vaccine with needle pricks requires extensive veterinary infrastructure and therefore significantly affects disease control programmes. In this context, an edible vaccine against PPR could be an attractive perspective. Recombinant RPV H protein produced in transgenic tobacco or peanut plants has shown reactivity against H-monospecific convalescent sera. When inoculated intraperitoneally in mice, transgenic plant-derived protein produced high titer antibodies and neutralized RPV infection. Similarly, when fed to mice and cattle, leaves of transgenic peanut expressing RPV-H induced neutralizing antibodies and lymphoproliferative response (15, 25). Though still at an early stage of development, these studies suggest the potential of the oral edible vaccine against morbillivirus infections;

h) Other recombinant vaccines. *Bombyx mori* nucleopolyhedrovirus displaying the immunodominant ectodomains of the H glycoprotein of RPV and the F glycoprotein of PPRV (23), the Semliki forest virus (SFV) expressing the H protein (6), and silkworm larvae expressing recombinant F protein (24) are some other recombinant vaccines which have been developed, but their protective efficacy has not yet been evaluated in natural hosts. Modified vaccine virus Ankara (MVA) expressing PPRV F and H proteins induced resistance to challenge with virulent PPRV, but two doses of vaccine were required prior to the challenge (27). To date, all of these recombinant vaccines are incapable of differentiating wild type virus infection from vaccinal immunity and currently remain at an experimental stage. Some of the above vaccines have also been evaluated successfully as multivalent vaccines in sheep and goats. Recently, two recombinant live attenuated PPR DIVA vaccines, in which the C-terminal variable region of the PPRV N-protein has been replaced with dolphin morbillivirus (DMV), have been developed and successfully evaluated in goats. Both DIVA vaccines were safe and potent and produced immune response similar to that produced by their parent Nigeria/75/1 and Sungri/96 live attenuated vaccines (26). Furthermore, two newly developed ELISAs were capable of differentiating between infected and vaccinated animals. Therefore, these DIVA vaccines and the associated ELISA tests can facilitate the sero-monitoring process and speed up global PPR eradication through vaccination. It must be noted that establishing the minimum vaccine dose for efficient protection, large scale clinical trials, extensive safety trials and validation of companion diagnostic tests are some of the key issues that need to be addressed before these next-generation vaccines are used in the field for control and eradication of PPR. A novel DIVA approach for PPRV that does not require a DIVA-compatible vaccine or a negative marker-specific serological monitoring technology has recently been described (30). The authors designed a diagnostic hybrid protein-peptide microarray that can discriminate between distinct IgG sero-dynamics against 4 epitope-containing short peptides (ECSPs) induced by vaccination or infection. The anti-ECSP IgGs of uninfected goats existed only 10-60 days after vaccination. Sixty days after vaccination, the microarray detected positive anti-ECSP IgGs in 13 of 26 goats, indicating that the flock was infected with the wild strain. This method can be used to differentiate infection by field PPRV strains from vaccination with live attenuated PPR vaccines. However, this microarray method may not be easy to adopt in a PPR laboratory

and needs further validation in a large number of animals in the field (30);

i) Combined vaccines. In order to reduce the stress to animals and the cost of the overall vaccination package, mixtures of organisms have been commonly used in a single vaccine called a combined vaccine (17). Some combined formulations of PPR vaccine, such as sheep pox and PPR or goat pox and PPR, have also been developed (7, 12) and found to induce protective immune response without any side effects. Diseases that could be potentially combined with PPR in vaccines are sheep and goat pox, pasteurellosis, brucellosis, contagious caprine pleuropneumonia (CCPP) and FMD (16).

In conclusion, it can be stated that a live attenuated vaccine providing long-lasting immunity and effective diagnostic tools are currently commercially available for control of PPR. The only limitation in using the current vaccine is that vaccinated animals cannot be differentiated from naturally infected ones. This would be essential to evaluate the effect of vaccination in a serosurveillance programme. Since other diseases can also be included in the PPR control programme, multi-disease diagnostic assays need to be developed for effective containment of the disease. In order to overcome the need for cold chain, a technology for a thermo-stable vaccine should also be developed.

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