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Review

Toward peste des petits virus (PPRV) eradication: Diagnostic approaches, novel vaccines, and control strategies

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ABSTRACT

Peste des petits ruminants (PPR) is an acute transboundary infectious viral disease affecting domestic and wild small ruminants' species besides camels reared in Africa, Asia and the Middle East. The virus is a serious paramount challenge to the sustainable agriculture advancement in the developing world. The disease outbreak was also detected for the first time in the European Union namely in Bulgaria at 2018. Therefore, the disease has lately been aimed for eradication with the purpose of worldwide clearance by 2030. Radically, the vaccines needed for effectively accomplishing this aim are presently convenient; however, the availableness of innovative modern vaccines to fulfill the desideratum for Differentiating between Infected and Vaccinated Animals (DIVA) may mitigate time spent and financial disbursement of serological monitoring and surveillance in the advanced levels for any disease obliteration campaign. We here highlight

what is at the present time well-known about the virus and the different available diagnostic tools. Further, we interject on current updates and insights on several novel vaccines and on the possible current and prospective strategies to be applied for disease control.

1. Introduction

Peste des petits ruminants (PPR) is recognized as kata, ovine rinderpest, goat plague, or stomatitis-pneumoenteritis syndrome. It is a highly infectious viral disease of domestic and wild small ruminants across Asia, the Middle East, and Africa (Banyard et al., 2010). PPR is considered an emerging disease in new geographical regions that have not been identified triggering substantial socioeconomic deficits (Banyard et al., 2014). PPRV is included in *Morbillivirus* genus within the family Paramyxoviridae. Over decades, te two available attenuated vaccine strains Sungri 96 and Nigeria 75/1 have been utilized in several vaccine formulations for controlling the disease in endemic regions with outstanding achievement (Sen et al., 2010). At the time, different commercial enzyme-linked immunosorbent assay (ELISA) kits are used for evaluating the seropositivity in a population with higher sensitivity and specificity to detectantibodies targeting the virus H and N proteins (Balamurugan et al., 2014). Yet, there are presently no tools that empower DIVA capability. Several novel vaccines have a promising clue to the DIVA idea that may have a central role in mitigating PPR disease in endemic regions where they are required for succeeding the eradication campaign.

2. PPR taxonomy

PPRV is an RNA virus belonging to genus *Morbillivirus*, within Paramyxovirinae sub-family inside Paramyxoviridae family of the order Mononegavirales. together with other important veterinary viral microbes such as *rinderpest virus* (RPV), *canine distemper virus* (CDV), the *marine morbilliviruses phocine distemper virus* (PDV), *dolphin morbillivirus* (DMV) and *porpoise morbillivirus* (PMV) and the only *human measles virus* (MV) (Barrett et al., 1993; Taubenberger et al., 2000). Recently, new morbilliviruses have been characterized and reported, containing innumerable morbilli-like viruses in bats or rodents (Drexler et al., 2012) and *feline morbillivirus* in cats (Woo et al., 2012). This order incorporates relevant viral pathogens in the veterinary and medical discipline.

While some members of morbilliviruses have a restricted host range (e.g., the rinderpest virus) which infects only the members of Artiodactyla order and to date only reported aquatic mammals cetacean morbilliviruses, other members can infect multiple species such as measles virus which infects humans and non-human primates. Other members (e.g., PPRV) are characterized by their broader host range as they are even capable of infecting not only small ruminants but can also cause massive camelids mortalities (Roger et al., 2001) and have in felids a single event (Balamurugan et al., 2012a), even though

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additional verifications of these reports are required. This is similar to morbillivirus *CDV* that had been ab initio deemed limited to canids, but it has been depicted in many species, encompassing polar bears, tigers, lions, hyenas, and non-human primates (Buczkowski et al., 2014). *Feline Morbillivirus* had also been originally stated in Hong Kong in domestic cats (Woo et al., 2012), However, recent identifications were also reported in Japan (Furuya et al., 2014; Sakaguchi et al., 2014), with proof of genetic recombination occurrence in few isolates (Park et al., 2014).

Although the PPRV replication and transcription are still uncharacterized, most of our knowledge regarding PPRV molecular biology and virus structure is mainly based on their comparison to a large extent to the well studied members of the family such as measles and some extent to CDV and RPV. This is attributed to the fact that distinct species in the morbillivirus genus share similar characteristics with conserved properties. Based on these similarities, many deductions can be obtained from the same genus members studies

3. PPRV characteristics

3.1. PPRV genome structure

The size of PPR viral particles lies between 400 to 500 nm (Gibbs et al., 1979). PPRV is a polymorphic envelope virus as shown by negative-stain electron microscopy getting from the infected cell membrane during virus budding. This envelope contains many peplomers of glycoproteins as the viral fusion (F) and haemagglutinin (H) glycoproteins (Fig. 1).

PPRV genome made up a single-stranded non-segmented negative-sense RNA molecule encapsidated by nucleoprotein (N) constituting a helical nucleocapsid, combined with the phosphoprotein (P; polymerase complex) as co-factor and the RNA-dependent RNA polymerase (L; large polymerase) to make up the ribonucleoprotein (RNP) complex. These RNP complex are found inside the viral envelope and look as a helical structure having a herringbone appearance. The matrix protein (M protein) forms an envelope inner surface serving as a bridge between the RNP and cytoplasmic tails of the F and H membrane glycoproteins. This virus is polyploidy and as such incorporate more than one functional and independent encapsidated genome in the appearance of RNPs (Rager et al., 2002). The polyploidy results in virions general pleomorphic shape.

The PPRV genome consists of 15,948 nucleotides (Bailey et al., 2005) and adapted as a multiple of six (rule-of-six) like a typical feature for other paramyxoviruses (Calain and Roux, 1993), even though a single virus has an insertion of hexameric nucleotide in an untranslated region (Bao et al., 2014). The encapsidated genome by nucleoprotein is pivotal for efficient propagation and replication of the genome (Bailey et al., 2007).

PPRV genome comprises six transcriptional units called 3' N, P, M, F, H and L 5' in order which encode the structural proteins N, P, M, F, H and L, respectively (Bailey et al., 2007). A more two non-structural proteins are evoked from the P gene, namely C and V via utilization of a substitute start codons and RNA editing, consecutively (Mahapatra et al., 2003). The conserved intergenic (IG) trinucleotides separate transcriptional units from each other. The 3' and 5' terminal sequences of PPRV genome are conserved and complementary. Similar to other morbilliviruses, they have a vital role in regulating RNA genome replication, transcription, and packaging during viral growth (Banyard et al., 2005). The virus leader region together with the 3' untranslated region (UTR) of N gene comprise the genome promoter (GP). In a similar way, the 5' UTR of the L gene together with a short trailer sequence form the anti-genome promoter (AGP) (Fig. 1). UTR between the F and M gene open reading frame (ORF) is extremely abundant in G and C nucleotides with 68–72% GC and is unusually longer than other UTRs. PPRV genome is relatively maintained with 8% at the amino acid level and a topmost difference of 12% at nucleotide (Muniraju et al.,

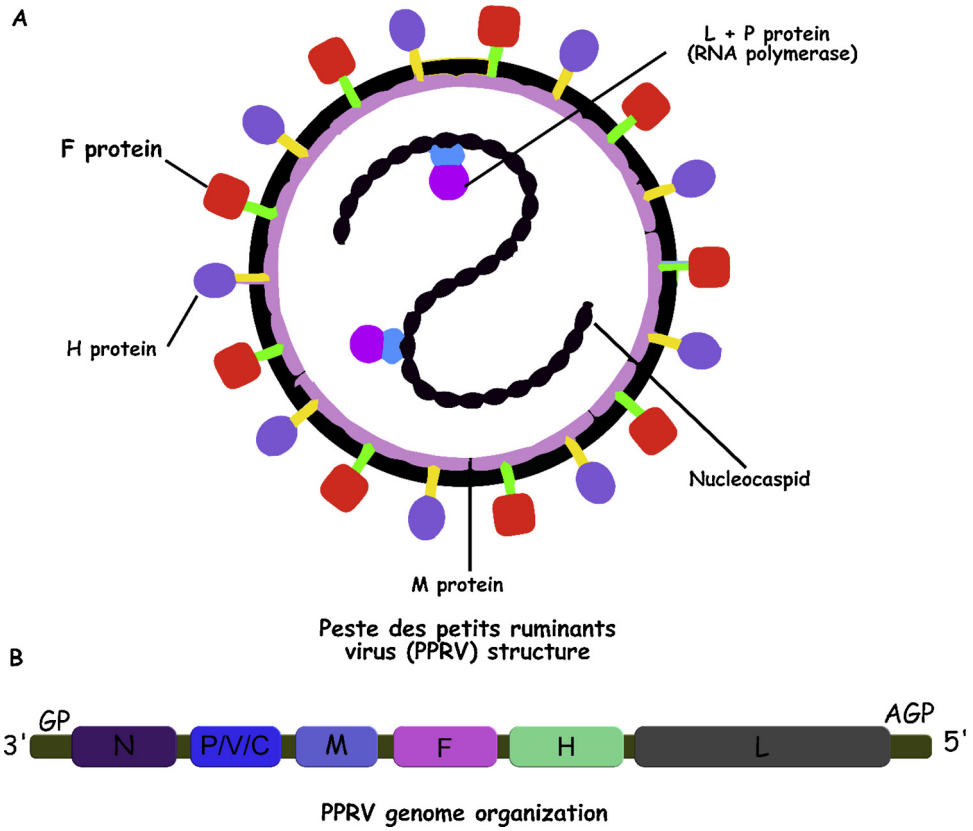

Fig. 1. Schematic illustration of PPRV structure (a) and PPRV genome organization (b).

2014).

The large protein 'L' of the morbillivirus genus is a multifunctional catalytic protein. It is necessary for viral genomic RNA transcription and replication. In addition, it has mRNA capping, polyadenylation activities and its methylation. The L protein of RPV has also guanylyltransferase (GTase), methyltransferase and RNA triphosphatase (RTPase) activities. It follows the ordinary pathway for capping mRNA. Recently the domain within PPRV L protein had been identified to have RTPase activity (Ansari et al., 2019).

4. Diagnosis

Similarities of PPR clinical signs and those of several diseases as bluetongue, rinderpest and contagious caprine pleuropneumonia hampers disease diagnosis. Therefore, disease occurrence should be confirmed by laboratory diagnosis. A complication of PPR clinical signs may occur due to secondary bacterial infections particularly *Mannheimia haemolytica*. The laboratory diagnosis of PPR disease is mainly based on virus isolation, the detecting viral antigens using lateral flow rapid tests or antigen capture ELISA or the viral RNA by RT-PCR, real-time (rt) RT-PCR, Loop-mediated isothermal amplification (LAMP) PCR. The diagnosis can also be performed by immunological / serological assays aiming to detect anti-PPRV specific antibodies by virus neutralization tests (VNT) or ELISA (Fig. 2). There is no doubt that sample collection and transportation affect sample integrity which in turn affects the efficacy of laboratory test. According to partial sequences of the N or F genes, PPRVs have been genetically categorized into four lineages associating with the geographic virus distribution.

In addition, the need for the region-specific test is essential due to cross-reaction among members of Morbilliviruses such as measles or canine distemper. False diagnosis is often seen in clinically healthy serologically positive cases. Such conditions are usually attributed to cross-reaction, previous vaccination, or subclinical infections as observed in Lao goat population (Burns et al., 2019).

After successfully eradicating the rinderpest, the FAO and the OIE have embarked an eradication strategy for global PPR control by 2030. This is one of the three key goals resulting from GF-TADs Global Steering Committee between FAO and OIE which as well includes strengthening the veterinary services and in parallel, preventing and controlling other major diseases of small ruminants.

The peak time for detecting PPRV nucleic acid in various body fluids is from 5 to 10 dpi which regard the most infectious period for contact transmission, the higher viral loadcan be detected via viral RNA detection techniques in nasal excretions from two days post infection (PI) until at least two weeks PI. On the other hand, percentage sample positivity is usually low in both saliva and eye swabs with intermittent detection in later PI in individual animals in fecal material than in other body fluids. Nasal swabs are considered the most suitable sample for molecularly diagnosing PPRV and for supporting the eradication program (Parida et al., 2019).

Although virus isolation is considered the gold standard test for diagnosing PPRV and is very useful for virus characterization and repository (Brindha et al., 2001; Sreenivasa et al., 2006), it detects only live virus, requires laboratories with tissue culture facilities and is less sensitive. However, diagnosis based on viral isolation is usually more accurate than those based on sandwich ELISA.

For antibodies detections, many assays are in use such as VNT, blocking ELISA, competitive (cELISA), and indirect ELISA. Filter papers represent a cost-effective and acceptable method of transporting whole blood samples to be later used for serological analysis (Torsson et al., 2019).

Due to the high sensitivity of VNT, it is commonly used for antibodies titration, seromonitoring and serosurveillance, and is considered the gold standard test representing the true indication for protection and OIE recommendation with high sensitivity and specificity. However, other types of ELISAs can also be used for seromonitoring and serosurveillance(Singh, Sreenivasa, Dhar, Shah et al., 2004). Although VNT is the most reliable test in differentiating the antibodies from different members of morbillivirus as the level of neutralization is higher in homologus PPR viruses than rinderpest virus, it needs tissue culture, live viruses, good quality samples and not feasible for a large number of samples. VNT depends on detecting the differences of paired serum samples collected during the outbreak or when clinical signs exist and following three weeks of the disease outbreak from the same animal. A significant 4-fold titer increment is relevant to the outbreak of specific disease. As an alternative to VNT, a haemagglutination inhibition (HI) test has been applied for quantifying virus neutralizing antibodies. For performing HI, the PPRV HA property is revealed to be changed in cell-culture-cultivated virus, and fresh RBCs are compulsory (Dhinakar Raj et al., 2000). To detect antigen, the counter Immunoelectrophoresis (CIE) techniques are to be generated for detecting antibodies resulted from PPR infection (Anderson and McKay, 1994; Tahir et al., 1998). Even though HI and CIE are straightforward to carry out tests and offer an alternative solution in limited-resources laboratories having lower sensitivity compared to the other antibody detection assays. The competitive and blocking ELISAs are primarily dependent on the hemagglutinin-neuraminidase (HN) protein of PPRV. The relative sensitivity and specificity of cELISA in reference laboratories are 94,5 and 99.4% respectively (Libeau et al., 1995). In case of a baculoviral expressing the recombinant N protein antigen the diagnostic sensitivity and specificity were (92.4%) and (98.4%) of this test respectively compared to those of VNT and commercial ELISA kits (Singh et al., 2006, 2004a).

The blocking ELISA had a 98.9% specificity and 90.4% sensitivity in comparison to the VNT (Anderson and McKay, 1994). Both anti-H and anti-N protein monoclonal antibodies-based cELISAs are convenient as commercial kits for detecting antibodies of PPRV. (Anderson and McKay, 1994; Libeau et al., 1995). Due to the non-infectious nature of the N protein antigen, their based cELISA kit has promising use in wide geographical regions, involving PPR free countries (Couacy-Hymann et al., 2007; Libeau et al., 1995), handling the live viruses should be done in PPR free countries under strict biosecurity levels and hence would not be regularly applied as a diagnostic tool.

For viral genome detection, several assays have been used. The multiplex TaqMan-based qPCR panel represents a rapid, sensitive and specific diagnostic tool for accurately detecting several sheep and goat viral pathogens (Xu et al., 2019).

For targeting the M gene, two tests (rt RT-PCR based on SYBR green and other based on hydrolysis) have been applied. Although both of them are used for the routine diagnosis, the latter has more sensitivity than conventional reaching 0.5 pg from total RNA and 0.1 of TCID50 (Balamurugan et al., 2010). The sensitivity of the rt RT-PCR based on SYBR green may reach 0–4 TCID50 of PPRV (Balamurugan et al., 2012b), however cautions must be undertaken to prevent cross-contamination. the one-step RT-LAMP Assay represents another simple, easy to use, and highly sensitive assay. Its sensitivity is comparable with that of rt RT-PCR ($1.41*10^{-4}$ ng total RNA) and could obviate the need of thermocycler that direct M gene. However, the presence of false positive results and is inapplicability as a field test limit its use (Li et al., 2010).

Tests targeting N gene or protein such as immunocapture ELISA or sandwich ELISA can be applied in diagnosis and clinical surveillance. These tests are user-friendly tests and can also be used in preliminary vaccine quality control, although their sensitivity is less than RT-PCR-ELISA and RT-PCR (Singh et al., 2004b). Another test targeting N gene or protein is the immunocapture ELISA/sandwich ELISA. The application of PCR-ELISA is promising as it delivers more sensitive results than RT-PCR and sandwich ELISA during the mild form and in early and late phases with a sensitivity detection of 0.1 TCID50/mL (Saravanan et al., 2004). Cell-ELISA has a 97.26% sensitivity in comparison with PPRV infectivity titration and possibility to circumvent the bias during PPRV titration (Sarkar et al., 2012). Radiolabeled cDNA probes assay is one of

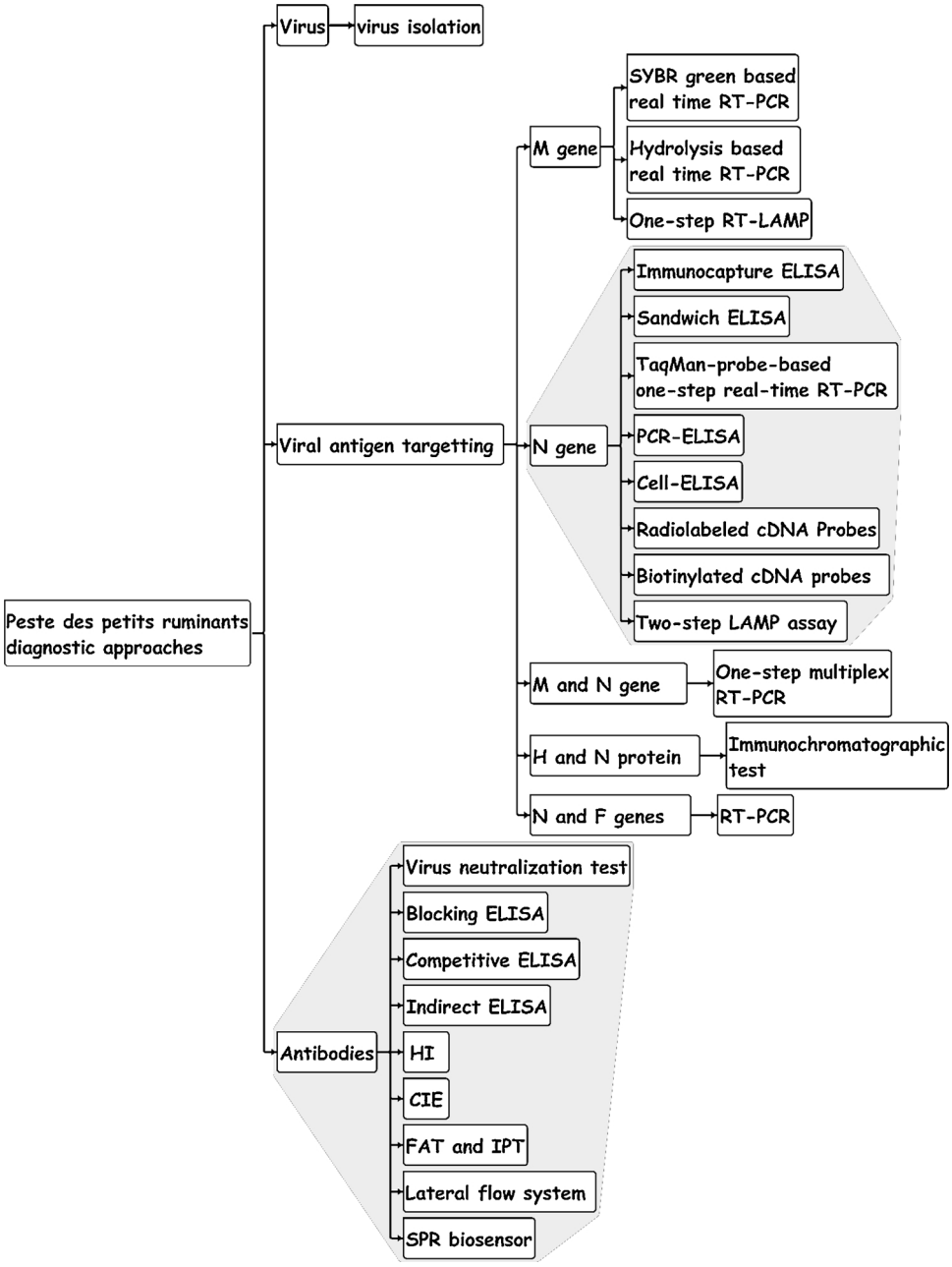

Fig. 2. Schematic illustration representing the available diagnostic techniques for PPR disease.

the sensitive assays that does not require live virus and can differentiate PPRV from rinderpest virus (Diallo et al., 1989), but it has hazardous to handlers unlike the Biotinylated cDNA probes that are safe for use, but are less sensitive (Pandey et al., 1992). Two-step LAMP assay has a greater sensitivity than conventional RT-PCR as it could detect 0.1 TCID 50/mL which can be visually assessed and could be applied as a regular diagnostic test in resource-poor laboratories. Although one-step rt RT-PCR based on taqMan-probe is a sensitive and rapid assay over traditional RT-PCR, with less prone for contamination to be utilized for detection and quantification, it needs a sophisticated instrument that is expensive, and its availability for routine diagnosis is limited. Its sensitivity in one study was 32 PPRV RNA copy and in another study was 8.1 cRNA copies (Bao et al., 2008; Kwiatek et al., 2011).

One-step multiplex RT-PCR is used for targeting M and N gene, but economically it cannot be used in routine diagnosis. Its diagnostic sensitivity reaches 100 fg of RNA (Balamurugan et al., 2006). Another test utilizes M, and N protein is the Dot-ELISA that can be used for easy and quick visual diagnostic techniques. Its 82% sensitivity compared to sandwich ELISA must be taken into consideration (Saravanan et al., 2006).

The use of field pen-side immunochromatographic test targeting virus monoclonal H protein is rapid and an easy to perform test with less sensitivity than RT-PCR and ELISA as it can only detect 10^3 to 10^4 TCID50 (Baron et al., 2014). Their relative sensitivity and specificity is 84% to 95% respectively compared to RT-PCR. This test can diagnose PPR in the first four days PI. The normal RT-PCR can be used for N and F genes for clinical surveillance or diagnosis in a large scale. While false negative and false positive results come from RT-PCR based on F genes, the N gene-based RT-PCR showed high sensitivity than infectivity titration with 1000 fold increment (Couacy-Hymann et al., 2002; Forsyth and Barrett, 1995).

5. Control strategies

For global PPRV eradication, collaboration among governmental authorities, research centers, international organizations and funding agencies are needed. PPRV is an endemic disease in most African and Asian countries. It causes great economic losses of livestock to farmer and herders so that the application of an international control program is urgently required (Singh and Bandyopadhyay, 2015). However, it is preferred to use region-specific vaccines prepared from local isolates as the PPRV tends to mutate extensively. Alternatively, vaccine combination strategies are cost-effective and can be employed than the individual vaccination strategies containing one strain.

The epidemiological pattern of PPR and rinderpest (RP), as well as the techniques associated with their diagnosis and control, are comparable. The circumstances that enabled RP eradication are also largely present for PPR. The evolving strategy and opportunities for PPR eradication in light of current challenges, but also the lessons learned from other eradication strategies in human and animal health integrating epidemiology, economics and social science as tools for targeting and motivating vaccination which is very crucial to know for learning the strategical efforts from previous eradication strategies (Mariner et al., 2016). Cattle vaccinated with wild-type PPRV vaccine failed to develop RP infection following their challenge with living RPV experimental infection. However, vaccinated cattle with PPRV/Sungri/96 gave partial protection. Meanwhile, vaccination with PPRV/Nigeria/75/1 was no efficient to protect event infections of challenged cattle with RPV (Holzer et al., 2016a).

Preventive control measures should be applied in PPR free regions involving strict restriction of importing living animals or their products from PPR-endemic regions. The PPR could be expeditiously harnessed via isolating and sanitary slaughtering of infected animals (herds), proper disposable of carcasses, disinfecting the environmental materials, strict quarantine and animal movements control. PPR immunization is carried out with the commercial usable attenuated vaccines that stimulate an effective durable immune response for at least three years post-vaccination (PV) (Sen et al., 2010). This immune response results from solid cellular immune response and plays a significant role in PPR prophylaxis after a single inoculation without any side effects. The protection is conferred regardless of the circulating lineage type. Vaccination schedules currently require immunization at least every three years (Diallo et al., 2007; Sen et al., 2010). Animal vaccination starts at 4- to 6-months years old (Balamurugan et al., 2012c). Vaccination time is an essential hotspot in the PPR control programs, as introducing unvaccinated animals into susceptible population can result in the advent of the virus causing a fresh outbreak of the disease. The current vaccines need cold-chain to ascertain sustainment of inoculating maximal virus titer and the needed serological response to vaccination.

Another strategy (mass vaccination) needs to be replicated in countries having similar rearing environments and socio-economic concerns (Govindaraj et al., 2019). In addition, refugee camps, trade routes, animal markets and regions of animal crowding through droughts must be focused on monitoring, surveillance and interventions as a part of PPR control in a region (Spiegel and Havas, 2019). Vaccination of pregnant females against PPR indeed gives / induces a protective maternal immunity to their kids that can last up to 10 weeks of the age (Markus et al., 2019). Vaccination is one of the chief tools used nowadays for disease control. It prevents disease transmission by decreasing the number of susceptible population. Although mass vaccination strategies may be very expensive, classification of the resources into eight categories: vaccines, injection supplies, transport personnel, training, maintenance and overhead, surveillance, monitoring, and social mobilization will provide the decision-maker the cost of each step. In pastoral and mixed-crop livestock systems, components covered: vaccine cost; vaccine delivery from the manufacturer to the regional storage center; vaccine storage at the local facility; administration and transport of vaccine in the field; opportunity cost of farmer's time to be present during the vaccination; coordination of vaccination campaign; advertising and mobilization costs; vaccine wastage from missed shots and vaccine discards (Lyons et al., 2019). The high serum antibody titer recognized in local non-descript breed might be owing to their greater accommodation to the environmental condition (Begum et al., 2016). Mass vaccination of concentrated animals costs is lower than systems with scattered and less accessible animals. Concurrent vaccination of goats with PPR and foot and mouth diseases (FMD) vaccines or PPR vaccine alone revealed similar antibody kinetics against PPR virus up till 60 DPV (Mansoor et al., 2018).

As PPR outbreaks in Georgia revealed a closer phylogenetic relationship to viruses from eastern and northern Africa than to viruses from closer countries (Donduashvili et al., 2018), this raises the alert for controlling the PPR as an international mass vaccination for all countries together. The control phase of the global eradication and progressive control strategy founded on mass vaccination in endemic areas or countries was embarked by international organizations targeting animal health. This eradication is aimed by 2030. For ensuring PPR spread control in a specific epidemiological unit, a 70% post-vaccination immunity rate (PVIR) is required. Although mass vaccination implementation is very essential in PPR control, it is expensive and difficult in small farming systems with scattered livestock with restricted facilities. Utilization a PVIR seasonal matrix population model in different environmental conditions (sub-humid areas or semi-arid areas) and different vaccination scenarios (overall schedule, their vaccination coverage, and their delivery month) to attain the 70% PVIR. In sheep raised in semi-arid regions, the vaccination month did impact PVIR decline, although it did not occur in goats in rainy areas. Mass vaccination is expensive and difficult in small farming systems with scattered livestock with restricted facilities. Utilization a PVIR seasonal matrix population model in different environmental conditions (sub-humid areas or semi-arid areas) and different vaccination scenarios (overall schedule, their vaccination coverage, and their delivery month) to attain the 70% PVIR. In sheep raised in semi-arid regions, the vaccination month did impact PVIR decline, although it did not occur in goats in rainy areas (Hammami et al., 2018).

It is advisable to make seroconversion annually according to the world health organization (WHO) recommendation with the appropriate sampling methods to augur the control program efficiency and vaccination status effectiveness to reach ~ 70% (Balamurugan et al., 2018). A higher vaccine coverage inside villages and annual vaccination campaigns with the need of vaccination tactics adaptation to particular small ruminant population aspects and regional epidemiological context will lead to enhanced allocation of restricted resources and boost probability for eliminating PPR (Fournié et al., 2018).

All of these tactics are necessary for keeping the fraction of immune animals more than 71% threshold. The recombinant HF bestows earlier and more robust protection against both PPR and sheep and goat pox (SGP) protecting the exposed and unexposed sheep in against the disease with DIVA capability (Fakri et al., 2018).

Reduction the time from PPR identification in a herd to the herd vaccination will radically reduce the percentage of deaths resulting from PPR. This information will help in developing effective containment strategies for combating PPR outbreaks. A model using memoryless state transitions allowing Sensitivity Analyses (SA) to carry out to study how the virus propagation through a herd, and to identify effective control strategies for disparate herd configurations and environments (Mitchell et al., 2017).

As well, it is better to develop a good animal model for control strategies which expresses the clinical signs specific to each strain (Enchery et al., 2019). The inoculation route is also decisive in the degree and severity of the clinical signs (Enchery et al., 2019). These equirement are very essential in expressing the strain virulence in the animal model as the protection against infection with strains from lineages could be conferred via vaccination with one strain from other

lineages. The rat model is found to be a useful model to predict vaccine responses in goats (Ronchi et al., 2016). The inactivated vaccine formulated with a delta inulin adjuvant constitutes an attractive alternative to living attenuated vaccines for PPR vaccination campaigns in the non-endemic areas (Ronchi et al., 2016).

The main limitation of the existing PPR vaccine in developing countries is the need for continuous refrigeration. Efficient control programs require the development of a lyophilized vaccine that can extend its utility in the field without refrigeration for a long time. Vaccines produced using lactalbuminhydrolysate sucrose (LS) and the rinderpest method of lyophilization characterized by their high thermostability for utilization without the need of a cold-chain containment for up to 30 days. Such formulation will greatly impact vaccine delivery for PPR global eradication (Kumar et al., 2017).

PPR affects many of the worldwide poorest communities and developing countries which depend on farming small ruminant for their continual and subsistence. PPRV endemicity is an everlasting risk to their livelood. Moreover, PPRVs outbreaks usually have severe socio-economic consequences on the population, there is a lack of basic and applied virological research in several critical regions with respect to PPRV. The development of strong diagnostics and next-generation advanced vaccines based on a better understanding of disease epidemiology and transmission, taking into consideration the role of wildlife reservoirs are urgently required (Baron et al., 2017).

Substantial seasonal and annual variation in mating, offtake rates and mortality lead to complex population dynamics which possibly change the consequential population PVIR (PIR) (Hammami et al., 2016) and consequently be momentous to cogitate for implementing vaccination campaigns.

6. Vaccines types for combating PPR

6.1. Attenuated vaccines

As PPRV is antigenically close relative to RPV, utilization of attenuated tissue culture RP vaccine is found to be protective as a heterologous vaccine in spite of the shortage of detectable PPRV-neutralizing antibody (Mariner et al., 1993). Even so, the employment of this vaccine was forbidden during the rinderpest eradication campaign, inability for DIVA and the probability of PPR replication in the challenged animals and their spread to the contact animals. Attenuation of PPRV was attempted to be done after 65 serial passage in primary cell culture after their growth on sheep liver cells-based cell lines (Gilbert and Monnier, 1962). Nigeria 75/1 strain, a virulent strain can be attenuated by 63 serial passage on Vero cells (Adu et al., 1990) Other PPRV strains such as Sungri 96, and Coimbatore 97, Arasur 87 can also be utilized for vaccination after 75 passage in Vero cells (Singh et al., 2010). Although nowadays, Sungri 96 and Nigeria 75/1 are commonly used vaccine preparation, the use of vaccine based on Arasur 87 is restricted to India (Fig. 3). Serological investigation by ELISA and VNT concluded that the use of PPRV/Nigeria/75/1 (N75) based vaccine induces a stronger antibody response than those based om PPRV/India/Sungri/96 (S96). However, S96 based vaccines lead to a stronger cell-mediated immunological response, as detected by interferon gamma production and virus antigen-induced proliferation. Although both vaccines evoked similar numbers of PPRV-specific CD8 + T cells, S96 based vaccines could stimulate a much higher number of CD4 + T cells particularly reacting with the virus. In spite of these qualitative and quantitative variations in the triggered immunity subsequent to vaccination, both vaccine types protected clinically against challenge with all four PPRV lineages (Hodgson et al., 2018).

With the aid of various chemical stabilizers, these attenuated vaccines are nowadays available in freeze-dried form. The stabilizers are used to decrease the virus thermolability and diminish the necessity for the cold-chain (Mariner et al., 1993; Sen et al., 2010; Worrall et al., 2000). As thermo stabilizers, LS is found to be superior to weybridge medium (WBM), trehalose dihydrate (TD), and buffered gelatin sorbitol (BUGS) when applied for constructing vaccine utilizing PPRV Nigeria 75/1strain (Yaqub et al., 2016). The appropriate stabilizer formulations, suitable PPRV inoculums MOI and their working seed quality control will actually avoid the effective interfering particles (DIPs) that affect viral dynamics (Bora et al., 2018).

The peak PPRV replication at 9 dpi is correlating to the significant antiviral molecules (ISG15, IRF3, and IFN gamma) expression in both species. With PPR progression, decreased IRF3, ISG15 and IFN gamma expression is correlated to the decrease in N gene expression. The predominated IFN gamma expression in both infected and vaccinated animals shows a robust Th1 response. Persistent upregulation of the antiviral molecular signature - ISG15 and IRF3 even after 14 days PV most probably displays the continual stimulation of innate immune cells (Wani et al., 2018). Several immune key sensors and antiviral genes have been upregulated following 6 h PI including enrichment of immune system processes with 233 genes such asIRF7/IRF1, TLR7/TLR3, IFIT1/IFIT2, ISG20, IFITM3, TREX1 and IL27 (Manjunath et al., 2019). Actually, 2 weeks PV, upregulation of the antiviral molecular signature -interferon regulatory transcription factor 3 (IRF3), and the Interferon-stimulated gene 15 (ISG15) are still noticed/persisted. This reflects the continuous activation of innate immune cells. The lamp gamma expression is also predominating over IL4 in infected and vaccinated animals (Hodgson et al., 2018).

Vaccine-derived virus circulation would have a wider effect on effective monitoring of trade and movements of animals and disease spread, Furthermore, residual pathogenicity, which has not been seen during field trials in endemic countries (Saravanan et al., 2010).

6.2. Recombinant subunit vaccines and viral vector vaccines

As the thermosensitivity of the PPR vaccine, needs of combination program with other diseases and some levels of immunosuppression induced by PPR vaccine have encouraged researchers for developing subunit vaccines (Fig. 3). The two immunodominant PPRV integral membrane glycoproteins are the F and H or HN proteins. While the F protein is conjectured to virus-cell and cell-cell fusions by disrupting the target cell membrane, the H/HN glycoprotein is the key factor for virus attachment to the cells. These surface glycoproteins, especially morbillivirus fusion proteins are highly immunogenic and stimulate protective immunity.

Using the capripox vector as a vector virus against capripox and PPR has been well investigated. Capripox harboring H or F gene of rinderpest or PPR conferred protective immune response against PPR (Romero et al., 1995). Molecularly modified *capripoxvirus* strains to deliver homologous PPRV proteins H (Berhe et al., 2003) have also been demonstrated to protect goats or sheep against PPRV infection (Chen et al., 2010). Preexisting immunity against Capri pox is one of the hindrances affecting massive application of live vector vaccines in the field. It diminishes the capripox vector Kenya sheep-1 harboring F or H gene replication which sequentially decreases their expression. In turn, the produced immunity will be partially triggered (i.e. reduced antibody levels) for protecting animals against PPR challenges (Caufour et al., 2014). In addition, the preexisting immunity against PPR offers / provides complete protection only against capripox with partial immunity against PPR.

Other combinations were also developed such as the small ruminant morbillivirus (SRMV) delivering *echinococcus granulosus* (EG) 95 antigen. This combination triggers protective immune responses toward both pathogens and therefore can be considered as a potential candidate of bivalent vaccines. (Liu et al., 2019).

Recombinant adenoviruses (rAds) expressing PPRV glycoproteins have also been generated (Qin et al., 2012; Rojas et al., 2014a; Wang et al., 2013) eliciting strong cell-mediated and humoral immune response that protected goats (Herbert et al., 2014) and sheep (Rojas et al., 2014b). These types of vaccines could promote PPRV-specific T-

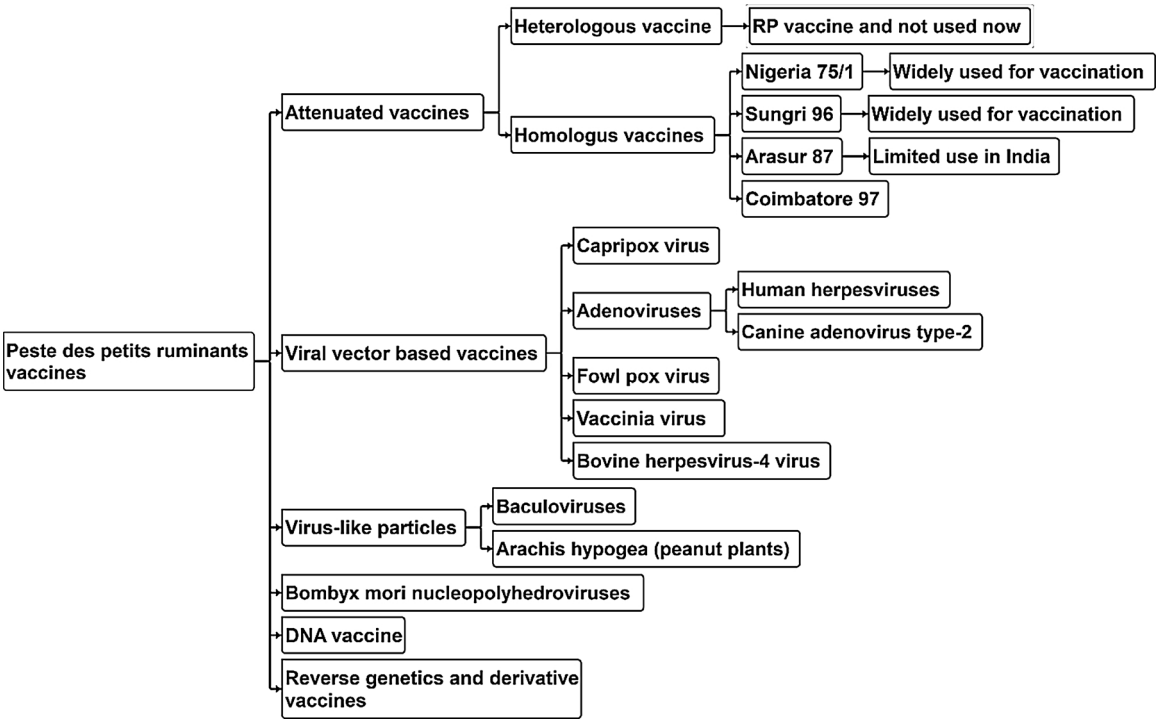

Fig. 3. Schematic illustration of different traditional and novel vaccines against PPR disease.

cell and B- response with no clinical symptoms and undetectable PPRV shedding were seen after their challenge in the vaccinated animals. These vaccines also could overcome the PPR induced T cell immunosuppression.

Three rAds what are rAd-F, rAd-H, and rAd- F-H might be promising candidate DIVA vaccines. The rAd-F-H delivering F-H proteins are found to be the most effective candidate one (Wang et al., 2013). Besides the human herpesviruses, a replication-competent canine adenovirus type-2 (CAV-2) delivering PPRV H gene has been used and stimulated a long-lasting immune response in goats (Qin et al., 2012). Such recombinant vaccines need to be tested on a large scale to investigate the duration of generated immunity, their potency, and safety as they generate immunity against some and not all viral proteins compared to live attenuated vaccine.

These recombinant adenoviruses expressing PPRV-H or -F proteins induce T cell responses to the same epitopes and result in memory T cell differentiation that could protect PPRV-challenged animals and permit DIVA capabilities (Rojas et al., 2017). Actually, 10^7 pfu of AdH can protect against PPRV challenge in goats. On the other hand, 10^8 pfu of either AdH or AdF provides apparent sterile protection (Holzer et al., 2016b).

Goats immunized with a fowl pox virus vaccine delivering PPRV F and H proteins showed a poor humoral immune in response to the heterologous proteins (Herbert et al., 2014). The modified vaccinia Ankara virus vector delivering PPRV H and F proteins protects goats against the disease appearance after two dose vaccinations (Chandran et al., 2010). This vaccine is very vital in DIVA and provides a stable inexpensive vaccine for the international PPR eradication Campania. Vaccinated animals produce antibodies that completely provide complete protection against virulent PPRV (Jones et al., 1993). Applying these types of recombinant viruses would help in the PPR eradication in endemic areas.

A recombinant bovine herpesvirus-4 (BoHV-4)-based live vector vaccine expressing a codon-optimized PPRV-H had been evaluated in immunocompetent C57BL/6 mice. This type of vaccine could elicit both humoral cytotoxic T lymphocyte, specifically T cell, and serum neutralizing antibodies against PPRV (Kamel and El-Sayed, 2019; Macchi et al., 2018).

6.3. Recombinant Bombyx mori nucleopolyhedroviruses (BmNPV) expressing the

RPV H protein and PPRV F protein on bud virions and the infected host cell surfaces promotes immune response toward PPRV or RPV in mice (Masmudur Rahman et al., 2003).

6.4. DNA vaccines

A suicidal DNA vaccine by virtue of *Semliki Forest virus* has been constructed using the PPRV H gene. This plasmid DNA vaccine induces strong specific Abs and cell-mediated lymphocyte proliferation response following BALB/c mice injection (Wang et al., 2015).

6.5. Virus-like particles (VLPs)

Several prokaryotic and eukaryotic expression systems have been employed for delivery of VLPs. VLPs consist of PPRV capsid proteins only and lack the infectious genome (Kamel et al., 2019). Their structures mimick the conformation and organization of parental virions but are unable to self-replicate in cells in order to construct safer vaccine candidates. Although baculovirus/insect cell systems, bacteria, plants, and larvae can be manipulated as systems for generating VLPs (Kamel et al., 2019), the process of assembly and release of VLPs from PPRV needs to be elucidated. The M protein is also shown to be essential for supporting VLPs assembly and release (Wang et al., 2017). The co-expression of all four proteins (N, M, H, and F) leads to the VLPs release with efficiency similar to that of the authentic virions (Wang et al., 2017). A recombinant baculovirus co-expressing PPRV H and N proteins within insect cells generates PPR VLPs that were then purified and induced antibodies in mice, potentiating their promising role as VLP-based vaccine candidate for providing protection levels (Liu et al., 2015; Liu, Wu, Li et al., 2014; Liu et al., 2014b). Co-expressing N and M proteins using baculoviruses in insect cells could be achieved at a relatively low level (Liu et al., 2014a). Codon optimization of the full-

length M and H genes with native N gene recombinant baculoviruses have co-expressed M, H and N proteins in insect cells at different levels (Liu et al., 2014b).

VLPs of PPRV could also be constructed with the same baculoviral system via simultaneously expressing PPRV M protein and F or H protein. The generated VLPs in such case demonstrate similar morphological feature to the native virus particles. Subcutaneous injection of PPRV-H or PPRV-F VLPs into goats and mice showing similar morphology to the native virus elicits IgG production specific to peste des petits ruminants (PRRV), high levels of virus neutralizing antibodies (VNA), and promoted lymphocyte proliferation. This type of vaccines induce comparable immune response with DIVA capabilities even without adjuvant to the PRRV vaccine (Li et al., 2014). Actually, the baculoviral expressing short hairpin RNAs (shRNA) have also the therapeutic potential to be used PPR (Nizamani et al., 2011).

PPRV HN protein has been expressed in *Arachis hypogea* (peanut plants) in a biologically active form which has a neuraminidase activity with retaining its natural conformed immunodominant epitopes. VNA responses were induced upon oral sheep immunization lacking any mucosal adjuvant. Additionally, specific anti-PPRV-HN cell-mediated immune responses have also been identified within mucosal immunized sheep (Khandelwal et al., 2011). This approach can be applied for the production of a heat-stable form of PPR vaccine.

Collectively, *Baculoviruses* subunit vaccines delivering H protein (Sinnathamby et al., 2001), F proteins (Rahman et al., 2003) or expressing H protein alone via transgenic peanut plants (Khandelwal et al., 2011) had been generated. However, further evaluation for potency and safety issues of the virus-like particle (Liu et al., 2014a) and DNA vaccines are needed (Yang et al., 2013).

7. Improvement of current attenuated vaccines

The ideal vaccine for a successful PPR eradication program should be thermostable, has DIVA capabilities and finally to be incorporated with other diseases as polyvalent vaccines. Combining the two antigens sheep pox/PPR or goat pox/PPR have shown a great promising result (Hosamani et al., 2006; Rajak et al., 2005). While only thermostable compounds are principally requisite for controlling the disease, vaccines that would significantly decrease the economic vaccination costs, which represents a significant issue in developing countries.

Reverse genetics advances lead to more progress in vaccinology especially for DIVA vaccines or marker vaccines by manipulating the cDNA from the RNA genome vaccines. These marker vaccines can be achieved by tagging (negative or positive) (Hu et al., 2012), modifying specific epitopes or inserting immunogenic antigens or heterologous epitopes (Das et al., 2000; Gao et al., 2008; Takeda et al., 2006; Walsh et al., 2000; Yamaji and Nakayama, 2014). Recently, positive or negative marker vaccines have been developed against PPR (Muniraju et al., 2015).

Establishing stable reverse genetics is not only supporting the progress of DIVA vaccines and associated diagnostic tests but it could also establish PPRV as a virus vector because many studies implied utilizing recombinant paramyxoviruses due to their genetic stability and relative easy reverse genetics systems (Ge et al., 2011; Niyokwishimira et al., 2018). Besides, stable reverse genetics improves the current understanding of the nature of PPRV and provides accurate and comprehensive molecular mechanisms of immune induction determining the viral factors implicated in immunosuppression during its early infection. Reverse genetics techniques are also great tools for studying the interplay between viruses and cellular receptors and supporting the discovery of the new receptors required for virus pathogenesis (Baron et al., 2017; Birch et al., 2013). Although these convenient reverse genetics systems for PPRV, data concerning additional application is still lacking (Niyokwishimira et al., 2018). Consequently, there is still a necessity to establish or upgrade existing systems to efficiently investigate the biology and pathogenicity of the virus, epidemiology, mechanisms of disease transmission, virus life cycle the molecular biology and pathobiology of PPRV which are not well defined (Munir et al., 2013; Niyokwishimira et al., 2018). Via these optimistically improved systems, various disciplines of fundamental and applied virology involving virus pathobiology, molecular biology and developing next-generation diagnostic tests and vaccines will be unveiled and subsequently will support the planned PPRV eradication program.

A negative marker vaccine based on the epitope binding site of the C77 monoclonal antibody which is the key monoclonal antibody that competes against in test sera antibodies in the competitive H ELISA. This vaccine is safe and as potent as the current Nigeria 75/1 strain vaccine (Muniraju et al., 2015). Unfortunately, accompanying test for DIVA capability using the C77 mAb failed under field conditions which open questions and investigations for altering to the epitope within H

8. Conclusion

PPR is a serious disease in Africa, Asia, the Middle East and at the borders of Europe (Bulgaria). Great efforts must be concentrated to control it. Deep understanding of the close-related RP and the utilization of strategies and lessons learned during its eradication will help us a lot to eradicate PPR. The use of different diagnostic methods and techniques directed for the identification of the virus itself and part of it, whether serologically or molecular biologically tests having high sensitivity and specificity is very important for the molecular epidemiological tracing needed for PPR eradication. The use of different strategies applied in different environmental conditions with use of novel vaccines (DNA, viral vector and VLP vaccines) or the improved living attenuated vaccines via reverse genetics will support the DIVA will facilitate PPR eradication.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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