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The threat of peste des petits ruminants: progress in vaccine development for disease control

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Abstract

Peste des petits ruminants (PPR) is a highly contagious animal disease caused by a virus in the genus *Morbillivirus*, family *Paramyxoviridae*. This infection is responsible for high morbidity and mortality in sheep and goats and in some small wild ruminant species. The huge number of small ruminants, which are reared in the endemic areas makes PPR a serious disease threatening the livelihood of poor farmers. Taking advantage of the closely relationship between rinderpest and PPR viruses, the attenuated rinderpest vaccine was used in the control of PPR. It is now replaced by the homologous attenuated PPR vaccine. Unfortunately, animals that have received this vaccine cannot be distinguished serologically from infected animals. With the advent of DNA recombinant technology, efforts are being made to develop effective PPR marker vaccines to enable such differentiation and which would allow countries to implement both vaccination and disease surveillance programmes at the same time.

Keywords: Peste des petits ruminants (PPR); Morbillivirus; Marker vaccine; Reverse genetics; Poxvirus recombinant vaccines

1. Introduction

Peste des petits ruminants (PPR) is a highly contagious disease of domestic and wild small ruminants. It is caused by a virus, peste des petits ruminants virus (PPRV), which is classified in the genus *Morbillivirus* within the family *Paramyxoviridae* [1]. The French nomenclature for this disease of small ruminants, *peste des petits ruminants*, which recalls "*peste bovine*" (rinderpest), is indicative of its clinical resemblance to rinderpest. However, it was also known as stomatitis pneumoenteritis complex [2,3] which better describes the clinical signs associated with this disease. PPR may manifest itself in different forms ranging from mild to severe but the latter form, the acute form, is dramatic and is the most characteristic. It is characterised by fever followed by oculo-nasal discharges, which are watery at the beginning of the disease but gradually become mucopurulent and may stick parts of the eyelids together (ocular discharges) or may partially block the nose (nasal discharges). At the time the fever starts to drop, appear diarrhoea and numerous necrotic lesions in the oral cavity. The mortality rate for this form of PPR is about 70–80%, most animals dying within the 10–12 days following the onset of disease. A consequence of this high mortality was the inclusion of PPR in the list A of the former animal disease classification of the OIE (Office International des Epizooties), the World Organisation for Animal Health. In the new OIE classification it is included

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in a group of economically important animal diseases, which must be notified to the Organisation. In all regions where PPR is endemic, it constitutes a serious threat to small ruminant production and thereby influences on the livelihood of poor farmers, the main owners of sheep and goats. Thus its control is a major goal for programmes aimed at poverty alleviation. Here we review the current epidemiological situation with regard to the disease and outline approaches adopted for the development of vaccines to control of PPR.

2. Epidemiology: PPR an emerging disease

2.1. Geographic distribution

Compared to rinderpest, which has been known for centuries, PPR is a relatively recently recognised disease. The first scientific description dates back to 1942. At that time Gargadennec and Lalanne [4] reported on an epidemic disease in Côte d'Ivoire which was clinically similar to rinderpest but which was affecting only small ruminants while in-contact cattle apparently remained healthy. Until the mid 1980s, PPR was regarded as a disease of West African countries but in 1984 its presence in Sudan was mentioned in a report [5] and this extended its endemic area to the eastern part of the continent. From that period onwards the known distribution of PPR has progressed to include the Middle East, Iran, the Indian sub-continent, Turkey and now some countries in Central Asia [6]. This expansion of our knowledge in the geographical distribution of PPR is certainly a consequence of the development and use of specific diagnostic tests, which can distinguish PPR from diseases with similar signs:

- Pasteurellosis due to the severe bronchopneumonia seen in the acute form of the disease. In fact, pasteurellosis coexists with PPR in many cases as a consequence of superinfection by *Pasteurella* [7].
- Rinderpest infection in small ruminants, the two diseases being difficult to differentiate clinically, apart from the bronchopneumonia which is common in PPR acute cases. Accumulated data on rinderpest in small ruminants indicate that they are less susceptible to this disease. Their infection by rinderpest viruses, even by highly virulent strains, is either sub-clinical or results only in mild clinical signs [8–11]. Therefore, some of the supposed rinderpest outbreaks documented in the past in small ruminant populations, particularly in India, may in fact have been due to PPRV infections [12].

2.2. Host range

At first, sheep and goats were considered the only animals susceptible to PPRV but its host range was extended to wild small ruminants in 1987 [13] after its identification in pathological samples from gazelles, which died in a zoo in the Arabian Gulf in the late 1980s. This virus was also suspected to have been involved in a respiratory disease, which affected camels in Ethiopia [14]. There was also a report of a rinderpest-like disease in Indian buffalo, which was caused by PPRV [15]. Rossiter and Wardley [16] reported that virulent PPRV strains can replicate in bovine lymphocytes, although less efficiently than in sheep and goat cells. Considering the immunosuppressive effect of PPRV as all other morbilliviruses [17,18], it may therefore be possible, depending on the age, and physical state of the host animal, that PPRV can occasionally overcome the innate resistance of large ruminants and lead to the development of clinical signs similar to rinderpest. This may explain the disease signs that had occurred in buffalo and camels following PPRV infection. This ability of PPRV to infect large ruminants could pose a serious threat to cattle populations in PPR endemic areas which, with the success of the global rinderpest eradication programme, are no longer vaccinated against rinderpest and so do not possess cross-protective immunity against this virus.

3. Structure of PPRV

Peste des petits ruminants virus (PPRV) is a paramyxovirus classified in the *Morbillivirus* genus along with rinderpest virus (RPV), measles virus (MV), canine distemper virus (CDV), phocine distemper virus (PDV) and dolphin morbillivirus (DMV). All these viruses are closely related and between them there are immunological cross reactions. PPR virions, as the other morbilliviruses, are enveloped, pleomorphic particles containing single strand RNA as the genome. It is composed of 15,948 nucleotides, the longest of all morbillivirus genomes sequenced so far (see Table 1) [19]. This genomic RNA is wrapped by the nucleoprotein (N) to form the nucleocapsid into which are associated two other viral proteins: the phosphoprotein (P) and the large protein (L). The phosphoprotein is the co-factor of L, the viral RNA dependant RNA polymerase (RdRp). To the viral envelope which derives from the host cell membrane are associated three viral proteins: the matrix protein (M) which is located inside the envelope and serves as a link between the nucleo-

Table 1
Comparison of rinderpest full-length genome sequence with those of some other morbilliviruses [19]

Virus	Genome length in nucleotides	Percentage of similarity with rinderpest
Rinderpest	15 882	100
Measles Virus	15 894	70.50
Peste des Petits Ruminants	15 948	66.98
Dolphin Morbillivirus	15 882	65.91
Canine Distemper	15 702	63.58

capsid and the two external viral proteins, the fusion protein (F) and the haemagglutinin (H). By this position, M plays an important role in ensuring efficient incorporation of nucleocapsids into virions during the virus budding process. The haemagglutinin allows the virus to bind to the cell receptor during the first step of the viral infection process. This binding is followed by the fusion of the viral envelope with cell membrane, a process mediated by F and this leads to the delivery of the nucleocapsids into the cell cytoplasm were takes place the viral multiplication. By their positions and their functions, both F and H are very important for the induction of protective host immune response against the virus and most of the neutralising antibodies are directed against H. However N, the most abundant and also the most immunogenic among PPRV proteins, does not induce protective immunity against the virus (A. Diallo, unpublished data). It has been used in the development of diagnostic tests [20–22]. Analysis of partial sequencing data of N gene has pointed out small variations between PPRV strains and has allowed their grouping into four lineages, which is better reflecting their geographical origins than the variations of genes of the external glycoproteins F and H ([6,23]; Shyam G. and Diallo A., unpublished data). Out of these four lineages (Fig. 1), three are from Africa and all Asian strains are grouped into lineage IV. This latter co-exist with lineage III, the East African PPRV group, in the Middle East, certainly as a consequence of small ruminant importations from both the East African and the Asian PPR endemic regions.

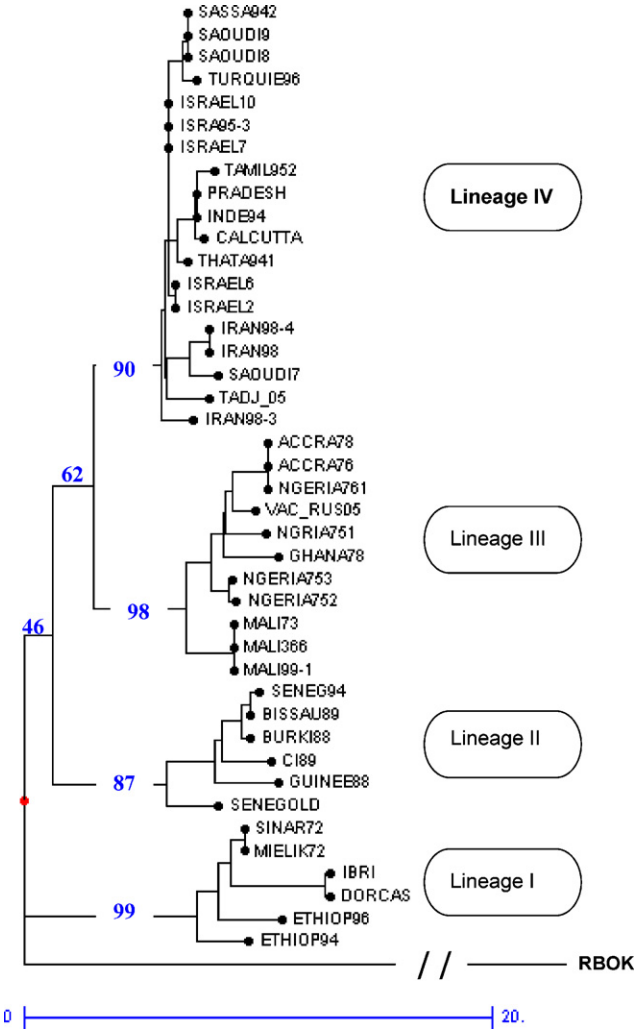

Fig. 1. Phylogenetic tree of PPRV based on the alignment of the nucleotide sequences (1232–1560) of the N protein gene (neighbor-joining method of the Darwin package). Distances were generated with TreeCon MATRIXW program. Percentages of 1000 bootstrap replicates supporting each group are indicated. The rinderpest vaccine RBOK strain N protein gene sequence is included as outgroup [6].

4. Progress in the development of PPR vaccines

The main characteristic of the pathogenesis of PPRV infection, as for all other morbilliviruses, is the profound but transient immunosuppression induced by this virus in its host with the consequence of increased susceptibility to opportunistic infections and increased mortality. This immunosuppression effect is a resultant not only of the direct effect of the virus multiplication in lymphoid cells but also of the different strategies morbilliviruses, as many other viruses, have evolved to overcome the host immune defence system [24,25]. However, despite the profound immunosuppression they may induce, this effect 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 [26,27]. In the case of MV, it is suggested that this apparent paradox may be explained in part by preferential long-term activation of type 2 CD4+ T cells by the virus [26]. In the case of PPR, as well as of rinderpest, information are lacking with regards to the immune response necessary for recovery from or for protection against infection. However, for the control of this disease, vaccines were developed or are on the development following the same strategy as for the other morbilliviruses.

4.1. Conventional attenuated vaccines

Soon after the first isolation of PPRV in tissue culture in the 1960s, preliminary attempts were made to develop an attenuated live vaccine but these were unsuccessful [28,29]. At that time, an attenuated tissue culture rinderpest vaccine, very effective against rinderpest, was available [30]. Considering the closely antigenic relationship between RPV and PPRV, this live attenuated rinderpest vaccine was tested in goats for vaccination against PPR. Evaluation of the serological immune response of these vaccinated animals demonstrated the presence of neutralising antibodies against RPV but not against PPRV, or only on few occasions [31]. However, all animals resisted to PPRV challenge and this was accompanied by rising levels of PPRV neutralising antibody activity [31]. This result indicates probably that some

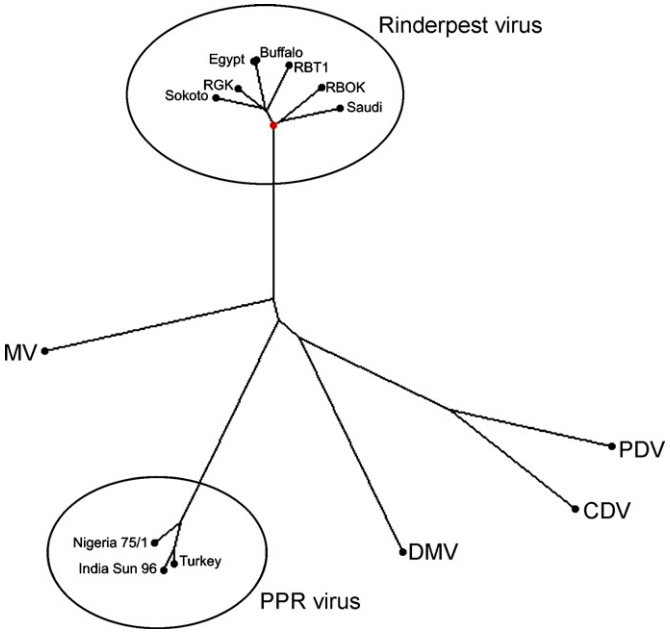

Fig. 2. Phylogenetic tree of morbilliviruses based on the alignment of the full nucleoprotein gene nucleotide sequences. For RPV and PPRV sequences of many strains were included to highlight the well separation of PPRV from RPV. Distances were generated with TreeCon MATRIXW program.

replication of PPR challenge virus occurs in animals vaccinated with this RP vaccine prior to its clearance by the rinderpest-primed immune response. Despite this possible PPRV transient replication in the vaccinated animals, rinderpest attenuated vaccine was successfully used to protect small ruminants against PPR disease, a protection which lasts for at least one and probably 3 years [7,31–33]. However it is not known if such vaccinated animals can then transmit the challenge virus during its short period of replication. If gene sequencing data have confirmed previous serological results on the closely relationship between RPV and PPRV, they however have shown that percentage the homology between H protein of the two virus is relatively low, the two proteins sharing less than 60% of amino acids [19]. Only F, the second protective viral protein, is well conserved with about 80% of homology. In fact, as it can been seen in Fig. 2 which has been constructed based on the sequencing data of the nucleoprotein gene, one of the well conserved proteins within the morbillivirus group, the closest virus to RPV is measles virus but not PPRV. The cross protection provided by RPV against PPRV infection is probably due to the fusion protein which is well conserved. This protein seems to induce mainly cellular immune response. The fact that PPRV neutralising was not detected in RPV vaccinated small ruminants before challenge has encouraged continuing research on the development of a homologous PPR vaccine. In 1989 this goal was finally achieved by the successful attenuation of PPRV strain Nigeria 75/1 through serial passages on Vero cells [34]. Several trials have demonstrated the efficacy of this vaccine on more than 98,000 sheep and goats in the field between 1989 and 1996. During those trials no unwanted side effects such as abortion in pregnant animals were recorded. It was demonstrated also that animals vaccinated with this attenuated PPRV were unable to transmit the challenge virus to in-contact animals. Anti-PPRV antibodies generated by vaccinated animals last for at least 3 years, the effective economic life of the animals. PPRV Nigeria 75/1 belongs to lineage I. During the development process of the attenuated vaccine based on this virus, different PPRV strains were used as challenge viruses and all failed to induce disease in the vaccinated animals, result demonstrating the potential worldwide effective use of this vaccine to control PPR. The availability of a homologous vaccine for PPR is fortunate since the use of rinderpest vaccine in all animal species has now been discontinued worldwide. This is to ensure a rinderpest serologically negative ruminant population to allow for effective epidemiosurveillance of rinderpest disease to fulfil the OIE requirements needed to obtain the status of a rinderpest free country or zone. The attenuated homologous PPRV vaccine is now the only vaccine permitted for use in sheep and goats to protect them against PPRV infections.

4.2. Vaccine stability

As with all members of the family *Paramyxoviridae*, PPRV is very heat sensitive and this is a serious drawback to the efficient use of the live attenuated vaccine in the endemic areas, which have hot climatic environments. In addition these regions usually have poor infrastructures and under these conditions it is difficult to maintain a cold chain to ensure the preservation of vaccine potency. This drawback was overcome by Worwall et al. through the development of a thermotolerant vaccine freeze dried in the presence of a cryoprotectant containing trehalose [35]. Under these production conditions the vaccine is stable at 45 °C for 14 days with minimal loss of potency (see Table 2). PPR control will benefit greatly from the use of this thermostable form of the

Table 2
Thermostability of PPR Xerovac at different concentrations of trehalose: titre of the vaccine in TCID50/ml at different days of post storage at 45 °C

		Titre, in TCD50/ml, of the vaccine stored at +45 °C				
% of trehalose in the vaccine	RM*%	Day 0	Day 3	Day 5	Day 8	Day 14
1	1.04	5.20	4.25	4.0	2.15	<1.5
2	1.8	5.10	4.55	4.40	3.30	2.6
4	2.0	5.20	4.80	4.75	3.45	2.75
8	1.3	5.00	4.75	4.85	4.15	3.10

RM*: percentage of residual moisture (RM) in the final vaccine product after dehydration.

attenuated vaccine. A similar vaccine was recently produced in India using a local strain of PPRV [36].

4.3. DIVA vaccines

A major disadvantage when using classical live attenuated vaccine is that the antibody responses they induce in animals cannot be distinguished from those following a natural infection. This makes sero-epidemiosurveillance of the disease impossible in endemic areas where a vaccination programme has been or is being implemented. A way to combine activities, vaccination and serosurveillance, for the better management of the disease would be the use of DIVA vaccines, the acronym used for vaccines which enable *d*ifferentiation between *i*nfected and *v*accinated *a*nimals [37]. Originally this term was applied to gene-deleted marker vaccines for large DNA viruses when used with their vaccine-specific serological tests, but it can also apply to sub-unit vaccines [38,39], heterologous vaccines [40] or some killed whole pathogen vaccines such as the highly purified Foot and Mouth Disease Vaccine which is used in conjunction with non-structural protein-based serological tests [41]. It can be used also for recombinant-based vaccines.

4.3.1. PPR poxvirus-based recombinant vaccines

PPRV, like other morbilliviruses, is an enveloped RNA virus with two external glycoproteins, the fusion (F) and haemagglutinin (H) proteins. These proteins are responsible for inducing protection against the disease in animals. The H and F protein genes of several morbilliviruses have been expressed in various vector systems and they can be used as effective sub-unit vaccines [42–48]. Following this approach, the F protein of PPRV was inserted into the genome of an attenuated capripox virus vaccine [49]. The resulting recombinant virus expressed the PPRV F protein on the surface of infected cells, which was recognised by an anti-F monoclonal antibody. This recombinant was then tested in goats and shown to be effective in protecting inoculated animals against PPR at a dose as low as 0.1 pfu. A similar vaccine which expressed the PPRV H protein was also produced and it is effective at a minimal dose of 10 pfu [50]. The duration of immunity provided by these two vaccines and also the effect of capripox pre-immunity over the vaccination have yet to be determined. They offer the advantage of being able to differentiate non-infected but vaccinated animals from those which have been exposed to PPRV. Indeed a competitive ELISA has been developed for the detection of antibodies to PPRV, test based on the use of PPRV nucleoprotein (N) produced in insect cells [21]. The N protein is the most immunogenic viral protein and induces in the host high amounts of antibodies anti N. In the present case of using recombinant vaccine devoted from PPRV N protein, anti N antibodies will only be detected in naturally infected animals or in animals vaccinated with the recombinant, which subsequently become infected with the PPRV. Apart from their advantage as DIVA vaccines, these capripox recombinant vaccines can be used to immunize animals against two major diseases of small ruminants in a single treatment, capripox and PPR.

4.3.2. Reverse genetics for vaccine development

The development of the reverse genetics technology for negative strand RNA viruses has given us another means of producing marker vaccines to combat viral diseases such as PPR. One of these recombinant vaccines has the rinderpest vaccine virus genome as the backbone into which the matrix (M), the F and H protein genes of RPV were replaced by those of PPRV. The resulting chimeric virus proved to be a safe and effective vaccine which could protect goats against virulent challenge with PPRV [51]. This chimeric PPR marker vaccine can be used in any endemic country without compromising the global rinderpest serosurveillance effort since all antibody tests are based on either the N or H virus proteins which are quite distinguishable serologically between rinderpest and PPR viruses. Animals which have never been in contact with rinderpest but which are vaccinated with this vaccine would test seronegative in the rinderpest H-based cELISA [52] but positive for the presence of anti-RPV N protein antibody [53]. Likewise, animals without any prior exposure to PPR will be positive for antibodies in the PPRV H-based cELISA if vaccination is successful, but negative in the PPRV N-based cELISA and so will be distinguishable serologically from naturally infected animals.

5. Conclusion

PPR is an important animal disease which now threatens the billion-strong small ruminant population in Africa, the Middle and Near East, South-West and Central Asia. Its economic importance was highlighted in a report on an international survey carried out by Perry et al. [54]. In that report they identified PPR as one of the priority animal diseases whose control is considered important for poverty alleviation in Western Africa and Southern Asia. In the same report it was also pointed out that PPR is still a poorly recognised disease, particularly with regard to epidemiological features such as transmission dynamics under different production systems. A great deal of more research into this aspect of the disease is urgently required. The fact that PPRV can infect cattle, buffaloes and camels [17,18] gives PPR an even higher priority, particularly in the current situation where vaccination against rinderpest in cattle has been stopped. The availability of an effective marker vaccine along with its companion serological tests will greatly assist in designing effective control programmes for this disease in future.

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