Journal of Animal Research: v.14 n.04, p. 239-249. August 2024

DOI: 10.30954/2277-940X.04.2024.1

Combatting Peste des Petits Ruminants: Vaccines and Future Hopes

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Received: 20 May, 2024 **Revised:** 18 July, 2024 **Accepted:** 26 July, 2024

ABSTRACT

Peste des petits ruminants (PPR), a disease with its high morbidity and mortality rates is one of the most destructive transboundary viral diseases affecting small ruminants. The disease is caused by the PPR virus (PPRV) which encodes six structural proteins, out of which Nucleoprotein is the most immunogenic but elicits the production of non-neutralizing antibodies; while Haemagglutinin and Fusion proteins elicit a protective neutralizing antibody response. Currently live attenuated Nigeria 75/1 strain vaccine is used for control of PPR worldwide while Sungri 96 strain is predominantly used in India. Even though these vaccines are effective in providing protection against PPRV in sheep and goats, they cannot differentiate between infected and vaccinated animals (DIVA). The ability of vaccines to allow this differentiation is believed to play a key role in PPR control and eradication programs and as such the focus of many researchers is to develop an effective DIVA vaccine. The current article provides an overview of PPR and discusses various vaccines for the control of PPRV infection with a focus on its eradication.

HIGHLIGHTS

- An overview of PPR virus has been provided.
- Various vaccines that have been developed against PPR virus have been listed including DIVA and other vaccines platforms.
- Possibility of global eradication of PPR has been discussed.

Keywords: PPR, Vaccines, DIVA, control, eradication.

Peste des petits ruminants (PPR), commonly referred to as goats plague, is one of the most widespread and devastating contagious viral diseases which primarily infects goats and sheep, but can also infect wild small ruminants (Kinne *et al.*, 2010) and is even emerging to cause infections in camels (Kwiatek *et al.*, 2010). Clinically, the disease is characterized by pyrexia, anorexia, necrotic stomatitis, diarrhea, conjunctivitis, respiratory distress and bronchopneumonia followed by recovery or death due to bronchopneumonia or severe dehydration caused by acute diarrhea. PPR is caused by the PPR virus (PPRV) which is a linear, non-segmented, negative sense, single-stranded RNA virus belonging to the genus *Morbillivirus* of the family *Paramyxoviridae* (subfamily *Paramyxovirinae)* under order Mononegavirales. The virus is closely related to other Morbilliviruses viz. measles virus and canine distemper virus, but is especially related to Rinderpest virus (RPV) (Gibbs *et al.*, 1979). The virions are pleomorphic particles with the RNA genome enclosed in a ribonucleoprotein surrounded by an envelope. The

How to cite this article: Gazal, S., Gazal, S., Gazal, S., Tikoo, M., Kaur, P. and Sharma, N. (2024). Combatting Peste des Petits Ruminants: Vaccines and Future Hopes. *J. Anim. Res.,* **14**(04): 239-249.

Source of Support: None; **Conflict of Interest:** None

PPRV RNA genome constitutes six transcriptional units encoding two non-structural proteins (V and C) and six structural proteins viz. N (nucleocapsid) protein, P (phosphoprotein), M (matrix protein), F (fusion protein), H (haemagglutinin) protein and L (polymerase) protein. Out of all the proteins, N protein is the most abundant viral protein and is therefore considered most immunogenic; however, the immunity produced against N protein is not protective. In fact, the protective immune response i.e. neutralizing antibodies are elicited against the H and F proteins during PPRV infection (Diallo *et al.*, 2007).

PPRV has a single serotype but has been genetically classified into four geographically distinct lineages (I – IV) based on phylogenetic analysis of F gene sequences. The determination of lineage is important for tracing the source of an outbreak and in the selection of ideal vaccine candidates as it is believed that the vaccine based on heterologous lineage would risk the introduction of a new lineage. Out of four lineages, I to III circulate in Africa while IV is prevalent in Asia (Shaila *et al.*, 1996; Dhar *et al.*, 2002).

PPR is considered an important transboundary viral disease of small ruminants resulting in high morbidity and mortality rates of more than 90% in immunologically naive sheep and goats. The high case fatality rate of around 100% and the highly contagious nature of the disease further worsens the scenario. Even though the mortality rate may be lower in endemic areas, but the disease has a more insidious impact on flock productivity. PPR poses a severe threat to the global economy with estimated losses worth US$ 1.2 to 1.7 billion annually (Anonymous, 2015). In India alone, PPR causes an estimated annual loss of INR 1,800 million (US$ 39 million) due to morbidity, mortality, loss of productivity, and due to trade restrictions associated with the disease (Balamurugan *et al.*, 2012). PPR is included in list A of notifiable terrestrial animal diseases by the World Organization for Animal Health (OIE). Considering the importance of the disease, the article aims to briefly review the vaccines for combatting PPR virus with a focus on DIVA vaccines that could be employed in future PPR control and eradication programs.

Prevention and control strategies for PPR

An attempt to control PPR began with the efforts of Ihemelandu *et al.* (1985), who used hyperimmune serum collected from recovered or infected animals for control of PPR in susceptible animals. The hyperimmune serum could provide protection for at least 10 days which could be prolonged to 9 months when hyperimmune serum was inoculated with a virulent strain of PPRV. The method is no longer in use because of the short shelf life of virulent blood which could be maintained for a maximum of 10 days under the conditions of warm weather (Adu and Joannis, 1984), and the high cost of production.

Vaccines for PPRV

Vaccination is the most efficient way to control PPR. Since the attempts to develop a live attenuated vaccine for PPRV could not be successful, therefore, initial vaccines for PPRV employed the use of Rinderpest virus as heterologous vaccines (or Jennerian vaccines) for providing protection against PPR in sheep and goats. Since PPRV shares high nucleotide homology with the Rinderpest virus and due to cross-protection between the Rinderpest virus and PPRV, an attenuated Plowright Rinderpest vaccine was used in many countries and could provide protection at least for one year (Sen *et al.*, 2010). However, due to the development of a homologous PPR vaccine in the 1990s, the use of heterologous vaccines started diminishing (Sen *et al.*, 2010). Moreover, the use of these vaccines had to be discontinued in small ruminants due to the global eradication of Rinderpest in 2011 which poses strict restrictions on the use of heterologous PPRV vaccines, thus currently only attenuated homologous PPRV vaccines are permitted to be used in sheep and goats for protection against PPRV.

Among homologous vaccines, the first vaccine developed was a live attenuated vaccine, Nigeria 75/1, obtained by serial passaging of PPRV in Vero cells. The virus was isolated from a goat in Nigeria that died due to PPR in 1975. Various trials carried out to demonstrate the efficacy of this vaccine in sheep and goats revealed that the vaccine was safe for use in pregnant animals. Moreover, transmission of the virus to in-contact animals was not noticed. Furthermore, the vaccine provides protection against PPRV for at least 3 years (Diallo, 2007). Currently, Nigeria 75/1 is used globally and is the commercially available vaccine for PPR. The vaccine provides protection to all the four lineages of PPRVs, but since lineage IV is prevalent in Asia; use of this vaccine may introduce a new live virus of different genetic makeup not existing

in Indian/ Asian animal populations (Balamurugan *et al.*, 2014) and thereby result in mutants with increased virulence. Therefore, lineage-specific attenuated vaccines for PPR are available in India viz. Sungri 96, Arasur 87, and Coimbatore 97 (Saravanan *et al.*, 2010), all of them being from Indian isolates. Sungri 96 was isolated from a goat in Himachal Pradesh, India and was initially adapted in B95a (marmoset lymphoblastoid cells) for 10 passages followed by Vero cells for up to 59 passages. The vaccine has been tested under field conditions and has been found safe and effective in providing immunity to PPR for more than 6 years. The vaccine is extensively used to vaccinate sheep and goats throughout India. Other vaccine strains viz. Arasur 87 (sheep origin) and Coimbatore 97 (goat origin) have been attenuated in Vero cells and are used mostly in Southern states of India. The major limitation of these vaccines is their low thermostability due to which maintenance of cold chain during storage, transportation and distribution is required. This is a practical problem for tropical and subtropical countries as they are hot and humid and have limited infrastructure. To tackle this problem, freeze drying of the vaccine in the presence of trehalose has been done and the product, Xerovac, is stable at 45 °C for 14 days (Worrall *et al.*, 2000). Thermostability of PPR vaccines can also be improved by culturing PPR viruses at relatively high temperature for many passages (Liu *et al.*, 2014). Such viruses can survive better at relatively high temperature than conventional vaccine strains. However, the stability and immunogenicity of such vaccines have to be assessed before considering them as potential vaccine candidate (Li *et al.*, 2014).

Although currently available live attenuated vaccines are effective in providing protection against clinical disease, they do not allow differentiation of infected-recovered animals from that of vaccinated ones. This differentiation of infected from vaccinated animals is very important for post-outbreak sero-surveillance which can be a boon for PPRV control programmes as well as an eradication campaign (Buczkowski *et al.*, 2014). Therefore, developing an effective vaccine based on the DIVA strategy is the focus of many researchers.

DIVA vaccines

DIVA, an acronym for Differentiation of Infected from Vaccinated Animals (DIVA) was coined in 1999 by Jan T van Oirschot. DIVA based vaccines not only protect animals against PPRV infection, but also facilitate the differentiation of infected animals from vaccinated ones. This is possible as DIVA vaccines (unlike traditional vaccines) produce an antibody response that is different from the antibody response produced by the wild-type virus. DIVA involves the use of marker vaccines and the companion diagnostic tests. In general, there are two feasible methods for the development of genetically engineered PPRV to be used as marker vaccine for DIVA:

1. 'Positive marker' which contains at least one heterologous immunogenic protein or epitope in a potent vaccine.
2. 'Negative marker', by the deletion of at least one homogenous protein or epitope compared with a corresponding wild-type PPRV (Liu *et al.*, 2014).

For positive marker DIVA vaccines, H and (or) F proteins are used while for negative marker vaccines, N protein can be used. The reason for this selection is the fact that H and F proteins of PPRV produce protective/ neutralizing antibodies and therefore play a vital role in immune protection while N proteins produce non neutralising antibodies and its deletion has no effect on immune protection. The diagnostic test for detection of antibodies induced by either a positive or negative marker is competitive ELISA.

Vaccines based on reverse genetics

The production of infectious virus entirely from cloned genome (reverse genetics) is a fundamental step in understanding not only the biology of any virus, but this technology can be used to develop recombinant viruses for use as DIVA vaccine candidates. The development of such DIVA vaccine for PPR was prevented for long due to lack of efforts to develop reverse genetics system for PPRV, although a rescue system for Rinderpest virus (RPV), which is evolutionary closest to PPRV, had been known since 1997 (Baron, 1997). Reverse genetics allows site specific mutagenesis of virus genomes and makes it possible to produce chimeric vaccines by deletion or addition of desired genes from other morbilliviruses resulting in production of viruses with new immunogenic characteristics (Parida *et al.*, 2005) and can be used for developing new vaccines and diagnostic methods.

Due to the availability of reverse genetics for RPV, initial attempts were targeted towards rescue of recombinant RPV from cDNA copies of its genome. The cDNA copies of the RPV genome were constructed in such a fashion that the F and H genes of RPV were replaced with the corresponding genes from PPRV. The chimeric virus so obtained was able to express the glycoproteins of PPRV, but grew slowly in tissue cultures compared with parental virus with formation of abnormally large syncytia. However, goats when vaccinated with the chimeric virus were protected from subsequent challenge with wild type PPRV (Das *et al.*, 2000). Moreover, the chimeric vaccine may be used as a DIVA vaccine as it generated a serological response different from that of infection with RPV or PPRV with antibodies recognizing unique epitopes on Rinderpest virus N and PPRV H proteins (Das *et al.*, 2000). In order to improve the replication efficacy of these vaccines, a triple chimera was constructed with the M, F and H genes of Rinderpest virus replaced with the corresponding genes from PPRV (Mahapatra *et al.*, 2006). Interestingly, the chimeric virus grew as well as unmodified PPRV, but comparatively lower than the parental RPV. However, chimeric virus could provide protection to challenge by both the viruses. In a different study chimeric rinderpest virus with the N protein derived from PPRV was constructed as a potential marker vaccine candidate (Parida *et al.*, 2007). However, since these were vaccines based on RPV, field trials have never been conducted in the post rinderpest eradication era and hence such DIVA tools were unlikely to be used. Moreover, due to cross reaction between RPV and PPRV N proteins, competitive ELISAs had no efficiency to differentiate between both the infections, thus further limiting the application of this type of chimeric DIVA vaccines (Liu *et al.*, 2014).

The first successful rescue of recombinant PPRV from a full-length cDNA clone of the virus genome was achieved by Hu *et al.*, (2012). The group developed a system for recovering recombinant PPRV by using an RNA polymerase II promoter for transcription to full length virus antigenome and introduced the green fluorescent protein (GFP) open reading frame into a recombinant form of PPRV/N75/1 to create a marked recombinant PPRV which could express GFP. The recombinant virus was as efficiently replicating as the parental virus and could express GFP thereby allowing serological differentiation between vaccinated animals and those recovered from natural infection of PPRV (Hu *et al.*, 2012). Yin *et al.*, (2014) developed a chimeric PPRV vaccine expressing the VP1 gene of Foot and Mouth Disease Virus (FMDV). It was seen that the FMDV VP1 gene did not impair the replication of PPRV *in vitro*. Moreover, the vaccine not only produced PPRV neutralising antibodies (induced comparable titer to Nigeria 75/1 strain) in goats, but also elicited the production of FMDV neutralizing antibodies thereby protecting goats from challenge with virulent FMDV. Therefore, the chimeric PPRV expressing the FMDV VP1 protein can be a potential dual live vectored vaccine against PPRV and FMDV (Buczkowski *et al.*, 2012). Additionally, two live attenuated PPR DIVA vaccines (Nigeria/75/1 DIVA and Sungri/96 DIVA) were created via reverse genetics, and the dolphin morbillivirus was substituted for the PPRV N-C-terminal protein's variable region (DMV). Both of these DIVA vaccines were tested for safety and effectiveness in goats during pilot research, and it was discovered that all the animals were clinically protected against the intranasal virulent viral challenge, much like the parent vaccinations (Selvaraj *et al.*, 2021).

Recombinant multivalent vaccines

Another strategy for designing DIVA vaccines is by engineering other viruses in such a way that they express PPRV proteins. For generation of multivalent DIVA vaccines, Poxviruses have been extensively used because they can express several foreign genes in addition to their ability to activate both humoral and cellular immunity depending upon the promoter (Zavala *et al.*, 2001). Since capripoxviruses are host specific viruses with host range restricted to sheep (sheeppox), goats (goatpox), or cattle (lumpy skin disease) and do not cause disease in humans, they are thus an ideal poxvirus vector for delivery of immunogenic genes from other ruminant pathogens that share the same geographical distribution (Berhe *et al.*, 2003). Moreover, since concurrent infections of PPRV have been observed with sheep poxvirus and goat poxvirus (Saravanan *et al.*, 2007) various multivalent capripoxvirus vaccines with DIVA properties have been designed to provide economic vaccination for small ruminants in developing countries.

PPRV (Berhe *et al.*, 2003) have been developed previously and were able to provide protection against both PPR and

capripox. Recently Chen *et al.* (2010) developed two recombinant capripoxvirus vaccines viz rCPV-PPRVH and rCPV-PPRVF expressing PPRV glycoproteins H and F respectively. They found rCPV-PPRVH to be better and more potent inducer of PPRV neutralising antibodies than rCPV-PPRVF; and this rCPV-PPRVH vaccine could also protect goats from challenge virulent capripoxvirus in addition to PPRV. Moreover, vaccination with either of these two vaccines was capable of producing antibody response to either H or F protein and thus differed from the immune response seen in infected animals. Thus, both of these vaccines had the potential of being DIVA vaccine candidate. However, recombinant capripox vaccines elicited poor antibody response due to pre-existing vector immunity. Moreover, the duration of immunity conferred by the combined vaccine and field application of these vaccines still remain to be determined (Munir, 2013).

Other recombinant vaccines

Insect cell based baculovirus expression systems have also been exploited for production of PPRV vaccines. Baculoviruses can infect a wide variety of mammalian cells without replicating in them and hence, they can be used as an efficient system for delivering recombinant vaccines to antigen-presenting cells for better immune responses. A recombinant baculovirus vaccine carrying a membrane bound form of the H protein of PPRV which was able to activate both cell-mediated and humoral immune responses was developed by Sinnathamby *et al.* (2001a, b). Rahman *et al.*, (2003) developed a recombinant Bombyx mori nucleopolyhedrovirus displaying the antigenic epitopes of F glycoprotein of PPRV and the H protein of the Rinderpest virus.

Many adenovirus-based recombinant vaccines for PPR have also been constructed. Qin *et al.* (2012) produced a recombinant vaccine using replication-competent canine adenovirus type-2 expressing the H gene of PPRV in MDCK cells by inserting this foreign gene into the non-essential region of canine adenovirus type-2. The vaccine led to the production of neutralizing antibodies which were detected at least for seven months. No adverse effect associated with the recombinant virus vaccine was noticed in immunized animals and no adenovirus could be isolated from the urine or feces of vaccinated animals, this indicating that vaccine could be a safe DIVA vaccine for PPR. Unlike Qin *et al.* (2012) who used replication competent adenoviruses, Wang *et al.* (2013) developed three replication defective recombinant adenoviruses expressing F, H, and F-H proteins. When goats were immunized with these recombinant adenovirus vaccines, PPRV-specific virus neutralizing antibodies developed 3 weeks after primary immunization. Since recombinant adenovirus expressing F-H proteins performed better in terms of production of neutralising antibodies, it is a potent candidate for recombinant adenovirus-based DIVA vaccines. Similarly, Herbert *et al.* (2014) developed replication-defective recombinant human adenovirus 5 expressing PPRV F and H proteins. The vaccine induced both humoral and cell-mediated immunity and protected goats from challenge with PPRV after 4 months of vaccination. A novel recombinant Newcastle Disease Virus vectored DIVA vaccine based on the live-attenuated NDV Clone 30 that expresses the surface protein hemagglutinin (H) of PPRV strain Kurdistan/11 (rNDV_HKur) was produced by Murr *et al.* (2020). In the case of this vaccine both transgene expression as well as virus replication in different host cells such as avian, caprine, and ovine cells were observed. The vaccine reduced virus shedding to similar levels as observed with live attenuated PPRV Nigeria 75/1 strain. Additionally, it is also provided high thermal tolerance and DIVA-applicability.

In a different investigation, the PPRV hemagglutinin H antigen (BoHV-4-A-PPRV-H-DTK) was delivered using the bovine herpesvirus-4-based vector (BoHV-4-A). BoHV4-A-PPRV-H-DTK vaccination shielded sheep from a highly virulent PPRV challenge and stopped viral shed. Protection was found to be correlated with anti-PPRV IgGs, neutralizing antibodies, and IFN-g-producing cells brought on by the vaccine. Thus, it was determined that when utilizing BoHV-4-A-PPRV-H-DTK as a vaccine, the identification of antibodies specifically against H-PPRV in animal serum and not against other PPRV viral proteins like F or N might serve as a DIVA diagnostic test (Rodrıguez-Martın *et al.*, 2021).

Anti-idiotypic vaccine

Idiotype is defined as a three-dimensional structure within variable region of an antibody. Numerous idiotypic determinants (Ids) and their corresponding anti-idiotypic antibody (anti-Id), or Ab2, can control the immune response

(Jerne, 1974). Additionally, it has been demonstrated that in the absence of any viral antigen, the DNA encoding the VH region of Ab2 can cause a long-lasting antibody and cell-mediated immune response in mice (Vani *et al.*, 2007). This DNA vaccine was also discovered to be capable of inducing an antibody and cell-mediated immune response in sheep in the absence of any viral antigens. It codes for the heavy chain variable region of an internal image anti-idiotypic antibody (that resembles a region on the HN protein of PPRV) (Apsana *et al.*, 2015).

Edible vaccine

The enormous veterinary infrastructure required for vaccination administration using needle sticks has a considerable impact on disease control initiatives. An appealing idea in this situation might be an edible PPR vaccination. Convalescent sera have been reactive to recombinant RPV H protein made in transgenic tobacco or peanut plants. Transgenic plant-derived protein that was administered intraperitoneally to mice produced high titer antibodies that prevented RPV infection. Similarly, feeding mice and cattle leaves from transgenic peanuts that express RPV-H caused neutralising antibodies and a lymphoproliferative response (Khandelwal *et al.*, 2003 a, b; Khandelwal *et al.*, 2004; Satyavathi *et al.*, 2003).

Virus-like particles (VLPs)

Virus-like particles are promising candidates for use as vaccines and have the characteristics of DIVA. VLP vaccines have the advantage that they mimic the native virus capsid and envelope, but lack the viral genome (Liu *et al.*, 2013). Li *et al.*, (2014) developed two types of VLPs for PPRV (PPRV-H and PPRV-F) in a baculovirus system using viral M protein co-expressed with H or F protein. The VLPs had similar morphology as that of the native virus particles and elicited both humoral and cell mediated immune response in mice and goats immunized subcutaneously with the vaccines. PPRV-H VLPs elicited an immune response comparable with that of PPRV vaccine and therefore VLPs containing PPRV M protein and H or F protein are promising DIVA vaccine candidates for the surveillance and eradication of PPR (Li *et al.*, 2014). Additionally, two PPRV VLP candidates were created using a baculovirus system by co-expressing the PPRV matrix (M), hemagglutinin (H), and fusion (F) proteins in the high expression level cell line High Five. These candidates were derived from either Tibet/30 virulent strain (lineage IV) or Nigeria 75/1 vaccine strain (lineage II). Following the main immunization, these VLPs were administered to mice, goats, and sheep, followed by two boosters. The high ratio of immunoglobulin G1 (IgG1) to IgG2a revealed that both VLPs were capable of inducing a strong humoral immune response. Comparatively to the lineage II Nigeria 75/1 vaccine strain, VLPs produced from the virulent lineage IV Tibet/30 strain were more immunogenic, generating a stronger and more consistent humoral and cell-mediated immune response in vaccinated animals (Yan *et al.*, 2020).

Global eradication of PPR?

Since the first identification of PPR in Ivory coast in early 1942, PPR has steadily expanded its geographical distribution and today, it has spread across all the continents. Despite the fact that with well-planned control measures, 48 countries including the United States, Canada, South America, Europe and Australia have been declared PPR free, yet the global eradication of PPR is far from being a reality. At present, around 70 countries have reported infection to the OIE or are suspected to be infected. However, after the successful global eradication of Rinderpest, PPR eradication was considered and efforts have already started towards control and eradication of PPR. PPRV would be an excellent candidate for eradication because of high antigenic stability of PPRV which allows a single vaccine and a single diagnostic technique to be used against all four PPRV lineages. Moreover, the vaccinated animals develop a life-long immune response (Diallo, 2004).

It has been widely accepted that DIVA vaccines would play a pivotal role in combatting PPRV by facilitating PPRV sero-surveillance programmes thereby speeding up the steps leading to disease eradication. DIVA vaccines would be particularly advantageous in later stages of PPR eradication campaign and also for countries where PPR is not endemic. Furthermore, these vaccines could be a valuable tool to prevent restrictions on animal movements being imposed on countries which cannot prove that animals are vaccinated, not infected (Herbert *et al.*, 2014). However, despite numerous potential candidates for DIVA vaccines, an efficient DIVA vaccine is still lacking.

Table 1: Different Vaccines used for control of PPR

Type of vaccine	Name of vaccine	Reference
Live Attenuated PPR Vaccines	Nigeria 75/1	Diallo *et al.*, 1989
	Sungri 96	Adu *et al.*, 1990; Diallo *et al.*, 2007
	Coimbatore 97	Singh *et al.*, 2010; Sen *et al.*, 2010
	Arasur 87 (used only in India)	Hodgson *et al.*, 2018
Inactivated Vaccines	iPPRVac) formulated with either a water-in-oil emulsion (ISA 71 VG) or with delta inulin adjuvant (AFSA1), or combined with a TLR9 agonist oligonucleotide (AFSA2)	Ronchi *et al.,* 2016
	Inactivated Peste-des-petits ruminants virus (PPRV) vaccine.	Cosseddu *et al.*, 2016
DNA Vaccines	DNA coding for the variable region of anti-idiotypic antibody	Apsana *et al.*, 2015
	Idiotypic monoclonal antibody (Ab_1)	Vani *et al.*, 2007
Recombinant Subunit Vaccines	Baculoviruses	Sinnathamby *et al.*, 2001
	Bombyx Mori nucleopolyhedrovirus	Rahman *et al.*, 2003
	Arachis hipogea	Khandelwal *et al.*, 2011
VLPs	Insect cell	Li *et al.*, 2014; Liu *et al.*, 2015
	Mammalian cell	Wang *et al.*, 2017; Yan *et al.*, 2020
Recombinant vaccines using reverse genetics	Tracer protein (green fluorescent protein, GFP)	Hu *et al.*, 2012
	Expression of FMDV VP1gene	Yin *et al.*, 2014
	Expresses eGFP	Muniraju *et al.*, 2015
Viral vector-based Vaccines	Poxvirus vectored Vaccines Vaccinia Virus Fowlpox pox virus Capri pox virus	Chandran *et al.*, 2010 Herbert *et al.*, 2014 Berhe *et al.*, 2003; Chen *et al.*, 2010; Caufour *et al.*, 2014; Fakri *et al.*, 2018
	Herpesvirus vectored Vaccines Bovine Herpesvirus-4	Macchi *et al.*, 2018
	Newcastle virus vectored Vaccine	Murr *et al.*, 2020
	Adenovirus vectored Vaccines Human adenovirus Canine adenovirus	Wang *et al.*, 2012; Rojas *et al.*, 2014; Holzer *et al.*, 2016. Qin *et al.*, 2012

The World Organization for Animal Health and FAO have jointly proposed a global strategy for eradication of PPR. The strategy first aims to control PPR in highly endemic areas and then to consolidate control efforts in areas where a low endemic level has been reached and where eradication is feasible or already effective. For countries already free of PPR, early detection, early warning, rapid response and a robust risk analysis should be maintained to understand the potential pathways for the (re)introduction of the disease (Anonymous, 2015). However, before initiating a coordinated action against PPRV, our knowledge about the epidemiology of PPRV in wildlife has to be improved as several wild species have been reported as susceptible to PPRV (Kinne *et al.*, 2010). Moreover, the financial costs associated with possible eradication campaign although difficult may be estimated. All of these factors need to be addressed before formulating a viable eradication programme.

Many factors support the probability of PPR eradication including the fragility of virus outside the host, production of long-lasting immunity by vaccines, absence of known reservoir outside domestic small ruminants and reliable diagnostic assays for field and laboratories. However, a number of potential limitations exist in the path towards PPR eradication which include lack of information about the role of other animals in PPR epidemiology, such as dromedaries, wildlife, and cattle (Roger *et al.*, 2001). Moreover, PPR is exceedingly common and endemic in many areas with limited veterinary resources making eradication difficult. Furthermore, because small ruminants have a high population turnover, naive animals are quickly introduced into vaccinated populations (Mariner *et al.*, 2016). Within flocks, local animal density is high, allowing for rapid within-flock transmission. Transhumane and migratory management are common farming techniques in many endemic locations, increasing the possibility of disease spread. Additionally, the proportional cost of immunization is higher than it was for rinderpest because of short lifespan of small ruminants and due to the fact that even though the overall cost of disease is substantial, the value of individual animals (in comparison to cattle, for example) is far lower. Lastly, the clinical indications differ depending on the species and breed, and they are not specific, making a clear clinical diagnosis difficult or impossible. Viruses may circulate in endemic areas with little clinical manifestation.

CONCLUSION

PPR is one of the most devastating contagious viral diseases primarily infecting goats and sheep, even though it can infect wild small ruminants as well. The disease is caused by PPR virus which belongs genus *Morbillivirus* of family *Paramyxoviridae.* Because of close relatedness to Rinderpest virus, attempts are on way for eradication of PPR after the global eradication of Rinderpest. One of the key factors which can play a role in eradication programs is the differentiation of infected from vaccinated animals. The article describes the current vaccines including DIVA vaccines available for PPR virus and also describes the various factors which could allow the eradication of PPR.

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