

VETERINARY VACCINES

PRINCIPLES AND APPLICATIONS

FIRST EDITION

EDITED BY

SAMIA METWALLY | GERRIT VILJOEN

AHMED EL IDRISSI



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Peste des Petits Ruminants

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21.1 Introduction

Peste des petits ruminants (PPR) is a highly contagious viral disease of small ruminants. In its acute forms, it is characterized by high fever, nasal and ocular discharges, diarrhea, and death in 50–60% of cases, even more if it occurs in naïve populations (Diallo and Libeau 2014). The symptoms are like those of rinderpest, the related cattle disease that was declared officially eradicated from the world in 2011 (www.fao.org/docrep/018/i3366e/i3366e.pdf).

Rinderpest was known in the fourth century (Lefèvre 2010) but the first report on PPR dates back to only 1942 (Gargadennec and Lalanne 1942). For a long time, PPR reports were confined to West Africa. It was only after the 1970s that its geographical distribution steadily expanded across Africa (apart from southern countries), the Middle and Near East and Asia, extending from western Asia to China (Banyard et al. 2010; Libeau et al. 2014; Baron et al. 2016). Today, about 80% of the world's sheep and goat populations are threatened by PPR (Figure 21.1).

Currently, PPR is the fastest growing and potentially the most economically important disease of sheep and goats in many regions of the developing world where these domestic animals play an integral and important role in sustainable agriculture. PPR has spread so alarmingly during the last two decades that it has become a concern for the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE), which convened an international conference on the situation in April 2015 in Abidjan, Côte d'Ivoire (www.fao.org/news/story/en/item/282397/icode). At that conference, a strategy was adopted for the global control and eradication of PPR (PPR-GCES) by the year 2030 (Anonymous 2015).

21.2 Types of Vaccines Commercially Available

Peste des petits ruminants is caused by a virus, the peste des petits ruminants virus (PPRV) that belongs to the genus *Morbillivirus* within the family *Paramyxoviridae*. The other members of the *Morbillivirus* group include rinderpest virus (RPV), measles virus (MV), canine distemper virus (CDV), phocine distemper virus (PDV), dolphin morbillivirus (DMV), porpoise morbillivirus (PMV), and feline morbillivirus (FeMV) (Diallo and Libeau 2014; Parida et al. 2015). The virus particle is composed of an envelope, a genomic RNA, and six structural proteins, namely the nucleocapsid protein (N), the phosphoprotein (P), the matrix protein (M), the fusion protein (F), the hemagglutinin (H), and the large RNA-dependent polymerase RNA protein (L). While the N protein of morbilliviruses is the major viral protein, it does not induce a protective immune response, unlike the hemagglutinin (H) and fusion (F) proteins that mediate virus entry into the cell and its propagation in the host. Those two viral proteins induce immune protection against the virus infection and the disease (Barrett et al. 2006; Diallo and Libeau 2014). F and N protein gene sequences have been used for typing the different PPRV strains so far identified. They are classified into four genotypes: I, II, III, and IV (Figure 21.2).

All the four PPRV genotypes are endemic in Africa, while so far, only viruses of genotype IV have been identified in Asia (Libeau et al. 2014; Adombi et al. 2016; Baron et al. 2016). Despite this subdivision, there is only one PPRV serotype and an animal which has recovered from an infection by a PPRV strain or which has been vaccinated is protected against infection by any other PPRV strain. All PPR vaccines in use currently are live attenuated PPRV that

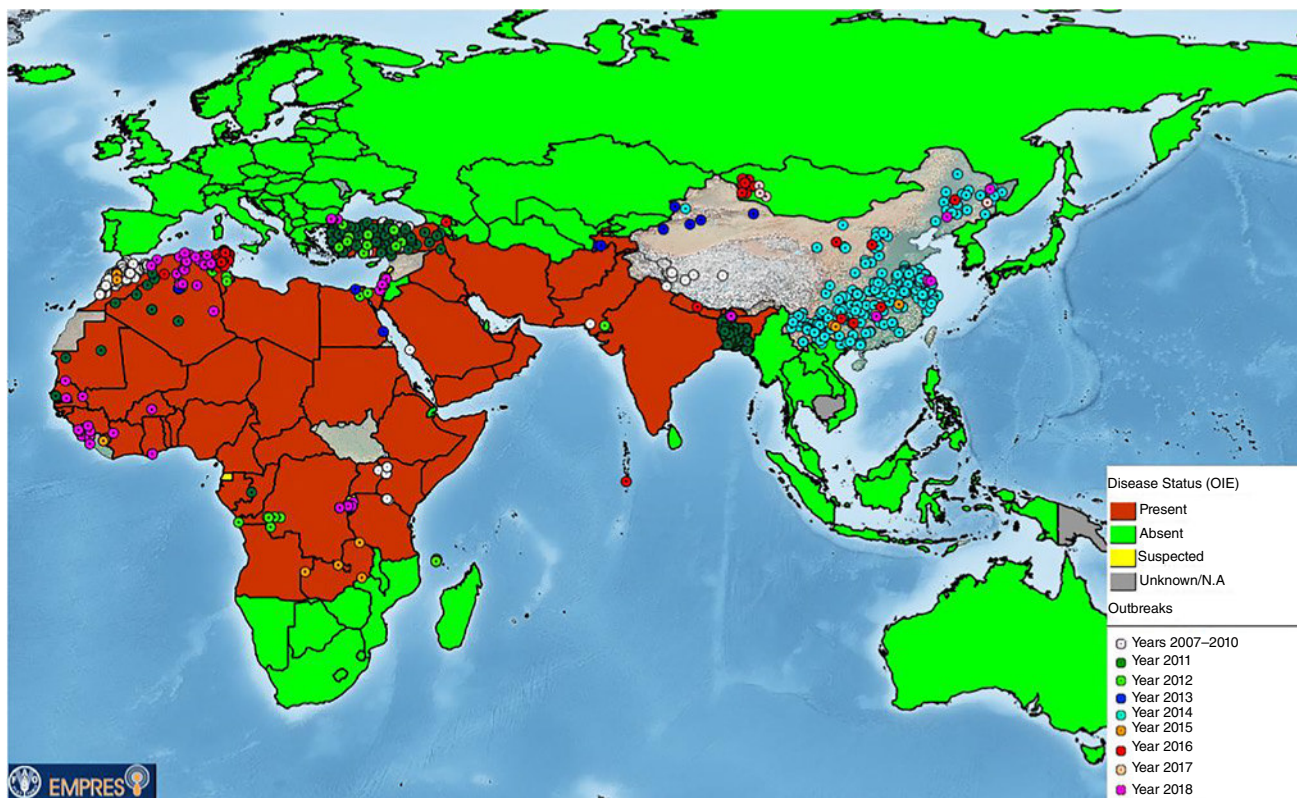


Figure 21.1 Peste des petits ruminants events from January 2007 to 31 December 2018 (by onset date). The map was produced by FAO AGAH/GLEWS using information from FAO EMPRES-i and OIE WAHIS.

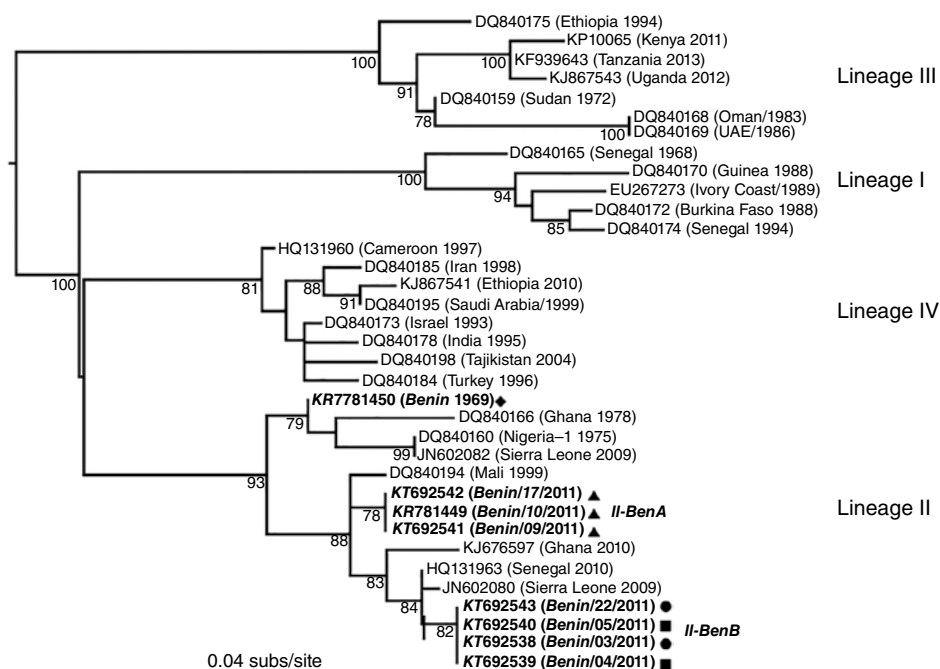


Figure 21.2 Phylogenetic tree of partial N gene sequences from different PPRV samples. Bootstrap support values (>70%) are shown. The tree is midpoint rooted for clarity only and horizontal branch lengths are scaled to the number of nucleotide substitutions per site. Source: Adombi et al. (2016).

have lost their pathogenicity through successive *in vitro* passages in cell culture (Diallo et al. 1989; Diallo 2004; Singh et al. 2009; Singh and Bandyopadhyay 2015). They all belong to genotypes II or IV (Table 21.1).

Among these attenuated PPRV vaccines, the PPRV Nigeria 75/1, lineage II and the PPRV Sungri 96, lineage IV are currently the most widely used. They are the strains for which most of the information on PPR vaccines is available (Diallo et al. 1989; Singh et al. 2009; Singh and Bandyopadhyay 2015; Hodgson et al. 2018). Both the Nigeria 75/1 and Sungri-96 vaccines have been extensively tested and validated. So far, no adverse reaction has been noted with those two vaccine strains after many years of

extensive use. Their genomes have been fully sequenced (Table 21.1). The recommended vaccination dose for sheep and goats is $10^{2.5}$ TCID₅₀/animal (OIE 2018).

21.3 Immune Response and Duration of Immunity

The main characteristic of the pathogenesis of PPRV infection, as for all other morbilliviruses, is the profound but transient immunosuppression induced by the virus in its host with the consequence of increased susceptibility to opportunistic infections and increased mortality (Rajak

Table 21.1 Live attenuated PPRV vaccine strains commercially available (2018).

Vaccine strain	Country of origin	Animal species of origin	Lineage	Full genome sequence availability
Nigeria 75/1	Nigeria	Goat	II	Yes GenBank no. X74443
Sungri-96	India	Goat	IV	Yes GenBank no. KF727981 GenBank no. KJ867542
Arasur 87	India	Sheep	IV	Not available
Coimbatore	India	Goat	IV	Not available
Titu	Bangladesh	Goat	IV	Not available

et al. 2005). This immunosuppression is a consequence not only of the direct effect of the virus multiplying in and killing lymphoid cells but also specific morbillivirus mechanisms that overcome the host immune response, such as interference with the action of innate or induced immune responses or the blocking of interferon synthesis (Servet et al. 2003). However, although profound, the immunosuppression induced by morbilliviruses is transient and recovery from the disease is usually followed by the establishment of a strong, specific, and long-term protective immune response of the host (Servet-Delprat et al. 2003; Cosby et al. 2006).

Attenuated morbillivirus vaccines seem to have less immunosuppressive capacity compared with wild-type viruses but to have conserved their strong immune-stimulating characteristic (Cosby et al. 2006). Antibodies to PPRV are detected in animals as soon as 1 week after PPRV infection/vaccination. The vaccinated animals are protected against PPR for at least 3 years, and probably for their lifetime (Diallo et al. 2007; Sen et al. 2010; Zahur et al. 2014). Young animals born from dams that have been previously PPRV vaccinated or that have recovered from PPRV infection retain maternal anti-PPRV antibodies for up to 3–4 months (Ata et al. 1989; Bidjeh et al. 1999; Awa et al. 2002; Bodjo et al. 2006; Diallo et al. 2007; Balamurugan et al. 2012).

21.4 Desired Specifications When Ordering Vaccine

All PPR vaccines currently in use are:

- live attenuated PPR virus and are produced in Vero cells
- thermolabile so the vaccine must be supplied in conditions that minimize the loss of activity: freeze-dried or dehydrated and kept cold
- not compatible with tests that allow differentiating infected from vaccinated animals (DIVA) (Diallo et al. 2007).

All the above characteristics should be taken into consideration when ordering PPR vaccine and desired specifications are as follows:

- *Type of vaccine*: freeze-dried or dehydrated PPR attenuated cell culture vaccine, produced in Vero cells in accordance with the OIE standards (OIE 2018).
- *Quality control certificate*: vaccine quality controlled by an independent institution recognized by the OIE and/or FAO for vaccine control. The vaccine quality control certificate issued by the independent institution should be made available to the buyer.
- *Cold chain*: vaccine should be stored and supplied in a cold chain (maintained at 4–10°C with ice packs during the

transport). Each individual package should contain vaccine vial monitors (VVMs) (www.who.int/immunization/documents/IIP2015_Module2.pdf).

- *Dose of vaccine*: one dose of the attenuated virus vaccine for a sheep or goat must contain at least $10^{2.5}$ TCID₅₀ of live virus, the OIE recommended dose (desired dose: 10^3 TCID₅₀).
- *Packaging*: the vaccine is to be supplied in vials of (number of doses/vial to be specified by the buyer) with the equivalent appropriate diluent to be used for reconstituting the freeze-dried vaccine just before use. Each vial should be labeled with the number of content doses, the identification number (production lot number), and an expiry date. An instruction manual must be provided with the vaccine.

21.5 Quality Assurance and Control Testing

Each batch of vaccine, before delivery, should be tested and certified as free of extraneous agents (bacteria, fungi, mycoplasma, and other viruses). Bovine viral diarrhea virus (BVDV) is a frequent contaminant of sera used for cell culture so care has to be taken to avoid using such contaminated sera at any step of vaccine preparation.

The safety of the vaccine master seed must be tested in laboratory animals to document its freedom from nonspecific toxicity. The PPR virus identity of the vaccine must be tested and its potency must be proved in animals (test to be done only with a sample of the master seed).

As the residual moisture can affect the half-life of the vaccine during storage, its content must not exceed 2% in the final freeze-dried (or dehydrated) vaccine.

A test should prove that no virucidal activity has been detected in the diluent to be used with the vaccine.

21.6 Vaccine Application for Disease Control

21.6.1 PPR Control: The Vaccination Strategy

As PPRV transmission from excreting animals to naïve animals is mainly brought about by close contact, PPR can be controlled efficiently by application of strict sanitary preventive measures which consist of: (i) restriction of importations of susceptible animals from infected areas to disease-free areas, (ii) in case of outbreaks, implementation of a stamping-out policy, followed by disinfection of premises and compensation of affected farmers.

As most PPR-endemic areas are developing countries, these drastic measures are difficult to implement. Therefore, the main means available for the efficient prevention and control of PPR in these countries is by vaccination. In the PPR-GCES (Anonymous 2015), PPR vaccination should be carried out according to the epidemiological situation of each area/country. It is suggested that vaccination of animals older than 4 months be implemented in two successive years followed by another one or two more years of vaccination targeted to only new animals in the flock or those which were less than 4 months old during the previous vaccination rounds. This strategy takes into consideration the fact that kids and lambs born from dams previously vaccinated or having recovered from natural infection have passive immunity that lasts for about 3 months (Bidjeh et al. 1999; Awa et al. 2002; Bodjo et al. 2006). As that immunity might interfere with vaccination, it is advised not to vaccinate animals less than 4 months old in PPR-endemic areas.

The actual vaccination program and number of vaccination rounds (one or two per year) may differ from this general scheme according to the specific epidemiological situation and the animal production system in the target area. In the PPR-GCES, three major production systems have been identified: rangeland pastoralism, mixed farming, and commercial periurban and urban systems. The flock population turnover (births and other introductions of unvaccinated animals on the one hand versus deaths and off-take due to sales, for example, on the other hand) will differ from one production system to another. Animal turnover tends to be higher in the humid farming and commercial production systems compared with the pastoralist ones. Preliminary epidemiological investigations may also identify critical areas where vaccinations may be needed to stop spread of disease to currently free areas. Depending on the assessment and surveillance data, the vaccination should be time-bound, with high coverage, to achieve a population immunity rate (PIR) of at least 70%, a rate that is estimated in the PPR-GCES to be needed for PPR elimination (Anonymous 2015; Hammami et al. 2016, 2018). This threshold has been suggested according to the experience in Morocco after its first PPR outbreak in 2008 (Ettair 2012; Hammami et al. 2018). The strategy of high-coverage vaccination is more efficient for PPR control and eradication and less costly than continuous, low-coverage annual vaccination campaigns. Hammami et al. (2018) indicated that vaccination coverage must be higher than 60% in order to reach the 70% threshold of postvaccination immunity rate recommended in the PPR-GCES. It is noteworthy that with the current live attenuated PPR vaccine, emergency vaccination of animals in the face of a PPR outbreak can prevent its extension.

21.6.2 Possible Combination of PPR Vaccination With That for Other Small Ruminant Diseases

Combining PPR vaccination with vaccination for other priority diseases is highly cost-effective, as the major cost of a vaccination program is related to the delivery system (storage, transport, technical staff, etc.), the cost of which does not change much whether one or more diseases are targeted for control at the same time. The disease(s) to be controlled along with PPR must be identified as priority disease(s) for the country/region by veterinary services. Good examples of such diseases are sheep pox and goat pox, which not only have a similar distribution to PPR but also are alike in being controlled by live attenuated viral vaccines produced in cell cultures. Some preliminary studies have demonstrated the feasibility of combined PPR and sheep pox/goat pox vaccination (Martrenchar et al. 1997; Hosamani et al. 2006; Chaudhary et al. 2009).

21.7 Monitoring and Evaluation of Vaccination Campaigns and Their Effectiveness

To assess the results of a vaccination campaign, the PPR-GCES includes a postvaccination evaluation (PVE) tool (Anonymous 2015). This is a guide, based on performance indicators, describing methods to assess the immunity of small ruminant populations and to measure changes in the level of PPR outbreaks and/or small ruminant productivity. When a failure of vaccination is noted, its cause has to be investigated and corrective measures implemented. The success of a vaccination program depends upon many factors such as: (i) the vaccine quality, (ii) the effectiveness of the vaccine delivery system, and (iii) the targeted population coverage. All these factors must be monitored regularly, along with the host immune response during the vaccination campaign.

21.7.1 Vaccine Quality

It is recommended that vaccination campaigns should use vaccines that have been quality controlled independently of the manufacturer.

21.7.2 Vaccine Delivery Chain

The vaccine delivery chain that starts from the vaccine producer up to the moment of vaccination in the field is critical for the success of a vaccination campaign. As all current commercial PPR vaccines are live attenuated PPRV that are

thermolabile, they must be maintained in a cold chain from production up to the moment of vaccination, in order to avoid inactivation of the virus and to ensure that the host has received the correct vaccine dose. The freeze-dried PPR vaccine is stable at +4–8°C for at least 2–3 years. As the half-life of PPRV in suspension is about 3 hours at 37°C (Diallo 2010), it is recommended to use the vaccine within 30–60 minutes after reconstitution of the freeze-dried product, depending on the diluent. Water, even of good quality, must never be used as a diluent to reconstitute the freeze-dried vaccine as this will result in a dramatic reduction of the vaccine titer (A. Diallo, personal observation).

The vaccination campaign must be planned and organized in a way that provides field users with sufficient vaccine at the right time. This is a challenging task in many developing countries, where veterinary services may not be well equipped and where access to remote and pastoral husbandry areas may be difficult. Such difficulties may have an important impact on the vaccine coverage. As already indicated above, it is estimated in the PPR-GCES that a coverage rate of at least 70%, based on the serology response, is needed for a successful eradication program (Anonymous 2015). Therefore, postvaccination serology surveys are important in evaluating vaccination effectiveness and success of the campaign.

21.7.3 Vaccination Campaign Coverage and Seromonitoring

Ideally, before the campaign, or on the day of vaccination, particularly in an enzootic zone, a sero-survey should be conducted to establish the baseline prevalence of PPR antibodies within the target population. Serological surveys that are conducted after vaccination will have the following objectives:

- to evaluate vaccination effectiveness by estimating the number of epidemiological units that show seroconversion after each round of vaccination
- to evaluate population immunity at a given time and over time after several vaccination campaigns by comparison with the results prior to vaccination of the target population.

Information on the age of animals from which sera are collected will allow the results to be stratified by age for more informed analysis.

In the PPR-GCES PVE tool, guidelines are provided for serum sampling protocols and for interpretation of the results. Although the prescribed test for PPR serology is the virus neutralization test (VNT), the assay that is most used currently for testing sera for PPR antibodies is the

enzyme-linked immunosorbent assay (ELISA) and commercial kits that are based on this technology (Saliki et al. 1993; Anderson and McKay 1994; Libeau et al. 1995; Singh et al. 2004a; OIE 2018).

In addition to serological monitoring, the effectiveness of the vaccination campaign can be evaluated by recording PPR incidence/prevalence following passive and active surveillance. The success of the vaccination should result in a dramatic reduction of the disease incidence, even its absence, and an increase of animal productivity in the vaccinated area. Any detected vaccination failure must be investigated to identify its possible cause and required corrective actions. The possible sources of failure and that need regular checks/evaluations are as follows:

- *Vaccine quality*: vaccine samples must be collected randomly and submitted to laboratory quality control, even if a quality certificate was provided by the vaccine producer.
- *Vaccine storage*: the quality of the cold chain from the central vaccine storage up to its delivery in the field. The vaccine should always be kept cool until the moment of vaccination.
- *Quality of veterinary services*: vaccination teams, public and private, have to be trained for the task.
- *Vaccine coverage*: as indicated earlier, a coverage rate of at least 70% of the target population should be obtained. This needs careful planning, including sensitization of sheep and goat owners, to encourage them to participate in the vaccination campaign.

21.8 Availability and List of Manufacturers

More than 30 institutions in Africa, the Middle East, the Near East, and Asia produce PPR vaccines. The list in Table 21.2 may not be complete.

The Pan African Veterinary Vaccine Centre of the African Union (AU/PANVAC) provides independent testing of the quality of PPRV vaccine to be used in Africa, whether produced there or elsewhere. Its activity is recognized by both the FAO and OIE and it is now the OIE collaborating center for veterinary vaccine quality control.

21.9 Summary and Conclusions

Peste des petits ruminants is an important livestock disease, present, in 2016, in about 70 countries in Africa, the Middle East, Near East, and Asia. It threatens the production of more than 1.7 billion sheep and goats, representing

Table 21.2 List of PPR vaccine manufacturers (2018).

Name	Address	Country	Tel	Fax	Email address/website
Botswana Vaccine Institute	Broadhurst Industrial Site, Lejara Road, Private Bag 0031, Gaborone	Botswana	+267 391 27 11	+267 3956798	bvigim@mega.bw
LANAVET	BP 503 Garoua	Cameroon	+237 227 13 05/999 98 18	+237 999 9875	lanavet@iccnnet.cm
National Veterinary Institute	P.O. Box 19, Debre-Zeit	Ethiopia	251-1-33 84 11	251-1-33 93 00	nvi-rt@telecom.net.et
Kenya Veterinary Vaccines Production Institute (KEVEVAPI)	P.O. Box 53260, Nairobi 00200	Kenya	+254 20 2611143; +254 20 3540071	+254 20 2472881	vaccines@wananchi.com; vaccines@kevevapi.org
Laboratoire Central Vétérinaire	BP 2295, Bamako	Mali	+223 224 33 44 /224 66 53	+223 2249809	labovetmali@labovetmali.org
Société De Productions Biologiques et Pharmaceutiques Vétérinaires BIOPHARMA	Avenue Hassan II km 2-BP 4569-10000 Rabat	Morocco	+212 537-69-16-92	+ 212 537-69-16-89	www.biopharma.ma/index.php/fr/info@biopharma.ma
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(Continued)

Table 21.2 (Continued)

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Intervet India Pvt Ltd, MSD Animal Health	33, Intervet House, Behind Eden Garden, Pune Nagar Road, Maharashtra 411014	India	+91-20-66207876, +91-9890623301, +91-20 6605 0410 +91-20 2705 1800, +91-20 6605 0400		info.india@intervet.com, sreenivasulu.kilari@sp.intervet.com sreenivasulu.kilari@merck.com
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Bio-Med Pvt. Ltd.	C-96, Site No. 1, Bulandshahar Road, Industrial Area, Ghaziabad-201 009 (U.P)	India	+91-120-2700881, +91-120-2753255, +91-120-4157534	+91-120-4340219	saryugarg@yahoo.com

Brilliant Bio Pharma Pvt. Ltd.	6-2-1012, TGV Mansions, 3rd floor, Khairatabad Rd, Indira Nagar, Khairatabad, Hyderabad, Telangana 500004	India	+91-40-66667464, +91-40-66772726 +91-40-66104915, +91-40-66772725	brilliantvetvac@rediffmail.com exports@bbpl.co.in domestic@bbpl.co.in
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Institute of Animal Health and Veterinary Biologicals (IAH&VB), Bengaluru	KVAFSU, Hebbal, Bengaluru-560024	India	+91-802341 1502	+91-8482-245107/245241 info@iahvb.com
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Disclaimer: It was the authors' intention to list all vaccine producers and are not responsible for the safety, quality, and effectiveness of the vaccines listed in the table.

nearly 80% of the global population, with a yearly loss estimated at about US\$ 2.1 billion (Anonymous 2015). Indeed, Perry et al. (2002) identified PPR as one of the priority animal diseases whose control was considered important for poverty alleviation in western Africa and southern Asia.

With the success of the global rinderpest eradication that was officially achieved in 2011, a consensus is building that eradication of PPR is the next most viable candidate for livestock infectious disease eradication (Anderson et al. 2011; Baron et al. 2011; Albina et al. 2013). Indeed, a number of factors that have made possible the success of rinderpest global eradication would also apply to PPR: (i) a virus inducing life-long immunity in animals that have recovered from infection, (ii) this induced immunity is a sterile immunity as no carrier state follows the recovery from an infection (at least not known yet), (iii) existence of live attenuated vaccines that have preserved this strong immune capacity of the wild type, (iv) existence of only

one virus serotype, i.e. a single vaccine strain will protect animals against all other strains (v) affordable vaccine that can be produced and delivered at low cost (Silva et al. 2008), and finally (vi) specific and highly sensitive diagnostic tests are available for the surveillance and detection of the disease (Anderson and McKay 1994; Libeau et al. 1994, 1995; Couacy-Hymann et al. 2002; Kwiatak et al. 2010; Ashraf et al. 2017).

Given the availability of modern tools, the global PPR control and eradication program being initiated by the FAO and the OIE can be started now, provided that the funds required are made available. PPR vaccines that are in use currently are thermolabile but research has been conducted to improve their thermostability (Worrall et al. 2001; Sarkar et al. 2003; Silva et al. 2011, 2014). It is expected that new products derived from this research will be commercially available in the near future.

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