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Advances in peste des petits ruminants vaccines

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ABSTRACT

Peste des petits ruminants (PPR) is a highly contagious disease of small ruminants that leads to high morbidity and mortality thereby results in devastating economic consequences to the livestock industry. PPR is currently endemic across most parts of Asia and Africa, the two regions with the highest concentration of poor people in the world. Sheep and goats in particularly contribute significantly towards the upliftment of livelihood of the poor and marginal farmers in these regions. In this context, PPR directly affecting the viability of sheep and goat husbandry has emerged as a major hurdle in the development of these regions. The control of PPR in these regions could significantly contribute to poverty alleviation, therefore, the Office International des Epizooties (OIE) and Food and Agricultural Organization (FAO) have targeted the control and eradication of PPR by 2030 a priority. 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 vaccine is thermolabile and needs maintenance of an effective cold chain to deliver into the field. In addition, the infected animals cannot be differentiated from vaccinated animals. To overcome these limitations, some recombinant vaccines have been developed. This review comprehensively describes about the latest developments in PPR vaccines.

1. Introduction

PPR is one of the most contagious and fatal disease of animals primarily affecting small ruminants and is currently endemic in most parts of Asia, Africa and the Middle East. For a long time in the past, PPR had been misdiagnosed as rinderpest. A major breakthrough in the history of animal plague took place in 1942 when Gargadennec and Lalanne, while working at Ivory Coast, identified a disease in sheep and goats that was similar to but different from rinderpest and was not transmissible to cattle. This disease was later named as peste des petits ruminants (PPR). In the past, it had several common names such as goat plague, ovine rinderpest, plague of small ruminants, Kata and peste des petits ruminants (PPR). PPR the French denomination stands for small ruminant plague has been adopted as the scientific denomination of the disease and is commonly used worldwide. In 1956, Mornet and colleagues demonstrated that PPR and rinderpest viruses are closely related antigenically (Mornet et al., 1956b). Causative agent, the PPR virus (PPRV) was isolated for the first time in sheep cell culture in 1962 by Gilbert and Monnier (Gilbert and Monnier, 1962a) while Bourdin and Laurent-Vautier (Bourdin and Laurent-Vautier, 1967) observed the virus for the first time under the electron microscope. PPRV was classified as a member of the genus morbillivirus under the subfamily *Paramyxovirinae*, the family *Paramyxoviridae* and the order *Mononegavirales* in 1979 (Gibbs et al., 1979). There are seven known members of the genus morbillivirus: measles virus (MV), rinderpest virus (RPV), PPRV, canine distemper virus (CDV), cetacean morbillivirus (CeMV), phocine distemper virus (PDV) and feline morbillivirus (FMV) (Kumar et al., 2014). Morbilliviruses cause disease both in humans and animals (Diallo, 1990).

Based on nucleotide sequence analysis of fusion (F) and/or nucleoprotein (N) genes, PPRV strains have been grouped into four genetic lineages (types I to IV). Whereas PPRV strains belonging to all four genetic lineages are prevalent in Africa, all PPRV strains from Asia belong to type IV lineage (Kumar et al., 2014). Introduction of Asian lineage (type IV) of PPRV into Africa was reported for the first time in 2008 from a PPR outbreak in Morocco (Kwiatek et al., 2011). PPRV lineage type III has also been reported only once from Asia (Shaila et al., 1996). Lineage classification may be useful in monitoring PPRV circulation and tracing the source of outbreaks. Although a perfect cross protection is believed to occur among various PPRV strains, lineage classification could help in preparing homologous vaccine for adequate immunization.

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2. The disease

The incubation period of PPR is 2–7 days (Kumar et al., 2014) and the disease is characterized by high fever, development of vesicular lesions on tongue and gums, ocular discharge, leukopenia, diarrhea, and dyspnea (Kumar et al., 2004; Mariner et al., 2016). Pregnant animals may abort. Animals usually die within 4–6 days after the onset of fever. PPR leads to high morbidity (up to 100%) and mortality (up to 90%) (Baron et al., 2016; Kumar et al., 2014) and occurs round the year, though a seasonal variation has been observed (Abubakar et al., 2009). The clinical disease may be complicated by secondary invaders such as *Pasteurella* spp., *Escherichia coli* and *Mycoplasma* spp. (Kumar et al., 2014). The clinical signs of PPR mimic other diseases like foot-and-mouth disease (FMD), capripox, contagious pustular dermatitis, bluetongue and contagious caprine pleuropneumonia (Singh et al., 2009), therefore, differential diagnosis should be confirmed by appropriate laboratory tests. Morbilliviruses are highly infectious and lead to profound immune suppression (de Vries et al., 2015), however the individuals that survive infection usually develop lifelong immunity (Kerdiles et al., 2006).

Since the virus is labile in the external environments, a close contact between infected and susceptible animals is required for effective transmission of the disease (Braide, 1981). Discharges from the nose, eyes and mouth contain high amount of virus that releases fine infective droplets in the air which could be inhaled by animals in close contact so as to become infected (Abegunde and Adu, 1977). Although close contact is the most important mode of transmission; contaminated water, feed troughs and bedding are additional sources of infection. The indirect transmission is unlikely as the virus is heat-labile and sensitive to lipid solvents (Lefevre and Diallo, 1990). The possibility of transmission of infection at market places is high wherein small ruminants from different sources gather for trade.

3. Host susceptibility

The PPRV primarily causes disease in goats and sheep but several other species may also succumb to infection. Cattle and pigs seroconvert upon contact with infected sheep and goats, but without detectable clinical disease (Nawathe and Taylor, 1979; Taylor and Abegunde, 1979), therefore, acting as dead-end hosts (Gibbs et al., 1979). However, evidences of pyrexia and oral lesions in calves (Mornet et al., 1956a, 1956b) and fatal infection in buffaloes (Govindarajan et al., 1997) have been observed during experimental infection of PPRV. Detection of PPRV antibodies in animals other than natural hosts such as cattle, buffalo and camel suggests natural transmission of the PPRV among these species under field conditions (Balamurugan et al., 2014a; Khalafalla et al., 2010; Khan et al., 2008; Woma et al., 2016a,b). The PPRV identified from camels have been found to be phylogenetically identical to small ruminants (Albina et al., 2013). Occasionally the virus may overcome the innate resistance of the host to produce clinical disease. Of late, the potential of camels to act as a reservoir host for PPRV infection has also been suggested (Abraham, 2005).

The epidemiology of PPR does not end at domestic animals; rather it also involves wild animals (Aziz Ul et al., 2016; Ratta et al., 2016). Severe clinical disease with high mortality due to PPRV infection has been recorded in Dorcas Gazelles (*Gazella dorcas*) (Gur and Albayrak, 2010), Nubian Ibex (*Capra ibex nubiana*), Laristan sheep (*Ovis orientalis laristani*) and Gemsbok (*Oryx gazellaa*) (Couacy-Hymann et al., 2005; Kinne et al., 2010; Lembo et al., 2013). Likewise, subclinical infection has been reported in Nilgai (*Tragelaphinae*) in Arabian Gulf (Furley et al., 1987). Experimental infection of PPRV in American white deer (*Odocoileus virginianus*) has also been reported (Hamdy and Dardiri, 1976). Clinical and serological evidences also suggested the involvement of Gazelle, deer, antelope and other small wild ruminants (Abu Elzein et al., 1990; al-Naeem et al., 2000). The peridomestic rats have also been suspected to play a role in the epizootiology of PPRV in goats in Nigeria, but experimentally infected rats (subclinical) failed to transmit the infection to goats (Komolafe et al., 1987). These evidences imply the maintenance of PPRV in the environment by the animals other than the natural hosts (wild animals) (Couacy-Hymann et al., 2005).

4. Earlier prophylactic methods

The most comprehensive description of effective prophylactic measures against rinderpest was provided by Lancisi (1654–1720) which is still valid for most of the infectious diseases and have been adopted by the OIE. The key prophylactic methods suggested include sanitary measures, quarantine, slaughter and compensation and, destruction of carcasses and infected materials (Blancou, 2006).

Since rinderpest in cattle was somewhat similar to smallpox in humans, it was assumed that like small pox, it could be controlled by variolation. Several such trials were conducted in Europe during 1711–1767, but it was realized that rinderpest inoculation could be dangerous and should not be practiced in disease free herds (Taylor et al., 2006). However, Layard (1757) made an interesting observation: if distemper was in the neighborhood of a herd, it prevented the animals against rinderpest, probably due to cross protection provided by distemper causing agent against rinderpest [reviewed in reference (Pastoret et al., 2006)].

Methods other than inoculations were also taken into consideration to protect cattle from rinderpest. Peter Camper tried inoculations with lung fragments containing small worm, which he found in dead animals and believed that these worms might harbour the causative agent of the disease (Leclainche, 1955). While such inoculation trials were continued, experts realized that stamping-out was not possible with free ranging animals. In 1896, Koch tried bile from rinderpest infected animals for inoculation but it increased the spread of the disease rather its prevention. Inoculation of the serum obtained from recovered animals resulted in protection of recipient from rinderpest (Koole and Turner, 1897). In 1917-18, Dr. William Hutchins developed an early vaccine for rinderpest which was based on organ extracts of treated animals (Pastoret et al., 2006). A major breakthrough was achieved in 1920 when Dr. J. T. Edward, Director at Imperial Bacteriological Laboratory Mukteswar, India, developed an effective vaccine for rinderpest through attenuation of the virus by serial passages (600 times) in goats. The vaccine provided long-lasting immunity against rinderpest in cattle and buffaloes without any side effects.

5. Vaccines

5.1. Inactivated vaccines

Before the development of a live-attenuated tissue culture vaccine for rinderpest, attempts were made for development of a formalin-inactivated rinderpest virus vaccine, however, the vaccine was not found suitable to protect cattle against RPV or any other morbilliviruses. The inactivated rinderpest virus vaccine produced only short-term immune response (Appel et al., 1984). Moreover, in the case of measles virus, the administration of the inactivated vaccine increased disease pathology when subsequently exposed to wild-type virus (Taylor et al., 2006). Likewise, hyperimmune serum also provided short-term protection (Taylor et al., 2006).

In the endemic regions, disease prevention can be accomplished by using live-attenuated PPR vaccines. However, in non-endemic regions which are under threat, such as Europe, live-attenuated vaccine is usually not recommended by veterinary authorities, thus inactivated vaccines remains only viable alternative. Therefore, in recents times some new formulations of inactivated PPR vaccines have been developed and tested. One such vaccine developed by Cosseddu provided sterile immunity and was found to resist challenge with virulent PPRV, though two doses of the vaccines were required (Cosseddu et al., 2015). Another inactivated PPR vaccine was formulated with delta inulin and TLR9 agonist oligonucleotide as adjuvants which induced 100% seroconversion in rats and goats after 2 injections. All the immunized goats seroconverted to PPRV by day 9 and remained seropositive for >133 days (end of the experimental period) (Ronchi et al., 2016) suggesting that the inactivated vaccine, in combination with delta inulin adjuvant, represent a promising alternative to live attenuated PPR vaccines. However, *in vivo* challenge studies are required to warrant its use in the field.

5.2. Live-attenuated vaccine

Sabin and colleagues established a landmark by adapting poliovirus to the cell culture system; a pioneer work which paved the way for attenuation and vaccine development against other viruses (Krugman et al., 1961; Sabin, 1957). It also facilitated the process of attenuation of RPV and hence developing tissue culture rinderpest vaccine (TCRV) vaccine which led to successful global eradication of rinderpest (Plowright and Ferris, 1962). It was observed during RPV attenuation that during initial passages, the virus exhibited a minor surge in its pathogenicity, which later waned off leading to development of an avirulent strain at passage level 40 (Plowright and Ferris, 1962). In the beginning when homologous PPR vaccine was not available, heterologous rinderpest vaccine, formalized rinderpest spleen (Gargadennec and Lalanne, 1942) and lapinised rinderpest vaccines (Mornet et al., 1956c) were used for the control of PPR with variable success. Subsequently, with the successful application of TCRV (Bourdin et al., 1970) in protecting goats against PPR, OIE recommended it for PPR prophylaxis. The TCRV vaccine provided protection for about a year against PPR (Mariner et al., 1993; Taylor, 1979). However, this vaccine was later banned because of its possible interference with Global Rinderpest Eradication Program (GREP) to achieve rinderpest free zone and hence necessitated the development of a homologous PPR vaccine.

The first successful *in vitro* adaptation of PPRV was carried out by Gilbert and Monnier in 1962. They successfully propagated PPRV in primary liver cells from sheep wherein cytopathic effect (CPE) was manifested by the appearance of large syncytia (Gilbert and Monnier, 1962b). Similarly, CPE manifestation in the form of cell rounding, detachment and syncytia formation (Laurent, 1968) was observed following infection of RPV in calf liver cells (Plowright and Ferris, 1959a, 1959b). Initially, PPRV forms micro-syncytia which become larger as the infection progresses. The successive passage of PPRV in sheep liver cells resulted in reduced pathogenicity but the authors could not obtain a completely avirulent strain even at passage level 55 (up to which the virus induced a slight hyperthermia). A study by Benazet (1973) wherein PPRV was serially propagated in sheep liver cells also did not result in a complete avirulent strain even up to 65th passage [reviewed in reference (Diallo et al., 1989b)]. The unsuccessful attenuation of PPRV by previous workers could be attributed to insufficient quantity of virus inoculums used to generate mutants, type of cell culture system employed and inherent nature of the PPRV strains used for attenuation.

In 1989, Diallo and colleagues were able to obtain the first attenuated PPRV strain by serial passages of PPRV in Vero cells (Diallo et al., 2007). During adaptation of PPRV/Nigeria/75/1, they observed that in the beginning of serial passages (up to passage level 10), CPE could not be observed until 4–7 days post-infection, however, after 50th passage, this period was reduced to 2 days. Like in case of RPV, PPRV also lost its virulence quickly upon successive passages in Vero cells; at 20th passage virus only induced slight fever in animals and became completely avirulent at 55th passage. It was also observed that this vaccine virus (at 63rd passage), when used to immunize goats, elicited protective antibody response as early as 7 days post-vaccination (Diallo et al., 1989a). Several vaccine trials of PPRV/Nigeria/75/1-based vaccine were conducted in more than 98,000 sheep and goats during 1989–1996 without any untoward effects. Besides, the vaccinated sheep and goats resisted challenge of virulent virus and did not transmit the challenge virus to in-contact susceptible animals. The protective antibodies persisted for more than 3 years in the vaccinated animals. Taken together the vaccine demonstrated its efficacy of protecting sheep and goats against virulent PPRV. Though in the beginning it was used worldwide for protection against all genetically defined lineages of PPRV but subsequently lineage type IV vaccine was also developed.

PPRV/Sungri/96, a goat isolate from Sungri, Himachal Pradesh, India was used to develop a lineage-specific (lineage type IV) PPR vaccine in India by propagating in B95a (Marmoset lymphoblastoid) cells and Vero cells (first 10 passage in B95a and then in Vero cells) wherein the virus became avirulent at 56th passage [reviewed in reference (Sen et al., 2010)]. The vaccine based on PPRV/Sungri/96 was extensively tested both experimentally as well as in the field and was found to be safe and efficacious to provide sterile immunity against PPR in small ruminants for at least 4 years (Sen et al., 2010). This vaccine is being used for mass immunization under PPR control program being carried out in India since 2010. Likewise, at Tamil Nadu Veterinary and Animal Science University (TANUVAS), India, PPRV/Arasur/87 (sheep origin) and PPRV/Coimbatore/97 (goat origin) were serially propagated in Vero cells to obtain avirulent strains at passage level 75 (Sen et al., 2010). These vaccines are being used in Southern Indian states and are equally efficacious and safe as is Sungri/96-based vaccine.

Vero and other cell lines have been tested to isolate PPRV from clinical specimens but with limited success (Kumar et al., 2014). Signaling lymphocyte activation molecule (SLAM) and nectin-4 serve as primary cellular receptors for morbilliviruses (Meng et al., 2011; Sarkar et al., 2009; Tatsuo and Yanagi, 2002). Introduction of SLAM into cells facilitates morbillivirus replication (Pawar et al., 2008). However, the amino acid sequence of SLAM varies between species, and often requires adaptation of a particular virus to different versions of the SLAM (human, canine, goats and cattle) (Meng et al., 2011; Sarkar et al., 2009). On the contrary, nectin-4 is highly conserved between different mammals, and unlike SLAM, does not need receptor adaptation by the virus. As compared to Vero cells expressing canine SLAM (VeroDogSLAM), nectin-4 expressing cells (VeroDogNectin-4) were found to be highly sensitive for PPRV isolation (23% versus 4.5% efficiency from swab samples and 89% versus 67% efficiency in tissue specimens) (Fakri et al., 2016). Moreover, virus titers were significantly higher in VeroDogNectin-4 suggesting their superiority over VeroDogSLAM for development of PPR diagnostics as well as virus titration.

PPR vaccine contains $\sim 10^3$ tissue culture infective dose 50 (TCID50) of cell culture attenuated PPRV, being administered via subcutaneous route and is believed to protect the vaccinated animals for >4 years (Singh et al., 2009). Maternal antibodies can interfere with vaccination, therefore kids born from vaccinated animals must be immunized at the age of 3–4 months, a stage

where level of maternal antibodies is not quite enough to interfere with the vaccine virus (Ata et al., 1989). PPR vaccine is considered quite safe without any immunosuppressive effects on the host (Rajak et al., 2005), though it is generally not recommended for sick animals or healthy animals in close contact with the PPRV-infected animals (during outbreak).

5.3. Thermo-stable PPRV vaccines

5.3.1. PPR vaccines with improved freeze drying methods

The shelf life of live-attenuated PPRV vaccine is ~1 year at 4 °C (Sen et al., 2010). Since the PPRV vaccine is mostly required for use in hot and humid climate in South Asia and Africa (Begum et al., 2016), therefore, maintenance of cold chain is essentially required for transportation of the vaccine in the field which significantly increases the overall cost of vaccine package. To circumvent the problem of cold chain maintenance, a range of improved freeze-drying methods have been developed to enhance the thermostabilty of the PPR vaccine. Mariner et al. developed a lyophilized Vero cell-adapted rinderpest vaccine, stabilized with lactalbumin hydrolysate and sucrose, wherein the moisture content of vaccine was greatly reduced, thereby increasing the thermostability of the TCRV vaccine (Mariner et al., 1990). Similarly, Worrall et al. developed a rapid method of dehydration and preservation of live attenuated PPRV vaccine (Xerovac) wherein the virus was diluted 1:1 with a sterile 5% w/v aqueous solution of trehalose dehydrate and then subjected to drying by simple dehydration. The resulting vaccine was able to resist 45 °C for a period of 14 days without any major loss of potency (Worrall et al., 2000). Silva tried various strategies to increase the thermostability of PPR vaccines (i) use of Tris/trehalose to increase the virus half-life in liquid formulation (21 h at 37 °C and 1 month at 4 °C) (ii) Tris/trehalose also enhanced the thermostability of the lyophilized PPR vaccine wherein viral titers were maintained for relatively longer time [0.6 log loss at 4 °C in 21 months, 0.6 log loss at 37 °C in 144 h and 1 log loss at 45 °C in 120 h] (iii) replacing fructose with glucose enhanced intrinsic PPRV vaccine stability in terms of higher stability and higher virus production (1 log increase) (iv) increasing concentrations of NaCl facilitated the release of the virus from infected cells and reduced the cell-associated fraction of the virus (Silva et al., 2011, 2014).

Heavy water has also been reported to increase thermostability of polio (Wu et al., 1995) and yellow fever vaccines (Adebayo et al., 1998). In order to further increase the thermostability of the PPR vaccines, combinations of stabilizers and heavy water were also explored. Reconstituted PPRV/Jhansi vaccine stabilized at 4–25 °C using stabilizer E (trehalose, calcium chloride and magnesium chloride) could maintain the protective titers up to 48 h. When reconstituted with diluents containing NaCl and $MgSO_4$, at 37 °C, the protective titers were maintained up to 42 h [reviewed in reference (Sen et al., 2010)].

Vaccine based on deuterated virus has also been developed wherein the virus was grown in cell culture media containing 20% heavy water and the vaccine diluents containing 87% heavy water and 1 M $MgCl_2$. On exposure at 37 °C and 40 °C, deuterated PPRV vaccine maintained titers greater than $10^{2.5}$ $TCID_{50}$/ml until 28 days as compared to conventional PPR vaccine which could maintain titers only for 14 days. Combination of heavy water/$MgCl_2$ was found to be better reconstituting diluent than heavy water alone for both the deuterated and conventional PPR vaccines (Sen et al., 2010). However, such vaccines have only marginal advantages in terms of thermostability (Table 1). Success of the PPR control program will depends largely on effective delivery of the vaccine in hot and humid climate (Asia/Africa), therefore there is a need for further research on the development of a thermo-stable PPR vaccine.

5.3.2. Vaccines based on thermo-adapted-PPRV

In addition to using new stabilizers and employing improved freeze drying methods, vaccines based on thermo-adapted (Ta) PPRV have also been developed (Balamurugan et al., 2014b; Riyesh et al., 2011). One such vaccine was developed using 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), when used as vaccine candidate in sheep and goats, was found to be safe, potent and efficacious vaccine candidate, thus providing an alternate to existing PPR vaccine (Table 1). However, extensive clinical trials need to be carried out before using such a vaccine in the field.

5.4. New generation vaccines

Like TCRV, live-attenuated PPR vaccine is an effective vaccine that provides long-lasting immunity following a single immunization. However, the vaccine has two main drawbacks, first the immune response is identical to natural infection, therefore it is not possible to differentiate infected from vaccinated animals (DIVA). 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 generally recommended that if a vaccine has been used for control of a disease, that region (country) must prove that their susceptible animal population is free from infection by employing DIVA tests. Secondly, the vaccine is thermolabile, requiring a cold chain to deliver the vaccine into the hot and arid environment of the endemic regions (Asia and Africa) which makes it a costly and inconvenient affair.

Recombinant DNA technology has been used to produce new vaccines against a plethora of organisms, the most successful of which has been the hepatitis B vaccine in humans. To overcome the thermolability, recombinant vaccines were developed against rinderpest (Belsham et al., 1989; Romero et al., 1994a). Likewise DIVA vaccines were also developed for rinderpest (Belsham et al., 1989; Romero et al., 1994a) but could not be implemented as the GREP was in its last phase.

5.4.1. Poxvirus vectored vaccines

Vaccinia virus has a very large genome containing several non-essential genes that can be replaced with foreign genes and therefore it is considered suitable for genetic manipulation. (Mackett et al., 1982). Vaccinia-rabies recombinant vaccine was the first such vaccine produced. It elicited a protective immune response and could withstand the extremes of temperature in the field, now commonly used in Europe and the USA to control rabies in the wild animals (Brochier et al., 1991). Vaccinia-rinderpest recombinants have also been developed (Barrett et al., 1989; Yilma et al., 1988) using “F” and “H” protein genes. However these vaccines were based on WR strain of the vaccinia virus which was not considered quite safe to be licensed in the absence of smallpox. One of the important concerns when using vaccinia virus vectored recombinant vaccine is the safety of vaccinators, particularly in Africa where a significant population is immunocompromised due to HIV-1 infection. Moreover, vaccinia virus vectored vaccine produced severe lesions at the site of inoculation in animals (Belsham et al., 1989), probably due to insufficient attenuation. Therefore, few more sufficiently attenuated strains such as LC16mO (Yamanouchi et al., 1993) and Wyeth (Verardi et al., 2002) have been examined subsequently.

The established vaccine strains of capripox viruses (the causative agent of sheep and goat pox) have also been used to produce recombinant rinderpest and PPR vaccines. Capripox vectored rinderpest vaccine had three main advantages; firstly, it had long-lasting immunity (>three years) in cattle, secondly, it

Table 1
Various types of PPR vaccines.

Vaccine Type	Reference	Remark
Inactivated vaccines	Ronchi et al. (2016); Cosseddu et al. (2015)	Safe to be used in counties at risk but immunity is of short duration. DIVA not possible
Conventional live-attenuated vaccine[a]	Diallo et al. (1989a,b); Diallo et al. (2007)	Most successful PPR vaccine that is being used all over the globe in PPR control programs. It provides long-lasting immunity but it is thermolabile and DIVA not possible
Conventional PPR vaccines with stabilizers and improved freeze drying methods		
Vero cell-adapted vaccine, stabilized with lactalbumin hydrolysate and sucrose	Mariner et al. (1990)	Relatively thermostable but DIVA not possible
Use of Tris-Trehalose and then quick drying	Worrall et al. (2000)	Relatively thermostable but DIVA not possible
Use of Tris-Trehalose, glucose and increased concentration of NaCl	Silva et al. (2011)	Relatively thermostable but DIVA not possible
Combinations of stabilizers and heavy water	Sen et al. (2010	Relatively thermostable but DIVA not possible
Vaccines based on thermo-adapted-PPRV (grown at 40 °C)	Balamurugan et al. (2014a,b); Riyesh et al. (2011)	Relatively thermostable but DIVA not possible
New generation vaccines		
Poxvirus vectored vaccines.	Berhe et al. (2003); Chen et al. (2010)	Relatively thermostable but pre-existing antibodies against vector may interfere vaccine intake
Adenovirus vectored vaccine	Herbert et al. (2014); Qin et al. (2012); Wang et al. (2013)	DIVA possible but immunity may be of short duration
Insertion of enhanced green fluorescent protein (eGFP) between P and M gene	Hu et al. (2012); Muniraju et al. (2015)	DIVA possible but immunity may be of short duration
Deletion of C77 monoclonal antibody binding site on H protein	Hu et al. (2012); Muniraju et al. (2015)	Immunity may be of short duration
Recombinant PPRV expressing the FMDV VP1 gene (rPPRV/VP1)	Yin et al. (2014)	Potential to serve as dual live vectored vaccine against PPRV and FMDV but duration of immunity is not well defined
Chimeric vaccine		
Chimeric RPV-PPRV recombinant virus vaccine	Das et al. (2000)	Towards end of GREP, the areas that had been declared free of rinderpest could not use the RPV vaccine strain to vaccinate against rinderpest or PPR, Chimeric vaccine could serve this purpose. DIVA is possible but immunity may be of short duration
N protein based, chimeric RPV-PPRV marker vaccine	Parida et al. (2007)	DIVA possible. Further clinical trials required to precisely evaluate immunity.
Anti-idiotypic vaccine	Apsana et al. (2015)	Quite heat stable and capable of eliciting antibody and cell-mediate immune response in complete absence of viral antigens
Virus-like particles (VLPs)	Liu et al. (2015)	Safe and does not require biocontainment facility to handle the virus
Other recombinant vaccines		
Bombyx mori nucleopolyhedrovirus displaying H glycoprotein of RPV and the F glycoprotein of PPRV	Rahman et al. (2003)	DIVA possible but protection has not yet been evaluated in natural hosts
Semliki Forest virus (SFV) expressing the H protein	Callagy et al. (2007)	DIVA possible but protection has not yet been evaluated in natural host. The immunity may be of short duration.
Silk worm larvae-expressing recombinant F protein	Saravanan et al. (2004)	DIVA possible but protection has not yet been evaluated in natural host. The immunity may be of short duration.
Modified vaccine virus Ankara (MVA) expressing PPRV F and H proteins	Sen et al. (2010)	DIVA possible but protection has not yet been evaluated in natural hosts. For optimum protection, two doses of vaccine are required prior to challenge
Combined vaccines		
Sheep pox and PPR and, goat pox and PPR	Chaudhary et al. (2009); Hosamani et al. (2006)	Cost effective. Reduce number of needle pricks and hence discomfort to the animals
Heterologous PPR vaccine (RPV vaccine against PPR)	Taylor (1979)	PPR virus does not required for vaccine production but duration of immunity is only for 12 months
Heterologous rinderpest vaccine (PPRV vaccine against rinderpest)	Holzer et al. (2016a,b)	No need to preserve stocks of live RPV in the laboratories for future emergence of rinderpest. However, only virulent but not live-attenuated PPRV provided immunity against RPV in cattle

[a] Vaccine currently being used for immunoprophylaxis in the filed.

could protect cattle against two diseases, rinderpest and lumpy skin disease (LSD) and thirdly, due to strong antigenic relationship within the genus morbillivirus, goats and sheep could also be protected against PPR (Jones et al., 1993; Romero et al., 1994a,b). However, the disadvantage is that the pre-existing antibodies against LSD virus (LSDV) interfere in vaccine intake (Ngichabe et al., 2002). Capripox virus vectored vaccines have also been developed against PPR which act as dual vaccine to protect against both PPR and sheep and goat pox (Berhe et al., 2003; Chen et al., 2010). Though, the vaccine was found to be relatively thermostable, it did not elicit optimum antibody response probably because of the pre-existing immunity against vector (Chen et al., 2010). Later on, fowlpox (FP) virus vector, which had been successfully used in humans, when used in ruminants, elicited very poor antibody- and cell-mediated immune responses (Cubillos-Zapata et al., 2011).

Since only a limited number of viral proteins (F and/or H) were used as recombinant antigen, absence of PPRV N protein in vaccine preparation allowed the serological identification of infected animals, therefore serving as a marker (DIVA) vaccine. However, such vaccines often require multiple doses and have reduced efficacy compared to live-attenuated vaccines. These vaccines have

not moved forward beyond the experimental stage because their licensing has been hampered due to the controversy over the release of genetically manipulated organisms.

5.4.2. Adenovirus vectored vaccine

Replication-deficient adenovirus 5 (Ad5) is considered as a better recombinant vector for use in small ruminants because unlike human beings these animals lack any pre-existing immunity to this vector (Thacker et al., 2009). Like live-attenuated PPRV vaccine, immunization of goats with Ad-H alone or in combination with an Ad-F have been found to induce potent antibody and cell mediated immune response (Herbert et al., 2014; Qin et al., 2012; Wang et al., 2013) though combination of Ad-H and Ad-F induced better protection than the Ad-H or Ad-F alone (Holzer et al., 2016b).

5.4.3. Positive and negative marker vaccine through reverse genetics approach

Reverse genetics, an approach to study the phenotypic effect of the engineered mutation in a gene, has it made possible to genetically alter the viral RNA genome through DNA copies (cDNA). RPV genome was manipulated using this approach to introduce site-specific mutations (Baron and Barrett, 1997, 2000), thereby allowing an alternative approach for development of marker vaccines. The approach can be used to add a marker gene (positive marker vaccine) or delete an antigenic component (negative marker vaccine). Initially such a vaccine was produced by inserting green fluorescent protein (GFP) gene between P and M gene of the RPV genome. The resulting vaccine was found to be efficacious and resisted virulent RPV challenge along with eliciting antibodies against the marker (GFP) (Walsh et al., 2000a). Another such vaccine was developed by inserting influenza virus hemagglutinin (HA) gene; the vaccine produced strong antibody response against RPV as well as against marker (HA) and resisted challenge by virulent RPV (Walsh et al., 2000a).

After the development of the reverse genetics system for PPRV (Hu et al., 2012; Muniraju et al., 2015), Muniraju et al. developed two types of recombinant PPRV constructs; a positive marker PPRV construct by inserting enhanced GFP (eGFP) between P and M genes and a negative marker construct by deleting C77 monoclonal antibody binding site on H protein [a key component of the current diagnostic competitive H ELISA (c-ELISA)]. Neither insertion of eGFP nor mutation in the H protein affected the functionality and viability of the recombinant PPRV. When such constructs were used as vaccine (using PPRV/Nigeria/75/1 vaccine strain as a backbone), they resisted challenge of virulent PPRV and did not transmit vaccine virus to the susceptible in-contact animals. However, C77 monoclonal antibody was not found to bind with mutated form of the PPRV H protein thus not allowing DIVA. Contrarily, epitope deletion has served as successful DIVA vaccine for RPV (Buczkowski et al., 2012), Newcastle disease virus (NDV) (Peeters et al., 2001) and classical swine fever virus (Wehrle et al., 2007).

A recombinant PPRV expressing the FMDV VP1 gene (rPPRV/VP1) has also been generated (Yin et al., 2014). Insertion of FMDV VP1 in PPRV backbone neither impaired replication of the recombinant virus *in vitro* nor did it affect immunogenicity in inducing neutralizing antibody against PPRV in goats. Administration of recombinant rPPRV/VP1 also induced FMDV neutralizing antibody in goats and resisted challenge with virulent FMDV. Such a vaccine has potential to serves as dual live vectored vaccine against PPRV and FMDV (Yin et al., 2014).

One of the potential problems with vaccines developed using reverse genetics approaches is that the marker protein may be incorporated into the virus envelope and therefore may alter the host tropism and pathogenicity. In order to avoid such complications, mutant version of influenza HA protein (mutant disrupts binding of the virus to the host cell receptor) has been employed to produced recombinant marker vaccines (Walsh et al., 2000b).

5.4.4. Chimeric vaccine

Towards end of the GREP, the areas that had been declared free of rinderpest could not use the RPV vaccine strain to vaccinate against rinderpest or PPR. Therefore, alternative negative marker vaccines were produced by generating chimeric viruses with genes for immunogenic proteins derived from related viruses i.e. PPRV and RPV. The H and F genes of the RPV were replaced by corresponding genes from PPRV, resulting in chimeric RPV-PPRV recombinant virus vaccine (Das et al., 2000). Virus-specific serological response in such vaccines can be identified by specific ELISAs and therefore allowing discrimination of infected and vaccinated animals. Later on, N protein-based, chimeric RPV-PPRV marker vaccine was developed which provided protection against challenge with virulent RPV in cattle (Parida et al., 2007).

5.4.5. Anti-idiotypic vaccine

Based upon the antigen binding specificity, an idiotype is a shared characteristic between groups of immunoglobulin or T cell receptor (TCR) molecules. Idiotype is located on the 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 (Jerne, 1974). An internal image anti-Id, Ab2 β resembles to the original antigen (McNamara and Kohler, 1984) and recognizes an idiotypic determinant within the antigen combining site. The internal image Ab2 β antibodies have shown immunogenicity against hepatitis B virus (Kennedy et al., 1986a,b) and bluetongue virus (Zhou, 1999). An internal image Ab2 against RPV and PPRV H/HN protein has also been shown to elicit virus specific antibody and cell-mediated immune response in the mouse model (Vani et al., 2007a). Moreover, DNA encoding VH region of Ab2 has also been shown to elicit long-lasting antibody and cell-mediated immune response in mouse in the complete absence of viral antigen (Vani et al., 2007b). Such DNA vaccine which codes for the heavy chain variable region of an internal image anti-idiotypic antibody (that mimics a region on the HN protein of PPRV) was also found capable in eliciting antibody and cell-mediate immune response in sheep in complete absence of viral antigens (Apsana et al., 2015). DNA-based vaccines are considered heat stable and generate immune response against a desired antigen (against PPRV HN protein in above vaccine), therefore it has potential to overcome both the limitations (thermo-sensitivity and DIVA) of current live-attenuated PPR vaccine being used for mass immunization in the field.

5.4.6. Subunit vaccines

Baculovirus-expressed RPV "H" and "F" proteins were used as an antigen for subunit vaccine (Yamanouchi et al., 1998); though they elicited a strong neutralizing antibody response but did not provide protection in cattle against virulent RPV (Bassiri et al., 1993). However, when baculovirus-expressed H protein was incorporated into immunostimulating complexes (ISCOMs), a good level of protection was achieved on virulent virus challenge. ISCOMs are known to induce cell-mediated immune response (Ennis et al., 1999), therefore, it appears that the cell-mediated immune response is a major factor in inducing protective immune response against morbilliviruses.

5.4.7. Virus-like particles (VLPs)

Recombinant baculovirus has been constructed to co-express the PPRV H, N and M proteins that allows budding of PPR virus-like particles (VLPs) from insect cell membranes (Liu et al., 2015). These

VLPs were found to induce potent virus-specific neutralizing antibodies in mice suggesting potential of VLP-based vaccine candidate against PPR (Zhong et al., 2016).

5.4.8. Edible vaccine

Administering vaccine with needle pricks needs huge veterinary infrastructure, and therefore significantly affects disease control programs. In this context, edible vaccine against PPR could be an attractive perspective. Recombinant RPV H protein produced in transgenic tobacco or peanut plant has shown reactivity against H-monospecific convalescent sera. When inoculated intraperitoneally, transgenic plant derived protein produced high titer antibodies in mice and neutralized RPV infection. Similarly, leaves of transgenic peanut expressing RPV-H when fed to mice and cattle induced neutralizing antibodies and lymphoproliferative response (Khandelwal et al., 2003a,b, 2004; Satyavathi et al., 2003). Though still at an early stage of development, these studies suggest the potential of the oral edible vaccine against morbillivirus infections.

5.4.9. Other recombinant vaccines

Bombyx mori nucleopolyhedrovirus displaying the immunodominant ectodomains of the H glycoprotein of RPV and the F glycoprotein of PPRV (Rahman et al., 2003), the Semliki Forest virus (SFV) expressing the H protein (Callagy et al., 2007) and the silk worm larvae-expressing recombinant F protein (Saravanan et al., 2004) are some other recombinant vaccines which have been developed but their efficacy with regard to protection have not yet been evaluated in the natural hosts. Modified vaccine virus Ankara (MVA) expressing PPRV F and H proteins that induced resistance to challenge with virulent PPRV was also developed but it needed two doses of vaccine prior to challenge [reviewed in reference (Sen et al., 2010)].

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 which need to be addressed before using these next-generation vaccines in the field for control and eradication of PPR.

5.5. Combined vaccines

To reduce stress caused to the animals and to economize the cost of overall vaccination package, mixtures of organisms have been commonly used in single vaccine called combined vaccine (Just et al., 1986; Lasaro et al., 2004). Combined vaccines have been developed for a wide range of organisms, for example, FMD and hemorrhagic septicemia (HS), FMD, HS and Black Quarter (BQ) (trivalent vaccine) (Chhabra et al., 2004), *Mycobacterium bovis* and *Brucella* (Hu et al., 2009), *Escherichia coli* and Rotavirus (Snodgrass, 1986; Waltner-Toews et al., 1985) and, bovine respiratory syncytial virus, bovine viral diarrhea virus, infectious bovine rhinotracheitis virus, parainfluenza 3 virus, and *Mannheimia haemolytica* have been developed. Some combinations of parvovirus, hepatitis, leptospirosis, parainfluenzavirus, coronavirus, adenovirus (DHLPP, DHLPPC, DA2LPPC) 6-Way, and 7-Way or 7-in-1, are also practiced in dogs and cats (Burgher et al., 1958; Gribencha and Selimov, 1969). No untoward effects have been observed due to presence of multiple antigens/pathogens in the combined vaccines. Considering the similar geographical distribution of diseases, some combined formulations of PPR vaccine such as sheep pox and PPR, goat pox and PPR have also been developed (Chaudhary et al., 2009; Hosamani et al., 2006) and found to induce protective immune response without any side effects.

A major cost for disease (PPR) control program would be in transport of the vaccine to the end user. This may create an opportunity for dissemination of other information and technologies and hence to manage other health problem of the animals as well. Vaccines against the diseases that could be potentially combined with PPR are sheep and goat pox, pasteurellosis, brucellosis, contagious caprine pleuropneumonia (CCPP) and FMD (Kumar et al., 2016). Additionally, deworming for internal and external parasites may also be included in the control program.

5.6. Cross protection among morbilliviruses

It has been well established that sera from morbillivirus infected animals cross react with other viruses within the same genus (Breese and De Boer, 1973; Gould et al., 1981; Norrby et al., 1985; Orvell and Norrby, 1974; Plowright, 1962; Sheshberadaran et al., 1986), though cross-protection is not always a reciprocal relationship and may depends upon virus strain and the nature of host involved e.g. CDV can protect cattle from RPV but RPV provides only partial protection of ferrets against CDV (Imagawa, 1968; Jones et al., 1997; Sheshberadaran et al., 1986). RPV protects dogs from CDV but CDV cannot protect cattle from RPV (DeLay et al., 1965). Inoculation of PPRV vaccine into goats elicits antibodies that neutralize RPV in the cell culture, though at lower titre than the neutralization of PPRV (Couacy-Hymann et al., 1995). Likewise, RPV vaccine strain elicits antibodies in goats that neutralize RPV but exhibits only trace neutralizing ability against PPRV (Taylor, 1979). More recently, inoculation of PPRV vaccine into cattle has been shown to elicit antibody and cell mediated immune response but failed to protect against virulent RPV challenge (Holzer et al., 2016a). When two independently developed PPRV vaccine strains (Nigeria/75 and Sungri/96) along with a virulent strain of PPRV were used to inoculate cattle, a cross protection against virulent RPV was observed only when virulent PPRV was inoculated in cattle (Holzer et al., 2016a), a finding which is in accordance with very early studies where crude material from animals suffering from PPR was shown to protect cattle from rinderpest (Mornet et al., 1956a). Increased disease outbreaks due to CDV in primates (de Vries et al., 2014) suggests that the presence of measles virus in human population would have prevented disease caused by CDV.

The cross-protection among various prototypes of morbilliviruses is considered to be mediated mainly via cell-mediated immunity rather than cross-reacting antibodies (Brown and McCarthy, 1974; Gerber and Marron, 1976). However, antibody-mediated cross protection may occur but that is not due to presence of neutralizing antibodies but rather due to cross-reactive antibodies that fix complement, resulting in death of infected cells without preventing virus infection in cell culture (Orvell and Norrby, 1980; Sheshberadaran et al., 1986). This might be due to conserved epitopes present on the surface of morbillivirus fusion glycoprotein (Orvell and Norrby, 1980; Sheshberadaran et al., 1986). For example, antibodies to the RPV F protein do not neutralize virus directly, but rather in the presence of complement, while similar anti-RPV-H antibodies are directly neutralizing (Sugiyama et al., 1989). Similarly, antibodies in measles infected sera that cross reacted (immunofluorescence) with the surface glycoproteins of CDV in the absence of CDV-neutralizing activity (Gould et al., 1981) were also identified.

The differences observed in the cross-protection among prototype morbilliviruses have been hypothesized due to (i) inherent ability of some virus strains to replicate sufficiently in a heterologous host to trigger a more potent immune response and (ii) Emergence of random nature of the attenuating mutations in vaccine strains during serial passage in the cell culture that prevent the reversion to virulence through any single random base change. Since these mutations are uncharacterized, it's quite possible that one or more of them would have a particularly strong effect on the replication/immunogenicity of the virus in heterologous host.

The exact mechanism of cross-protection between morbilliviruses remains elusive. Extensive work on cell-mediated and humoral immune response is needed to precisely understand the cross protection among morbilliviruses.

5.6.1. Heterologous PPR vaccine

Initially in the absence of homologous PPR vaccine, Taylor (1979) used attenuated RPV vaccine: goats vaccinated with attenuated RPV vaccine were protected from PPRV for at least 12 months without transmitting the challenge virus to in-contact susceptible animals. Though the vaccinated animals developed neutralizing antibodies that were primarily directed against RPV but following exposure to PPRV, a high antibody level was elicited to both viruses (Taylor, 1979). Later when homologous PPR vaccine became available, this vaccine was banned because it might have interfered with GREP.

5.6.2. Heterologous rinderpest vaccine

Rinderpest has been eradicated from the globe in 2011. This was the first livestock disease and the second viral disease after pox that was eradicated from the globe. Some of the laboratories around the world are also maintaining live RPV which could be released accidentally and could enter the environment to cause a devastating pandemic. It could also be released deliberately as an act of sabotage or bioterrorism either as natural isolate or one rescued by reverse genetics (based on RPV genome sequence available in the public domain). Therefore, alternative vaccine which could replace traditional live attenuated RPV strains is of utmost importance. These assumptions led Holzer et al. to evaluate if cattle can be protected from rinderpest by inoculating related morbillivirus, PPRV (Holzer et al., 2016a). Cattle immunized using the established PPRV vaccine strains viz: Nigeria/75/1 or Sungri/96 developed antibody and cell-mediated immune responses but failed to resist virulent RPV challenge, though the animals infected with wild-type PPRV were protected from RPV challenge (Holzer et al., 2016a). Therefore, use of PPR vaccine would not serve as a heterologous vaccine candidate against rinderpest in cattle and hence it would not be feasible to eliminate stocks of live RPV being held for development of RPV vaccine. This was probably the last study that was approved to handle live RPV.

5.7. Production of biosafe PPRV antigen

Due to the requirement of bicontainment facility, work on PPRV is often restricted to attenuated vaccine strain only. To overcome this issue, the entire viral RNA polymerase gene (Large, L gene) was removed and complemented with the viral polymerase constitutively expressed in host cell line thus creating a helper cell dependent form of PPRV which grew efficiently in the L-expressing cell line but not in other cells. Such a virus is indistinguishable from normal virus and can be grown in normal facilities without the need for high level biocontainment (Baron and Baron, 2015).

5.8. Is extensive spread of PPR in last decade due to eradication of rinderpest

It has been well established that PPRV circulating in small ruminants can subclinically infect cattle to make them sero positive against PPRV (Abraham et al., 2005; Couacy-Hymann et al., 2006; Haroun et al., 2002; Khan et al., 2008). Similarly, RPV has been shown to subclinically infect small ruminants (Kumar et al., 2014). In this context it is imperative to speculate whether anti-RPV antibodies prevent the transmission of PPRV in small ruminants and similarly whether the presence of anti-PPRV antibodies in cattle affect epidemiology and transmission of RPV. However, only the virulent virus but not the vaccine virus is able to self transmit from the infected animals to in-contact susceptible animals [reviewed in reference (Kumar et al., 2014)]. In this context, it is desirable to develop a vaccine against PPR that transmits the virus to self immunize in-contact susceptible animals including cattle. Though PPRV can infect cattle to make them seropositive, it has not yet succeeded in adapting as bovine PPRV which could be maintained in nature independently without the small ruminants.

5.9. Vaccination of animals other than small ruminants in PPR control program

PPRV and RPV produce similar clinical disease in their natural hosts. RPV causes a lethal infection in cattle but sheep and goats develop subclinical disease. In contrast, PPRV causes an acute lethal disease in sheep and goats with a mild infection in cattle. During GREP, mass vaccination was carried out only in cattle and buffaloes whereas sheep and goats were not covered (Couacy-Hymann et al., 2006). There have been speculations that PPRV may have emerged from RPV by natural passage in sheep and goats. In the recent times, evidences of PPRV infection in cattle and buffaloes (Abraham et al., 2005; Khan et al., 2008) suggest the possibilities of emergence of bovine PPRV. Therefore, it becomes pertinent to explore the possibility of inclusion of cattle in the mass vaccination campaign against PPR which is underway in Asia and Africa.

6. Concluding remarks

A live-attenuated vaccine that provides long-lasting immunity as well as effective diagnostic tools is already available for control of PPR. The only limitation in using the current vaccine is that the vaccinated animals cannot be differentiated from naturally infected animals. This would be essential to evaluate the impact of vaccination during serosurveillance program post-vaccination. Since other diseases can also be included along with the PPR control program, multi-disease diagnostic assays need to be developed for effective containment of the disease. In order to overcome the necessity of cold-chain, a technology for thermostable vaccine should also be developed. Besides, research should also be undertaken on the development of aerosol/eye drop vaccine. Classically the level of herd immunity required to prevent transmission of the virus is 80%, however, precise level of herd immunity required for blocking effective transmission of PPR needs further investigations.

Conflict of interest

Authors declare no conflict of interest.

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