PESTE DES PETITS RUMINANTS (PPR): GENERATING EVIDENCE TO SUPPORT ERADICATION EFFORTS

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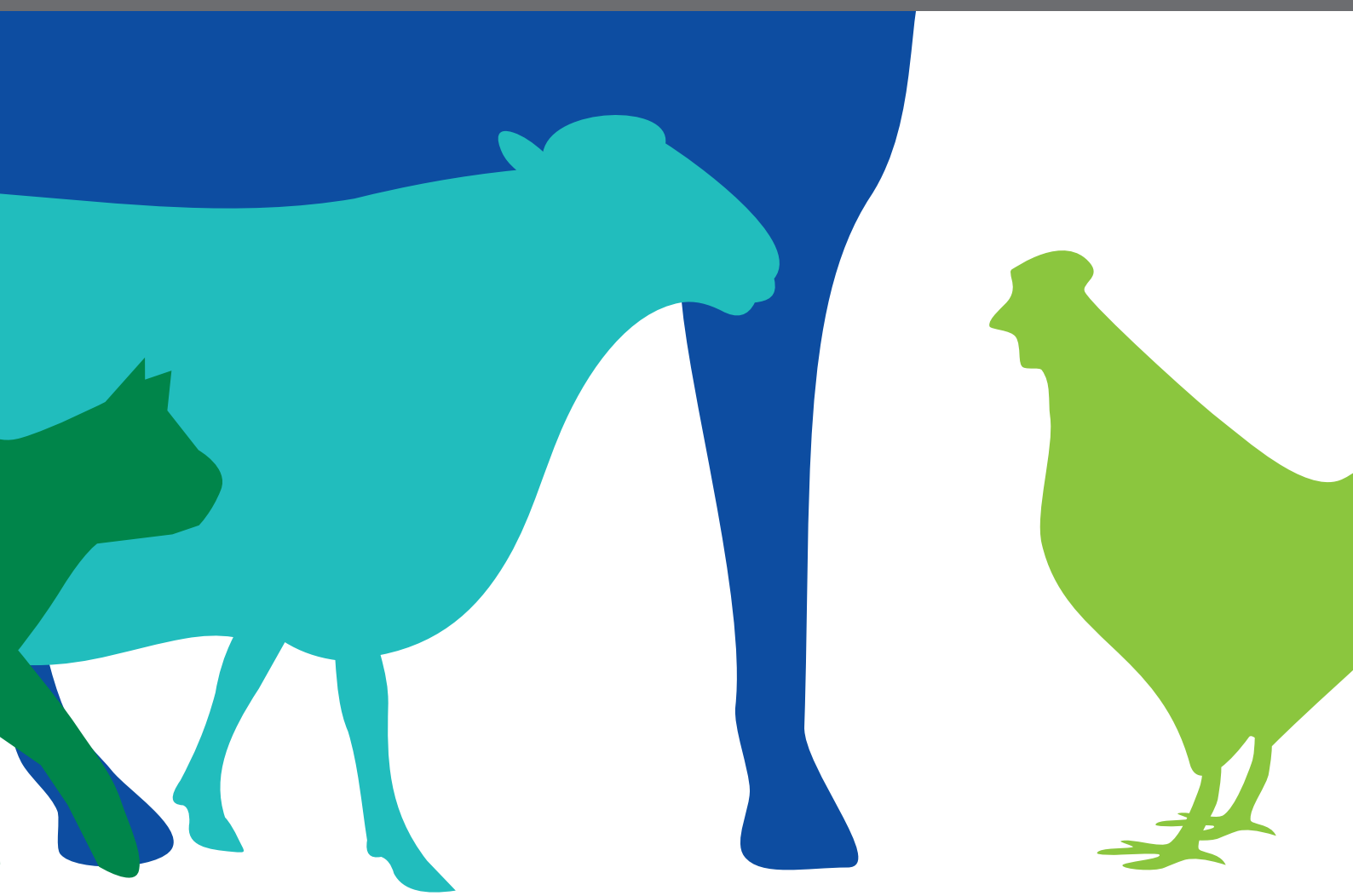

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PESTE DES PETITS RUMINANTS (PPR): GENERATING EVIDENCE TO SUPPORT ERADICATION EFFORTS

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EDITORIAL
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Editorial: Peste des Petits Ruminants (PPR): Generating Evidence to Support Eradication Efforts

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Keywords: peste des petits ruminants, epidemiology, ecology, surveillance, control, eradication

Editorial on the Research Topic

Peste des Petits Ruminants (PPR): Generating Evidence to Support Eradication Efforts

Peste des petits ruminants (PPR) is a major transboundary animal disease from a socio-economic point of view. It is also a disease that affects wildlife, threatens susceptible rare wild artiodactyl species and is of conservation concern. In most of Asia and Africa, where the disease is endemic, PPR has a considerable impact on rural economies and the livelihoods of smallholder farmers and pastoralists for whom sheep and goats are often the main assets. In 2015, FAO and OIE developed a global strategy that aims to eradicate PPR by 2030. This strategy heavily relies on large-scale vaccination of sheep and goats, vaccination monitoring and disease surveillance. However, the implementation of this strategy faces several logistical constraints and knowledge gaps, ones which can be addressed through dedicated research programmes. These include: the development of cost-effective thermotolerant vaccines, variations in PPR virus (PPRV) transmission levels in different settings, the structure of networks of contacts between small ruminant flocks and their role in short- and long-range PPR virus dissemination, the impact of small ruminant population dynamics on vaccination frequency and coverage, the roles of wildlife populations and domestic species other than small ruminants (e.g., cattle, camels) in PPR maintenance and spread (and susceptibilities), the socio-economic and biodiversity impacts of PPR disease, efficiency of PPR related animal health services, farmers' perceptions and acceptance of PPR vaccination and their decision making around disease control.

This Research Topic brings together a number of publications on the virology, epidemiology, ecology and control of PPR virus. Gaps in scientific knowledge and ways to enhance control and eradication strategies are also identified. Although PPR is endemic in both Africa and Asia, most publications presented here focus on sub-Saharan Africa, mainly Southern Africa and East Africa, with a few studies on West Africa. Some papers are not geographically tagged as they propose a more broad-based thinking.

Starting with Southern Africa, which is largely free of PPR infection, Mapaco et al. describe a serological survey coupled with event-based surveillance in Mozambique. No evidence of PPR viral circulation was found, despite the disease being endemic in neighboring Tanzania as described by Idoga et al.. Another study by Britton et al. demonstrates the need for enhancing the risk-based surveillance capacity and rapid response in the region, to prevent, and prepare for, possible incursions of PPR.

Multidisciplinary approaches and modeling methods can inform PPR surveillance and control. For instance, spatial modeling of the risk of PPR occurrence based on multicriteria evaluations was

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applied by Ruget et al. to East African countries, including nearby Indian Ocean islands. It made it possible to identify areas where PPR surveillance and control should be strengthened.

The identification of areas and farming systems which should be targeted by risk mitigation interventions was also the objective of another study carried out by Nkamwesiga et al. who combined participatory epidemiology, classical disease surveillance methods, and genetic analysis in Uganda and along its borders. The results highlight the need of transboundary interventions. This was also emphasized by molecular analyses of PPRV strains collected in West Africa. Indeed, the study by Tounkara et al. and Tounkara et al. suggests frequent transboundary spread of the virus, supporting the need for the genetic characterization of PPRV strains at an international scale, in order to better understand PPRV spatial dynamics and to adapt control measures accordingly.

Mathematical modeling is crucial to optimize vaccination strategies as shown by ElArbi et al., but engagement with farmers and other relevant stakeholders is also essential, as illustrated in Mali by Dione et al.. An important element in the planning of vaccination campaigns is also the willingness to vaccinate, and in places where vaccination is not provided free of charge, also the willingness to pay—both of which depend on different factors as investigated by Wane et al..

Uncertainties regarding the actual host range of PPRV could threaten the effectiveness of the current eradication strategy. Dou et al. reviewed the scientific literature regarding the potential roles of species other than domestic small ruminants in PPRV ecology and PPR epidemiology. For these authors, further investigations are needed in wildlife and atypical domestic hosts, especially in swine and carnivores. Bovines can become seropositive after infection by PPRV, but there is no evidence that they excrete the virus. Therefore, Agga et al. suggest that cattle could serve as sentinel animals for PPR surveillance as they are not targeted by vaccination programmes.

Fine et al. focus their report on wildlife-livestock socio-ecosystems in both Asia and Africa, and the risk of neglecting these complex systems for the eradication process. More evidence based on well-structured ecological and epidemiological studies at these interfaces are needed to make

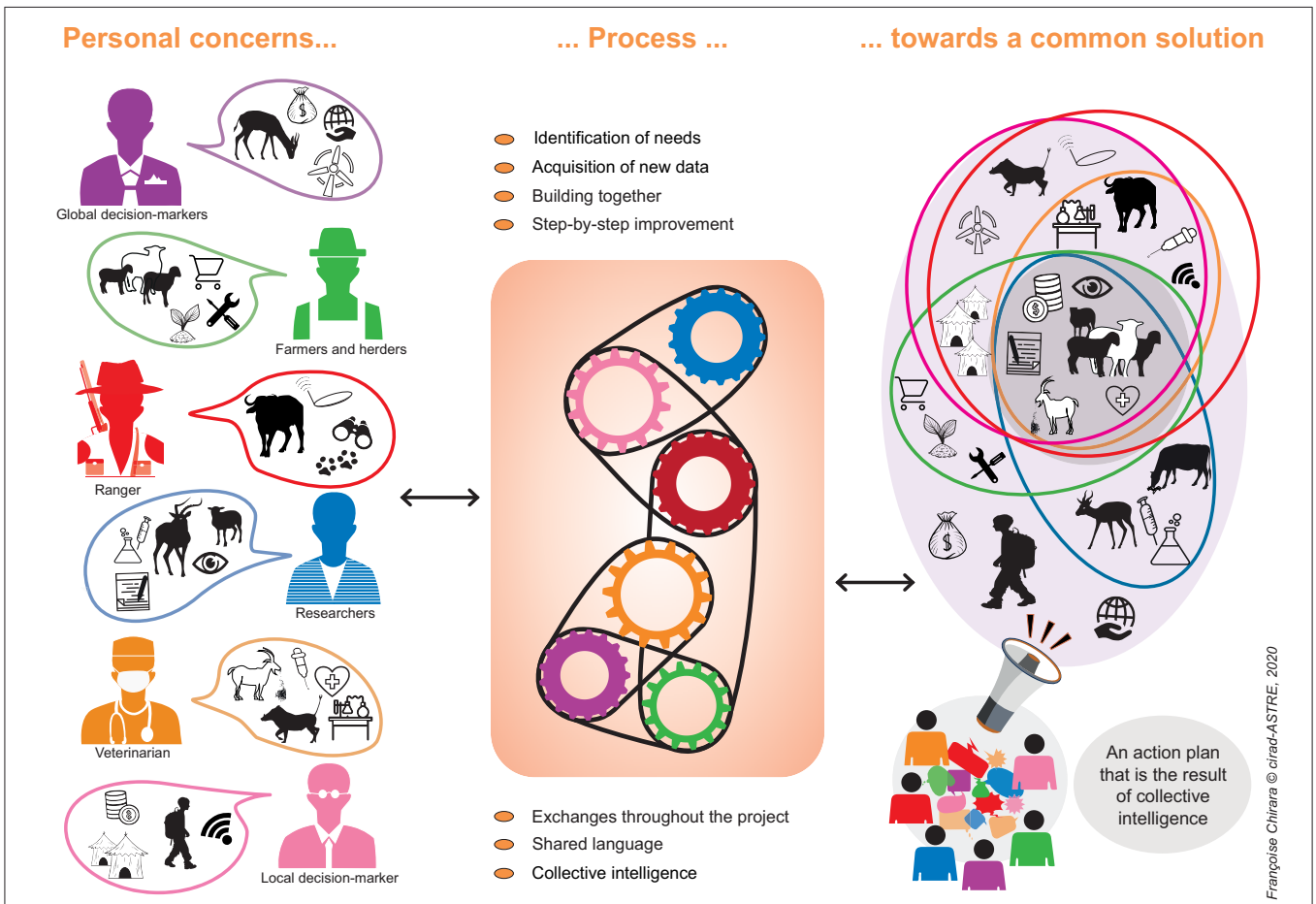

FIGURE 1 | Adapted from (1). Integrated approaches in animal health, CIRAD-ASTRE, *Salon International de l'Agriculture*, Paris, February 2019. This figure illustrates how an integrated approach to PPR needs to be designed in a given context by key players (farmers, veterinarians, rangers, traders, decision makers, etc.) who together characterize the problems and find solutions to be implemented step by step, taking into account the social and economic context, and environmental changes in addition to the animal health aspects.

sure that we understand the role of wild and atypical host species and progress along the eradication path without missing any blind spots. The authors also highlight that PPRV infection is a threat for the conservation of some endangered wild species, which could also help diversify sources for funding the eradication efforts.

The relevance of the global eradication approach is also discussed. For example, instead of large-scale vaccination coupled with monitoring and surveillance, Cameron argues for targeted and adaptive vaccination campaigns informed by real-time data collection, which however assumes the availability of sufficient capacity and resources. Rossiter recommends developing a global and multidisciplinary network linking those implementing field programmes with researchers.

This Research Topic presents some new findings, using a range of methods, from participatory approaches to mathematical modeling and phylogenetics. It also highlights gaps in knowledge, especially the role that atypical species might play in the maintenance of the virus.

Finally, this Research Topic points to the need for continued discussions and reassessments of the global strategy, and for the use of models, along with other scientific methods, to effectively tailor the implementation of this strategy to local contexts (2). Even if PPR is not a zoonosis, its impact on people, and wild and domestic animals, means that a One Health approach is recommended, which would strengthen system thinking around PPR control (3) and would help the integration of disciplines and sectors (**Figure 1**). Strengthening of wildlife health capacities in the affected regions and globally is important (4, 5) for diseases such as PPR (6) and more widely with other multi-host infections. Wildlife authorities need to be more integrated in the formulation of strategy and policy and in supporting surveillance, especially during the period of verification of freedom from infection and disease at national levels. The establishment of a new One Health Council incorporating United Nations Environment Programme along with WHO, FAO, and OIE is a step in this direction (7).

As the success of the eradication efforts will greatly depend on farmers' willingness to participate in vaccination and surveillance programmes, as demonstrated during the rinderpest eradication programme (8), greater consideration must be given to research in social sciences (9). The achievement of this international programme also requires economic perspectives (10). In this context, public-private partnerships need to be encouraged (11).

The FAO/OIE PPR global control and eradication strategy (PPR GCES) needs a huge financial commitment (12), capacity building and technical support, but also well-funded *ad-hoc* interdisciplinary research that addresses important knowledge gaps for eradication, and effective scientific networks through the Global Research and Expertise Network PPR GREN[1].

AUTHOR CONTRIBUTIONS

All authors have served as editors of the Research Topic. FR has written the draft of the editorial and it was amended and revised by the other authors.

[1]http://www.fao.org/ppr/news-and-events/news/detail/fr/c/1190842/ (Accessed January 11, 2020).

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ORIGINAL RESEARCH
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Identification of Peste des Petits Ruminants Transmission Hotspots in the Karamoja Subregion of Uganda for Targeting of Eradication Interventions

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This paper describes an assessment of the patterns of *peste des petits ruminants* virus circulation in the Karamoja subregion of Uganda conducted to identify the communities that maintain the virus and inform the development of a targeted vaccination strategy. Participatory epidemiological methods were used to develop an operational hypothesis for the patterns of PPR in Karamoja that was subsequently validated through outbreak investigation and genomics. The participatory epidemiological assessment included risk mapping with livestock owners, community animal health workers and veterinarians and indicated there were two critical foci of virus transmission on the Uganda-Kenya border. One was located in two adjacent subcounties of Kotido and Kaabong Districts in northern Karamoja and the other in Loroo subcounty of Amudat District in southern Karamoja. Participants reported that these were locations where outbreaks were usually first observed in Karamoja and subsequently spread to other areas. Following the participatory assessment, surveillance activities were implemented across the Karamoja subregion in 2018. Three outbreak were detected, investigated and sampled. Two outbreaks were located in the northern and one on the southern focus of transmission. No Outbreaks were diagnosed in Karamoja outside of these foci during 2018. Genomics indicated different clusters of viruses were associated with the northern and southern foci that were more closely related to other East African isolates than to each other. This indicates these are two separate systems of virus circulation which should be explicitly addressed in eradication as separate cross-border systems that require integrated cross-border interventions.

Keywords: Peste des petits ruminants, Uganda, participatory epidemiology, eradication, Karamoja

INTRODUCTION

Peste des petits ruminants (PPR) is a highly contagious and fatal disease of sheep and goats that negatively impacts the livelihoods, and food and nutritional security of livestock farmers throughout large parts of Africa, Asia, and the Middle East (1–4). Small ruminants play a central role in household economies as ready sources of cash and protein, especially for women and children. PPR virus is closely related to rinderpest (RP), the first livestock disease to be globally eradicated. Effective vaccines, including thermostable vaccines, are available for the control of PPR (5). After the successful global eradication of RP, the international community identified PPR, the closest relative of RP, for global eradication by 2030 (6).

The primary challenges to the eradication of PPR are the large size of small ruminant populations and their short life span. These demographic concerns create the need to target vaccination to critical points in viral maintenance systems using fit-to-purpose, public-private-community partnerships that effectively harness incentives for participation to interrupt disease transmission (7).

This paper describes an assessment of the patterns of PPR virus (PPRV) circulation in the Karamoja subregion of Uganda to develop a vaccination strategy targeted to the rural pastoral communities responsible for maintaining the virus. Karamoja is a pastoral region of Uganda bordering South Sudan and Kenya principally. This region is predominantly occupied by Karamojong and Pokot peoples practicing transhumance where cattle are kept in mobile camps often referred to in English as kraals. The Karamojong cluster of tribes speak related dialects and includes three communities in Uganda (Dodoth, Jie, and Karamojong), one in Kenya (Turkana) and the two in South Sudan (Toposa and Jie). The Pokot speak a Kalenjin language and occupy southern Karamoja residing on both sides of the Kenya-Uganda border. A combination of participatory and laboratory-based epidemiological methods were used in sequence to develop and then test an operational hypothesis for understanding the endemic patterns of PPR in Karamoja.

MATERIALS AND METHODS

The action research combined participatory epidemiological field assessments with participatory risk mapping exercises to develop qualitative risk maps. The surveillance system was then reinforced across Karamoja to actively search, sample and diagnose outbreaks of PPR using participatory methods. Finally, serology and genetic analysis was conducted on materials collected during investigations to test the epidemiological scenario developed during the participatory phase of the assessment.

Site Assessment and Risk Mapping

A site assessment of the Karamoja sub-region was undertaken to assess the patterns of PPR transmission in the area and identify transmission hotspots for targeting of control interventions using participatory epidemiology. The site assessment studied the animal health situation, community animal health knowledge, and the quality and availability of animal health services in the region. Semi-structured interviews with focus groups and key informants were conducted in all the seven districts of Karamoja as defined at the time of project design (**Figure 1**). Karamoja was redistricted over the course of project implementation and study results are presented using current maps at the preference of respondents. A minimum of three focus groups with kraal (livestock camp) leaders and livestock owners, and three key informant interviews with veterinary drug shop owners were conducted in each of the seven districts. Other key informants included governmental extension officials, district veterinary personnel, and animal health workers. The project team took the opportunity to conduct two interviews with Turkana herders present in Kaabong. Twenty-one focus groups, 14 veterinary drug shop interviews, and 9 governmental interviews were held. Semi-structured interviews with livestock owners and drug shop owner/operators followed an internal review board approved outline tailored to their livelihood. Mapping, proportional piling, and timelines were the main visualization techniques used during interviews (8). Data were collected in notes and pictures, and key themes were extracted. These data were combined and cross-checked with information on PPR disease, livelihoods, and animal health services from business model and epidemiology training workshops with community animal health workers, veterinary officials, and veterinary drug shop owners.

Risk maps were prepared in two meetings that included veterinarians, community animal health workers and kraal leaders from all districts of Karamoja. Participants were organized into focus groups according to their home areas and asked to produce local risk maps for PPR by listing the risk factors for PPR and then indicating the distribution of each category of risk on a poster paper. Groups presented their maps to the meeting and a discussion followed. The participants were then reorganized into two mixed groups with representation from all districts and asked to prepare a new risk map synthesizing all of Karamoja. Subsequently, these same groups drew timelines representing the epidemic curves of the annual incidence of PPR from the time of their first observation of PPR.

The project then defined target sites for vaccination interventions based on the risk maps, transmission foci indicated and available resources for vaccination.

Surveillance

Surveillance for PPR was supported through training in participatory surveillance (9, 10) and back-stopping outbreak investigation via an agreed protocol for integrated project partner response. Participatory surveillance is a sensitive technique for finding disease outbreaks using syndromic case definitions that are consistent with the target disease and subsequently confirming their diagnosis with biological tests. In the case of PPR, a suspect outbreak was defined as any clinical event that met a stomatitis-enteritis syndromic case definition. Suspect outbreaks were then confirmed with PPR rapid field tests and PCR.

Fourteen locally active individuals participated in a 10-day training on PS for PPR, including two non-governmental organization workers, two Makerere graduate students, and

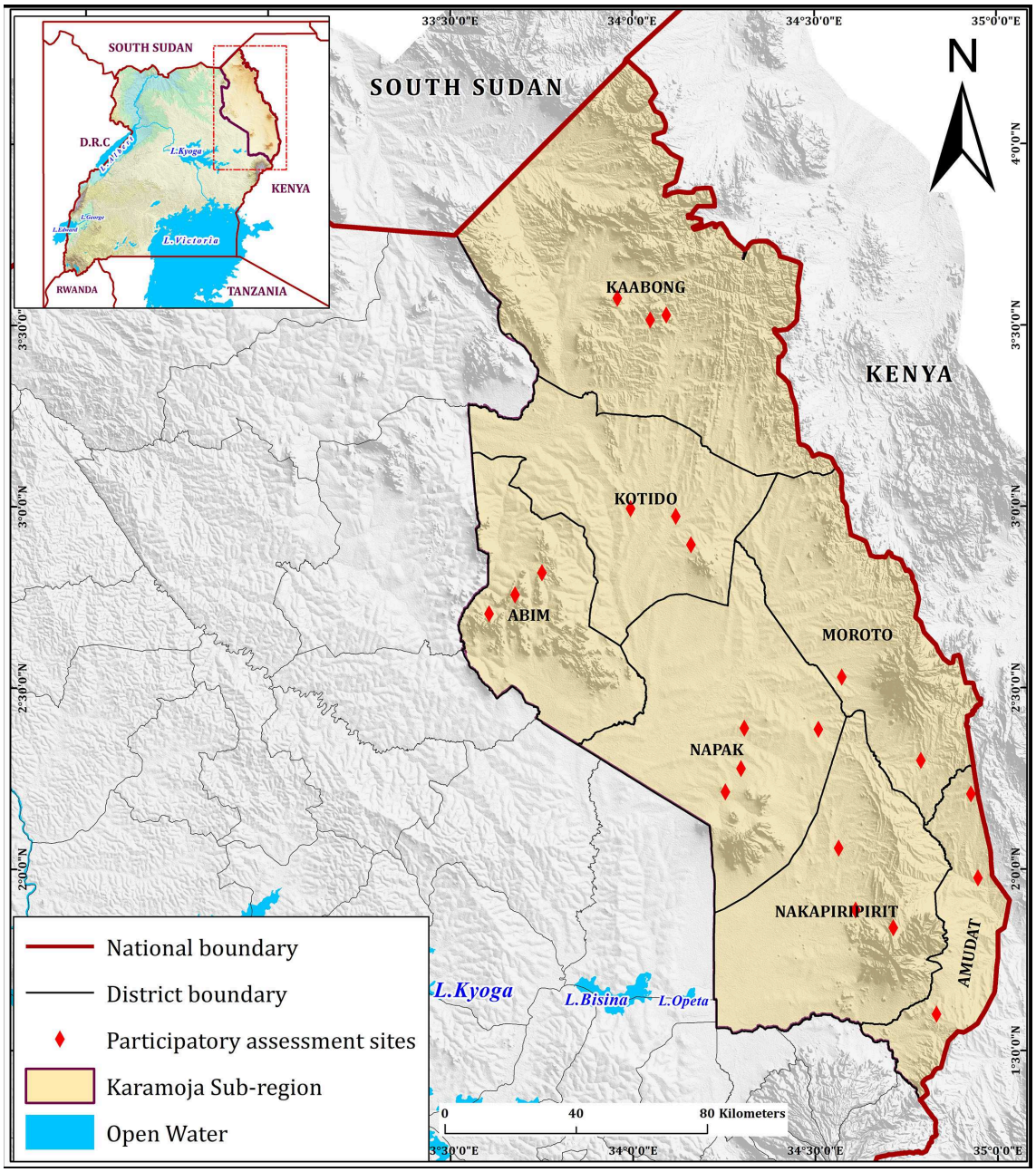

FIGURE 1 | Karamoja participatory assessment sites. Participatory assessment sites were distributed throughout all districts of Karamoja.

10 governmental veterinary officials from each of the seven Karamoja districts. One kit with appropriate materials for a PPR outbreak investigation was provided to each district veterinary office. Attendees were instructed in their roles in the outbreak investigation and response protocol. This protocol for outbreak investigation was agreed upon among project partners: Ministry of Agriculture, Animal Industries and Fisheries (MAAIF)-Uganda, Tufts University's Cummings School of Veterinary Medicine (Tufts), Makerere University (MaK), Mercy Corps Uganda, and the Karamoja Veterinary Laboratory (KVL). Communication with official channels was key to enable governmental officials to promptly respond to any new outbreaks. It included the use of interviews, rapid field tests (PESTE-TEST, Pirbright Inst) (11), and PCR tests to confirm suspected outbreaks.

Sampling at outbreaks included ocular and nasal swabs, serum and whole blood. All samples were stored on ice and delivered within 48 h to the Molecular Biology Laboratory, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University.

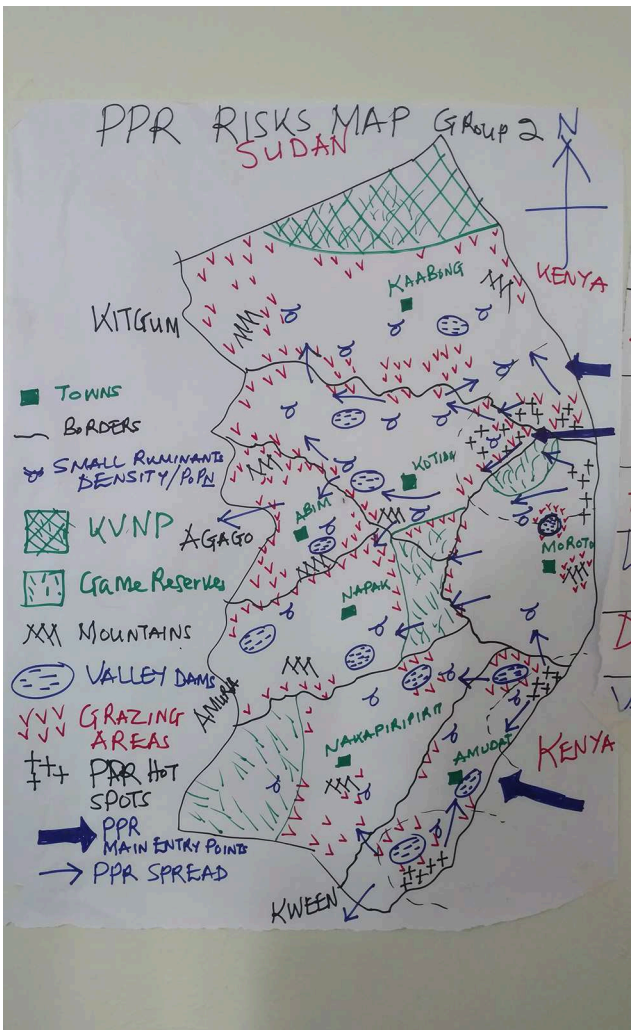

FIGURE 2 | Example of a Karamoja Risk Map. Example of a risk map drawn by a focus group of veterinarians, community animal health workers and kraal leaders from across Karamoja. The thick blue arrows indicate the perceived main entry points for PPR to Karamoja and the thin blue arrows represent spread across Karamoja. Black crosses are PPR transmission hotspots. The northern focus includes Nakapelimoru subcounty of Kotido, Loyoro subcounty of Kaabong District. The southern focus is centered on Loroo sub county of Amudat. A third focus is indicated in the extreme south in Karita sub county of Amudat was not included in the project for financial reasons.

Serology

Four sets of serological samples were collected. Each of the two hotspots identified in the participatory risk-mapping and the immediate areas of the Loroo and Kamion outbreak sites at the time of the outbreak were sampled. Sampling sites were selected using randomly generated geographic coordinates within the targeted communities; the nearest herd to the coordinates was selected. Sample size was estimated using a 70% estimate of prevalence, an error of ±4%, and a design effect of 1.2 to account for within herd clustering effects. In the two hot spots sampled, 25 sites in each of two communities were selected. A total of 28 animals, or all animal present in smaller herds, were sampled in each herd using a systematic sampling method. In the outbreak samples, 20 and 22 herds were selected in Loroo and Kamion, respectively. A total of 700 small ruminants were sampled for each of the two hotspots for serosurvey whereas 478 and 440 small ruminants were sampled during the Loroo Subcounty and Kamion Subcounty outbreak investigations, respectively.

Peste des Petits Ruminants virus specific antibodies in sera were tested using a commercial competitive ELISA platform, ID Screen® PPR Competition [ID_Vet Grabels, France]. The assay was performed following the manufacture's OIE-recommended protocol (12). The cutoffs were calculated as $\frac{S}{N}(\%) = \frac{OD_{sample}}{OD_{Negative\ contrrol}} * 100$.

The samples with percentage inhibition (S/N) ≤60% were considered positive whereas samples with (S/N) value above 60% were negative.

RNA Extraction From Swabs

RNA was extracted using a commercial RNA extraction kit (Zymo Research, USA). Two hundred and fifty microliter of each swab sample was homogenized with 500 µl of Trizol reagent™ with a vortex mixer for 30 s. Five hundred microliter of absolute ethanol was added to the sample homogenate and transferred into a Zymo-Spin™ III CG Column and centrifuged at 10,000 × g for 30 s until all was finished. Eighty microliter of DNAse 1 solution was added to each column and incubated for 15 min at room temperature before washing with 400 µl of Direct-zol™ RNA PreWash™ buffer. The column was then washed with 700 µl of RNA Wash Buffer and centrifuged for 2 min to ensure complete removal of the wash buffer. RNA was eluted in 50 µl of nuclease-free water. Extracted RNA was either immediately used for cDNA synthesis or kept at −80°C until required.

Copy DNA (cDNA) Synthesis

LunaScript® RT SuperMix Kit (New England Biolabs, USA) was used for cDNA synthesis. cDNA was prepared in a 20 µl reaction containing 4 µl of LunaScript® RT SuperMix (5X), 5 µl of extracted RNA and 11 µl of Nuclease-free water. The PCR tubes were then placed into a thermocycler for 1 cycle of primer annealing of 25° C for 2 min, cDNA synthesis at 55° C for 10 min and heat inactivation at 95°C for 1 min. The synthesized cDNA was immediately used for PCR or stored at −20° C.

F and N Gene PCR Amplification

Polymerase chain reaction (PCR) was performed on the synthesized cDNA with two pairs of primers PPRVF1b: [5′AG TACAAAAGATTGCTGATCACAGT 3′]

PPRVF2d: 5′GGGTCTCGAAGGCTAGGCCCGAATA 3′ and NP3 (5′-TCTCGGAAATCGCCTCACAGACTG-3′) and NP4 (5′-CCTCCTCCTGGTCCTCCAGAATCT-3′) which target 448 and 351 bp fragments, respectively, as previously described (13, 14).

The PCR reaction was performed in a 20 µl reaction containing 10 µl Taq DNA Pol 2.0X MyTaqRedMix (Bioline, UK), 1 µl (10 µM) of each primer, 3 µl of cDNA and 5 µl of nuclease-free water (Qiagen, USA). The mixture was

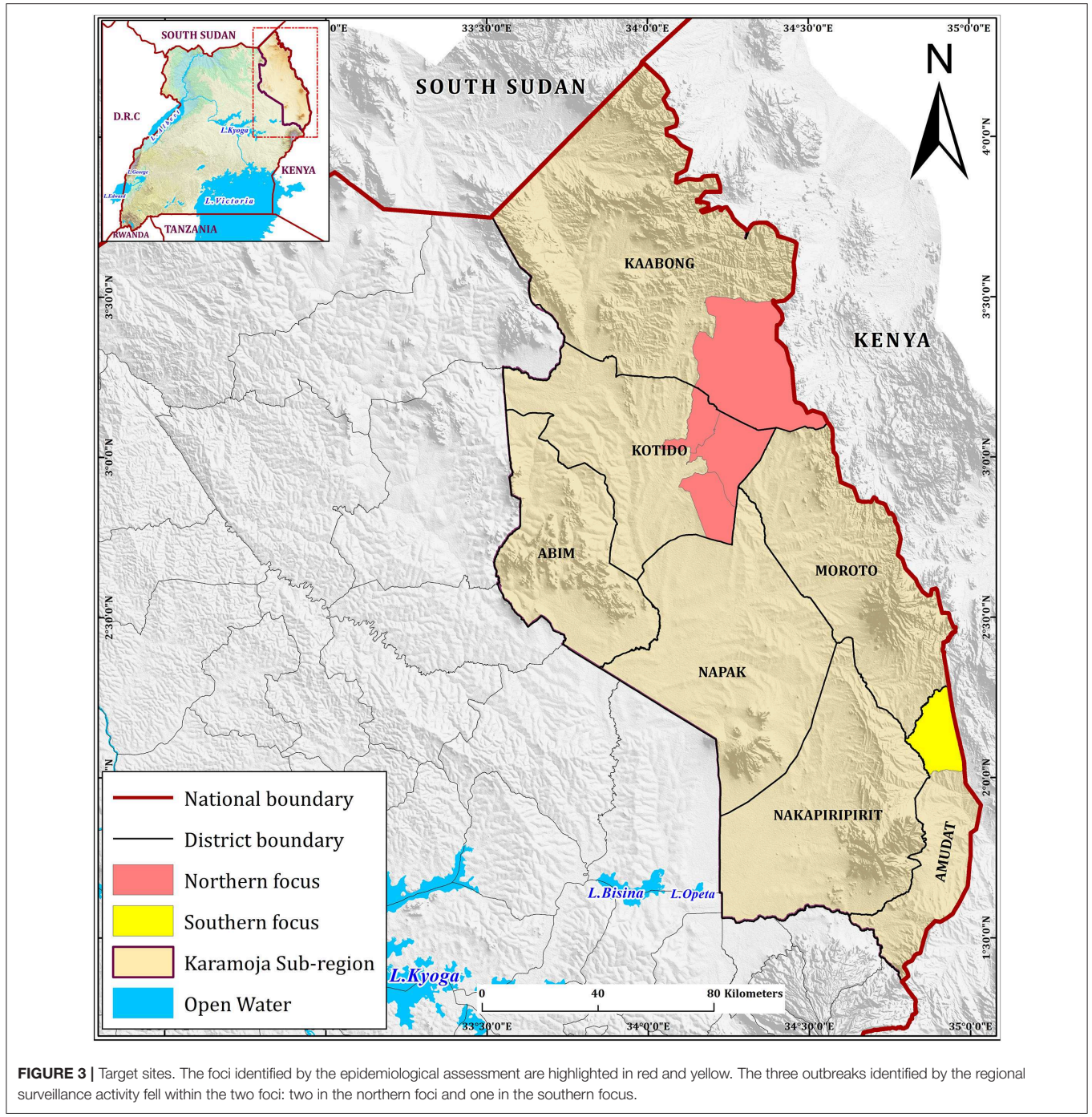

FIGURE 3 | Target sites. The foci identified by the epidemiological assessment are highlighted in red and yellow. The three outbreaks identified by the regional surveillance activity fell within the two foci: two in the northern foci and one in the southern focus.

then subjected to an initial denaturation at 95°C for 5 min followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s and extension at 72°C for 2 min and final extension at 72°C for 7 min. Amplification was performed in a S1000 ™ Thermal Cycler [BIO RAD, California, United states]. Ten microliter of each PCR amplicon were resolved on a 2% ethidium bromide-stained agarose gel as previously described (14–16).

Nucleotide Sequencing

Purified PCR products were shipped to INQABA BIOTEC (Pretoria, South Africa) and sequenced using the ABI 3500XL Genetic Analyzer, POP7™, BrilliantDye™ Terminator v3.1 [Thermo Fisher Scientific, USA]. The nucleotide sequences were deposited in the GenBank under accession numbers MK250004-MK2500011 and MK242028-MK2242037 for the Nucleoprotein and Fusion genes, respectively.

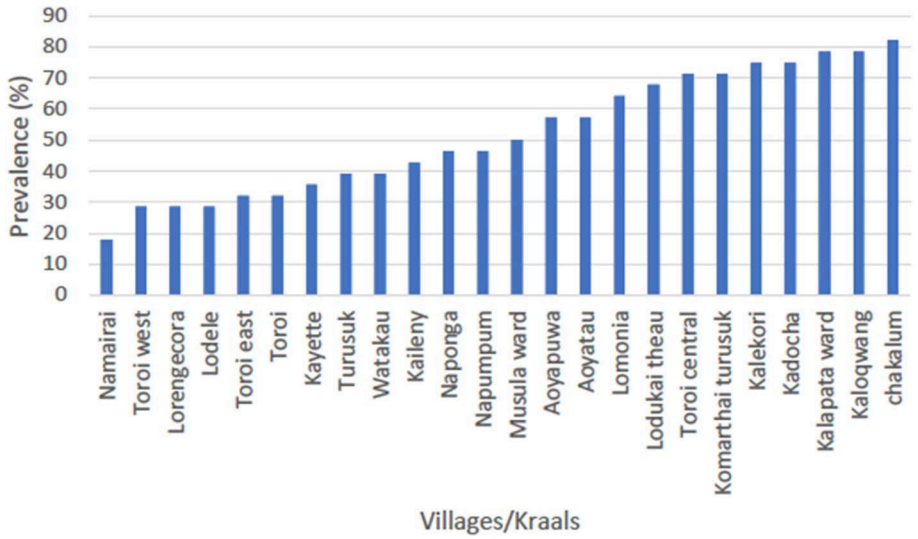

FIGURE 4 | Serosurvey result for the northern focus of transmission (Kotido-Kaabong). The average prevalence in the northern focus was 51.4% with the highest seroprevalence being 82.1% in Chakalum village whereas the lowest was 17.9% in Namairai.

Spatial Analysis

ELISA result data and GPS coordinates were entered in Microsoft excel office 2016 package and saved as coma separated files [.csv]. Seroprevalence data was used to map the spatial distribution of PPR antibodies in the foci in the Karamoja subregion. The shape files were obtained from the web-based GIS free resource while some were created in ArcMap ver. 10.5 software. Point prevalence data from the two foci were interpolated using an inverse-distance weighted (IDW) technique using the Geostatistical Analyst tool in ArcMap ver. 10.5.

Data Analysis

Triangulation of information, as practiced in participatory rural appraisal (2, 8) was utilized to compare results within the participatory assessments and with epidemiological data such as historical vaccination coverage. Triangulation was also used between the participatory assessments and laboratory-based test results.

In preparation for statistical analysis, data was entered into Microsoft Excel (Office 2016 Package) for curation. Overall seroprevalence was calculated by dividing the number of positive animals by the total number of small ruminants sampled whereas the herd level prevalence was calculated by dividing the number of positive animals the number of animals each herd (village) contributed.

The raw nucleotide sequences (ab1 files) were viewed and edited with BioEdit software version 7.0.0 (17) to remove any ambiguous sequences. Multiple sequence alignments and phylogenetic trees were constructed using MEGA X software (18, 19). The representative sequences for each lineage with which to compare were downloaded from the web-based GenBank housed at the NCBI for each gene sequence.

RESULTS

Site Assessment and Risk Mapping

The site assessment interviews indicated that PPR was a common and important problem. The majority of communities were able to recall and describe outbreaks of disease consistent with PPR. The names used by the Karamoja for the disease, 14 recorded in total, were diverse and localized whereas the Pokot tended to use a single name, *losür*. Not all respondents who could describe syndromes and events consistent with PPR used a name specific for the disease; some used a name that could describe multiple diseases. Commonly, participants stated the disease outbreaks were introduced to Karamoja region from Kenya and then move west deeper into Uganda as the communities practiced seasonal movements in search of grazing. No reports of outbreaks arising from the West were received.

Hot spots for PPR were delineated based on the triangulated site assessment data and the risk maps prepared by the focus groups (**Figure 2**). The map indicates that there are two principle hot-spots for PPR. The southern focus is centered on the border area between Loroo Subcounty of Amudat District, Uganda and the Alalae area of West Pokot District in Kenya. The local Pokot community reported that they were fully integrated across the border. They and their livestock moved freely between Uganda and Kenya. Many respondents used Kenyan cell phone numbers and Kenya currency was commonly used in the area.

The northern focus is at the intersection of Kotido, Kaabong, and Moroto Districts. It includes Nakapelimoru subcounty in Kotido District, Loyoro subcounty in Kaabong District of Uganda. The adjacent Kobebe dam area in the north of Moroto District was also mentioned in the focus groups and site assessments interviews as a component of the northern focus of transmission. Turkana from the Loima area of Kenya frequently share the grazing in the northern hotspot and reported livestock

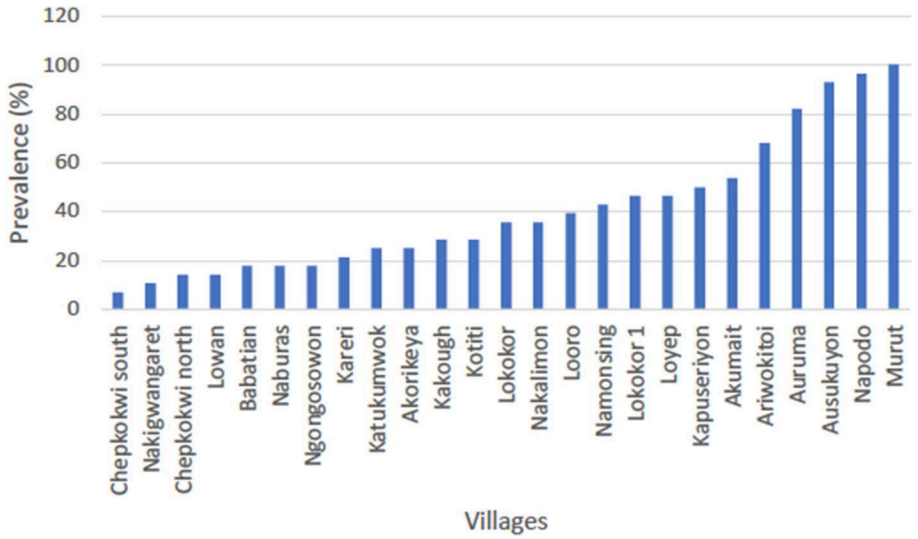

FIGURE 5 | Serosurvey result for the southern focus of transmission (Amudat). The average prevalence in Loroo subcounty was 40.7% with the highest seroprevalence being 100% in Murut village whereas the lowest was 7.1% in Chepkokwi south. More than half of the sampled villages (herds) had prevalence below 50%.

disease profiles that were consistent with the information provided by Karamojong participants.

In the focus groups, there was a broad consensus the first PPR compatible events in Karamoja in modern memory date from 2005. From the time of the first recognition of PPR by local communities in 2005 until present, the direction of virus flow was reported to be from the East to West (**Figure 2**).

The project then identified target areas in Uganda for the focus of control interventions along the border with Kenya (**Figure 3**). One hypothesized critical hotspot in the north is shown and includes Nakapelimoru Subcounty in Kotido District and Loyoro Subcounty in Kaabong District of Uganda. The second was to the south in Loroo Subcounty, Amudat district.

Surveillance

Surveillance identified three outbreaks, all of which were in the two hotspots identified in the participatory assessment and risk mapping. The locations were Loroo Subcounty in Amudat District, Nakapelimoru Subcounty in Kotido District and Kamion Subcounty in Kaabong District. The outbreaks in Loroo and Kamion were positive using the field rapid test. The Nakapelimoru outbreak was not tested with the field rapid test. All three outbreaks were positive on PCR. Herds in the Kamion outbreak were housed together in large defensive kraals due to recent problems with raiding. Herds in Loroo and Nakapelimoru were kept separately at homesteads.

Serology

- Of small ruminants surveyed from the southern focus, 40.7% (285/700) were positive for PPR specific antibodies whereas 51.4% (360/700) small ruminants sampled from the northern focus tested positive for PPR specific antibodies during the serosurvey. The distribution of herd prevalence is presented for the southern and northern foci in **Figures 4**, **5**, respectively. The spatial distribution of prevalence is presented as a map in **Figure 6**.
- For the outbreak investigation, 48.5% (232/478) of the sera from Loroo outbreak in southern focus and 94.3% (415/440) of the small ruminants from the northern focus outbreak (Kamion) were positive for PPR specific antibodies (**Figures 7**, **8**, respectively). As a whole, the individual herd seroprevalences in the Loroo outbreak were greater when compared to those found in the baseline survey conducted across the hot spot before the outbreak. For example, four herds seroprevalences over 90% were detected after the outbreak.

Sequencing

Representative samples from the outbreak hotspots were randomly selected from the PCR positives and sequenced. The sequences were deposited in GenBank under accession numbers MK250004-MK2500011 and MK242028-MK2242037 for the Nucleoprotein and Fusion genes respectively. Based on the BLAST search results, representative sequences from each virus lineage including sequences from countries neighboring Uganda were retrieved from GenBank. Phylogenetic analysis, by both gene fragments revealed that sequences from this study were lineage III as shown in **Figures 9**, **10**. Nucleoprotein gene phylogeny (**Figure 9**) clearly revealed two PPRV lineage III subclades (a and b) representing virus sequences from the two independent outbreaks. The northern subclade (b) was more closely related to KF939644.1 Ngorogoro than to the southern Karamoja focus. The southern focus grouped with KM 463083.1 KN5/2011, an isolate from Turkana Kenya, and KP691481.1 Uganda 2012 and KP691482.1 Uganda 2012 which originated from Kotido in 2012 in lineage III subclade a (**Figure 9**).

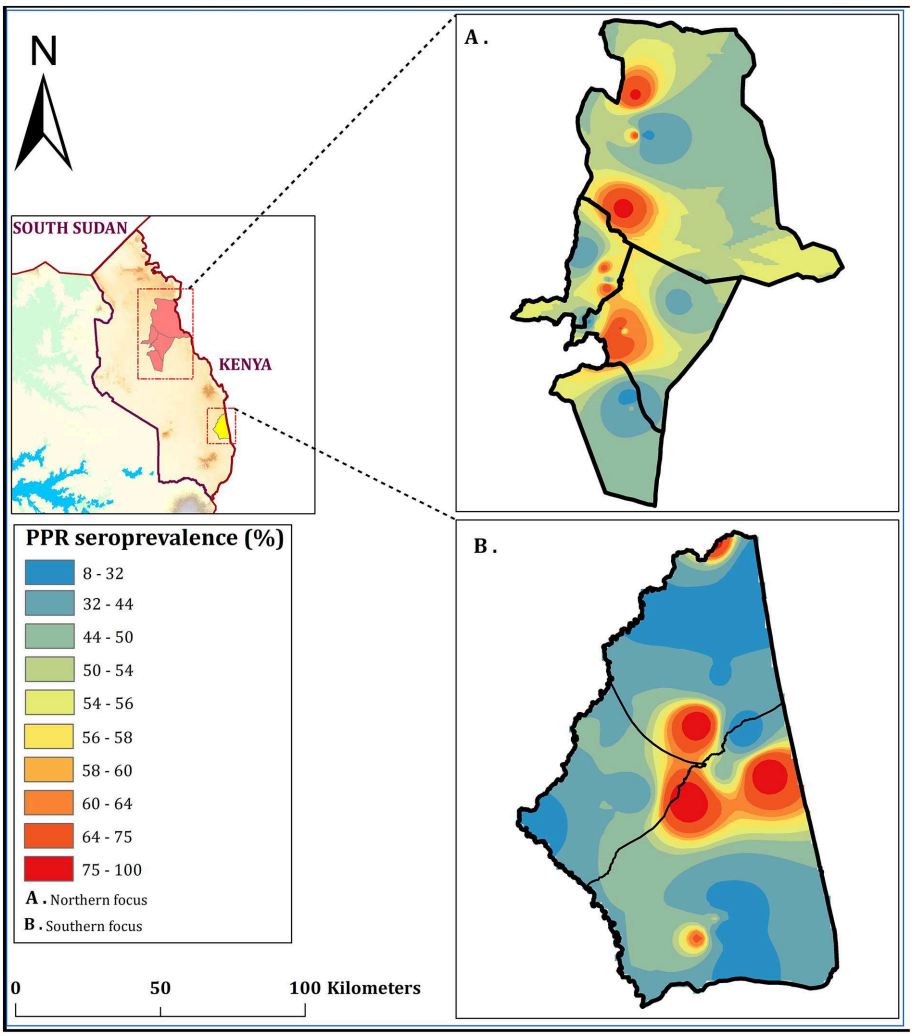

FIGURE 6 | Seroprevalence of PPR in Karamoja subregion (in set); May 2018. Shows the spatial distribution of PPR in the northern focus **(A)** and the southern focus **(B)** interpolated using 25 PPR point prevalence in each focus to create a focus-wide spatial effect. Interpolations were made using inverse-distance weighted (IDW) method using the Geostatistical Analyst tool in ArcMap ver. 10.5 software to produce a continuous *PPR* prevalence raster map on a spectral color ramp.

In our F gene re-analysis, previous sequences (20) formerly regarded as lineage I were classified as lineage IV whereas those regarded as lineage II clustered with lineage III in our F gene re-analysis. The F gene sequences from this study clustered with other lineage III sequences. The virus nucleotide sequences from the southern focus (Loroo) were identical or nearly so to each other but slightly different from those from the northern focus (Kamion) outbreak.

DISCUSSION

Most Karamojong and Pokot respondents recognized syndromes consistent with PPR and were aware of the availability of interventions to mitigate PPR. Frequently, detailed and patient dialogue on animal health issues was required to establish an accurate understanding of the experience and knowledge of the participants with respect to PPR. Practitioners of participatory epidemiology have had similar experiences in regard to PPR in Ethiopia and Tanzania (Jones et al., submitted). The complexity and diversity of language and local knowledge on PPR suggests that direct, structured questions in questionnaire surveys are unlikely to arrive at accurate understandings of community knowledge regarding PPR.

The participatory analysis identified separate northern and southern foci of PPRV transmission that were closely linked with transmission in Kenya. The presence of these transmission hotspots was supported by the surveillance exercise conducted throughout Karamoja that detected three PPR outbreaks, all located in the hotspots. Each of these virus clusters were more closely related to PPR strains of Kenyan or Tanzanian origin than they were to each other.

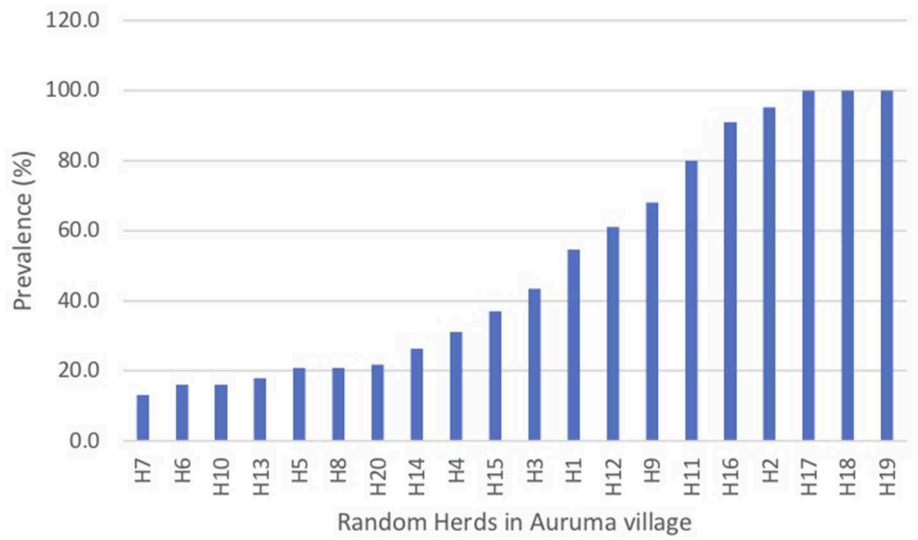

FIGURE 7 | Serosurvey results from the Loroo outbreak investigation in the southern transmission focus (Amudat). It showed the distribution of prevalences was uniformly greater in comparison with the baseline serosurvey conducted across the southern foci. Note 4 herds had a seroprevalence of >90% after the outbreak.

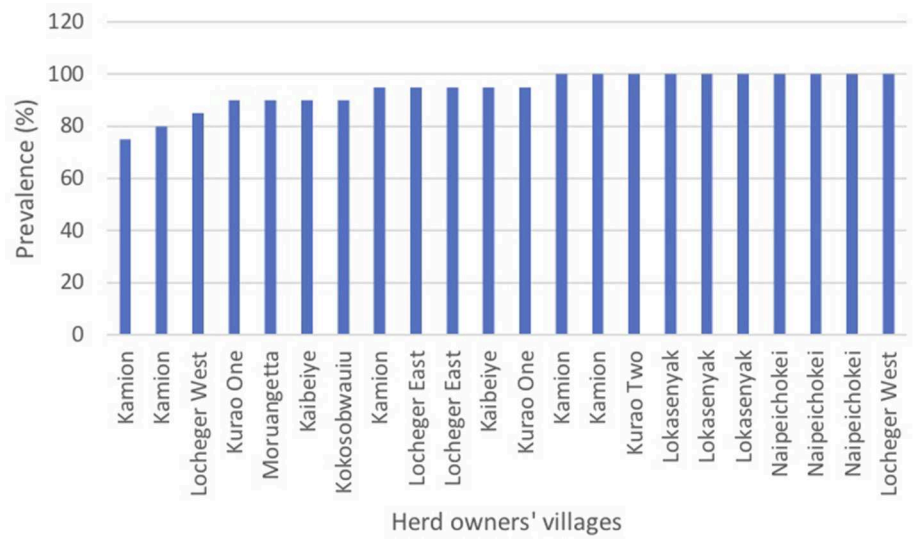

FIGURE 8 | Serosurvey results from the Kamion outbreak investigation in the northern transmission focus (Kotido-Kaabong). The serosurvey following the outbreak in the Kamion & Kalapata security kraals that housed herds from numerous villages found uniformly high seroprevalences. The labels represent the home villages of the herds sampled at the security kraals. Ten of the herds sampled were 100% positive.

N gene sequences from the Kamion outbreak virus isolates were more closely related to isolates from Tanzania (Ngorongoro) as compared to those in Uganda. Ngorongoro is a northern Tanzanian district that borders Kenya and previous research advances have highlighted a belief that PPR introduction to Northern Tanzania originated from Kenya around 2008 (21). This phylogenetic finding from this study indicates that probably the PPR viruses responsible for the outbreak in Amudat district in April 2018 originated from Kenya or vice versa. More PPRV sequence data in the East African region and future studies on transboundary and cross border movement of livestock will provide more insights into the PPRV epidemiology.

The F gene sequences from Kamion outbreak (MK242036 - MK242037) were closer to isolate KJ867543, a lineage III whole genome sequence recently isolated from Uganda (22). Reanalysis of all the PPRV sequences submitted to GenBank from Uganda between 2007 and 2018, confirmed that 90% of these sequences were PPRV lineage III. However, the six F gene sequences submitted by Luka et al. (20) from Uganda retrieved from GenBank, clustered in lineage III and

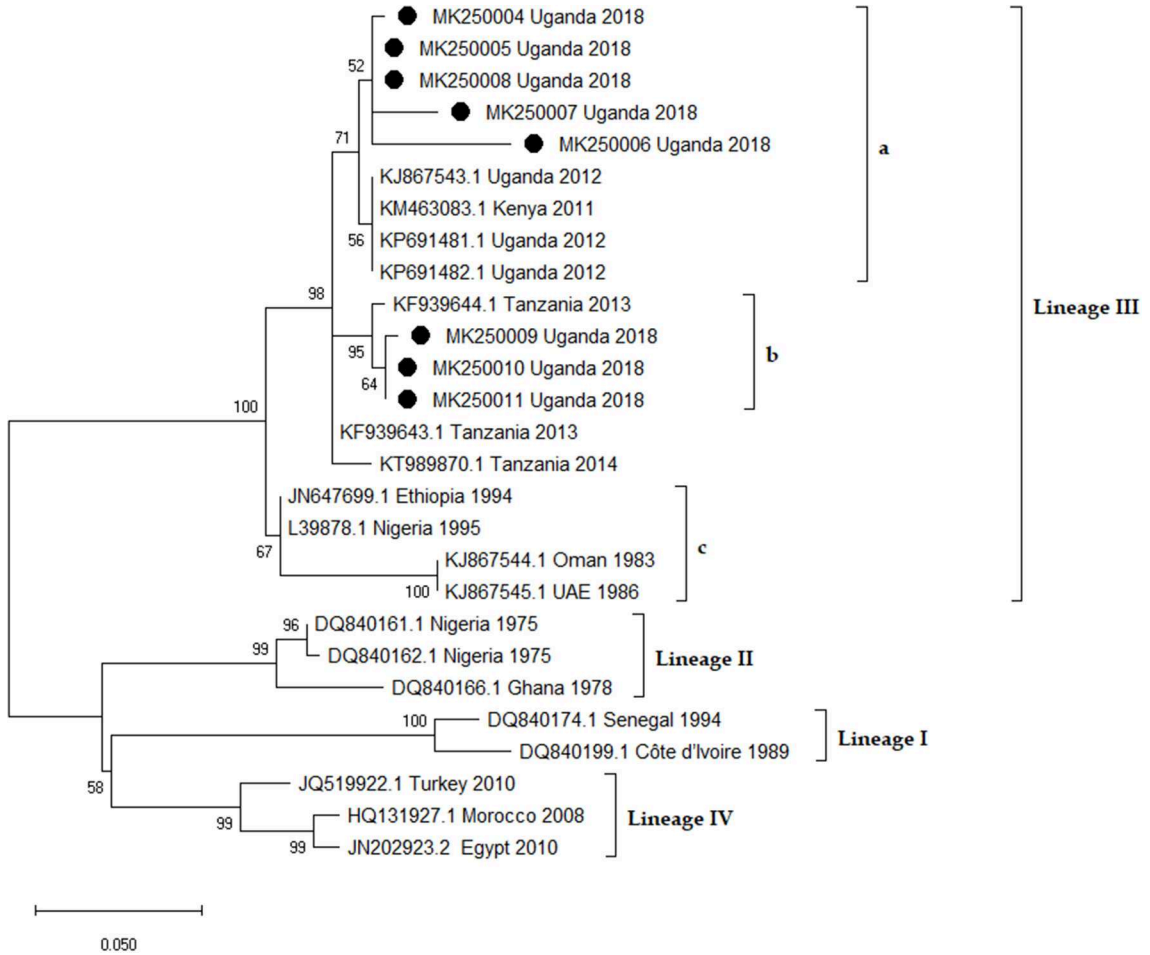

FIGURE 9 | Phylogenetic analysis of Peste des petits Ruminants virus Nucleoprotein (N) gene fragment in MEGA X software. The Maximum Likelihood method and the Kimura 2-parameter [+ I] models were selected to best infer evolutionary relationship. The tree is drawn to scale, and the branch lengths correspond to the number of nucleotide substitutions per site. Bootstrap values of 1,000 replicates are indicated at each node. The rate variation model allowed for some sites to be evolutionarily invariable ([+I], 30.00% sites). This analysis involved 27 nucleotide sequences and their accession numbers and countries of origin are indicated. The sequences from this study are denoted by black circles [●] and they form two sub-clusters (a and b) in lineage III. Sub-clusters a and b are from the southern and northern foci, respectively.

IV but not lineages I and II as reported by Luka et al. (20). This exact misclassification pattern of PPRV lineages in Uganda was observed and reported by the study (23). The Nucleoprotein gene sequences from this study better delineated the isolates from the two outbreak areas. This was probably so because the N gene is more polymorphic and has been credited by recent research advances as a better target for PPRV genotyping (24).

The serum sampling of the two hot spots was conducted to access population immunity level in relation to past vaccination coverage and establish a baseline herd immunity measure to support impact assessment of future vaccination programs. Small ruminant population figures for Karamoja are a subject of debate. At best, vaccine allocations do not account for more than 15–20% coverage and could not account for the level of herd immunity observed.

At the household level, a continuous range of prevalence were observed in the serosurveys from the two hot spots (**Figures 4**, **5**). It was not possible to clearly categorize households given the nearly linear distribution of household prevalence. On the other hand, the map (**Figure 6**) demonstrates clustering of households in areas of high prevalence. It is not known if this represents foci of transmission or clustering of vaccination. Although the aggregate serology results indicated the presence of endemic disease, in the absence of detailed data for mapping of vaccination, serology was not useful for conclusively identifying transmission sites.

The patterns in the distribution of household seroprevalence in the two post-outbreak samples showed a clear contrast. The sample from the Loroo outbreak came from 20 separate kraals in approximately a one km radius of the index kraal. Overall, the prevalence was higher than in the random sample taken from the whole of Loroo subcounty by 7.8%. The distribution of prevalence in the herds was uniformly greater when compared to the serosurvey conducted across the southern

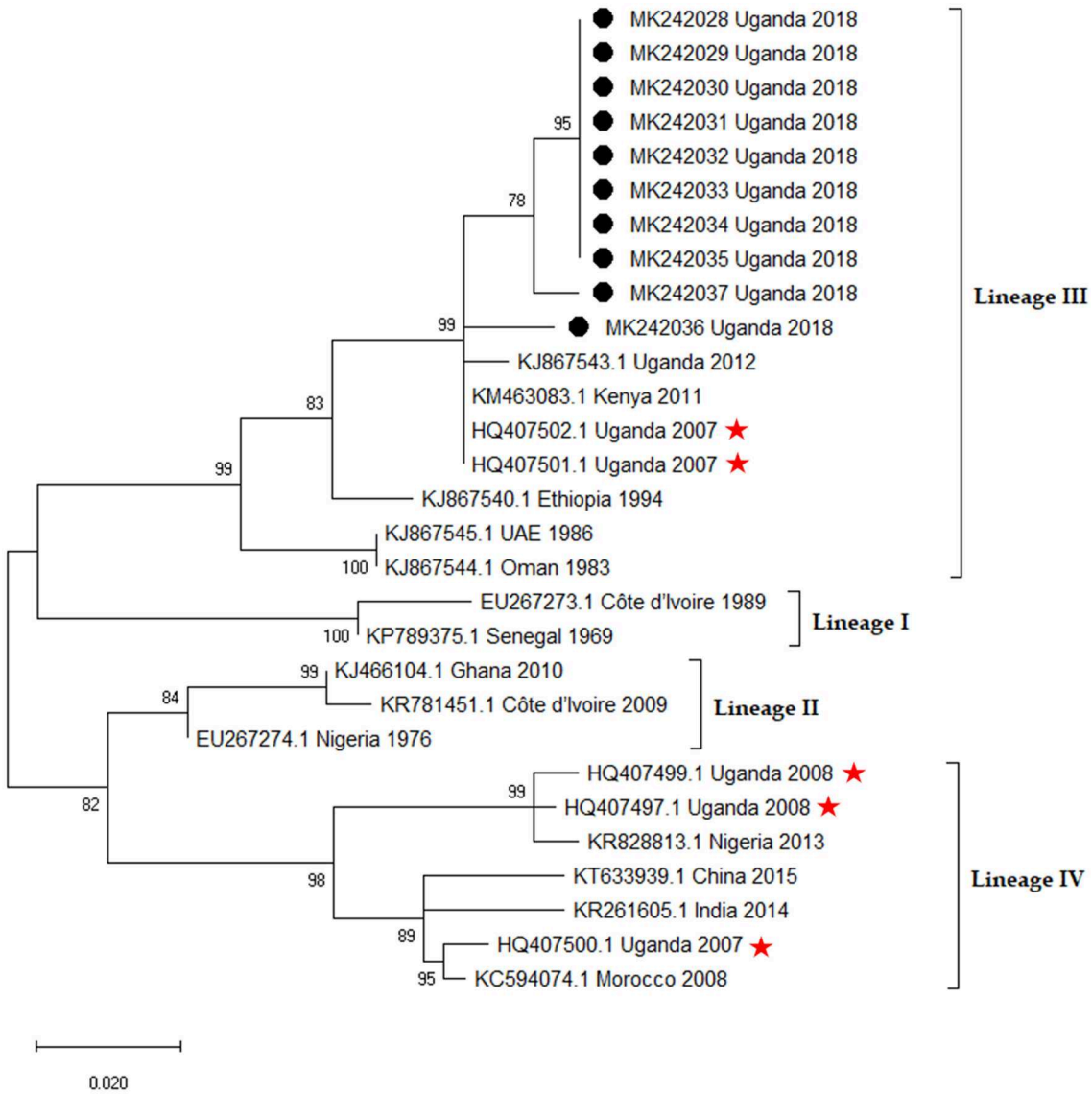

FIGURE 10 | Phylogenetic analysis of Peste des petits Ruminants virus Fusion (F) gene fragment in MEGA X software. The Maximum Likelihood method employing the Kimura 2-parameter (+ I) was selected as the best model to infer evolutionary relationship. The tree is drawn to scale, and the branch lengths correspond to the number of nucleotide substitutions per site. Bootstrap values of 1,000 replicates are indicated at each node. The rate variation model allowed for some sites to be evolutionarily invariable ([+I], 36.89% sites). This analysis involved 29 nucleotide sequences and their accession numbers, country of origin and year of isolation are indicated. The sequences from this study are denoted by black circles [●] and sequences with asterisks [★] are the ones misclassified by Luka et al. (20).

foci. Three herds had 100% and 1 more was over 90% prevalence (**Figure 7**). The Kamion subcounty outbreak sample was from 22 households whose livestock were kept in two large security kraals established to guard against stock theft in raids that had recently occurred. The seroprevalence of 94.3% indicates that transmission rates were high within these large kraals (**Figure 8**). The pattern at Loroo with 4 kraals with 90 to 100% prevalence suggest that the between herd transmission rate was moderate, whereas the within herd transmission rate was high.

It has been argued that larger pastoral areas maintain PPR as one continuous and relatively amorphous system of transmission. The distribution and timing of reported outbreaks, in the absence of good qualitative data and genomics, appear as diffuse endemism requiring a mass response. Our findings indicate that deeper investigation of the patterns of circulation of PPR within pastoral areas using good participatory inquiry and genomics can reveal finer structure that can facilitate eradication efforts. The distribution of outbreaks identified and the cluster of strains confirmed that Karamoja has at least two systems of PPR transmission. This finding is of great significance for the targeting of eradication interventions in the global eradication of PPR.

Our findings suggest that even within the relatively small area of Karamoja, the northern and southern foci are predominately

separate systems that should be explicitly addressed separately in the implementation of eradication. However, both these systems extend across the border into Kenya and any effort to address either system must be through a holistic program consisting of integrated cross-border interventions. One system is in the Pokot communities near Loroo, Uganda and Alalae, Kenya and the second in the Jie, Dodoth, Karamojong, and Turkana communities that occupy the Nakapelimoru, Loyoro, Kamion area of Uganda and the Loima area of Kenya.

The concept of targeting eradication interventions is based in an adaptive management approach. Adaptive management assumes that information is incomplete and strives to make the best decisions possible on available evidence while advocating for continued learning. The epidemiological scenario presented here is a significant step forward for the targeting of interventions, but should not be considered final nor permanent. Additional information would improve the accuracy of the scenarios and may reveal more foci or shifting relationships. Risk factors that shape transmission patterns will change over time. Participatory assessment, outbreak investigation and sampling leading to genetic analysis should be intensified within Karamoja, across Uganda and internationally.

It is proposed that the use of epidemiological analysis to target vaccination can enhance the efficacy of eradication interventions and reduce the costs of eradication. The cost of the delivery of one vaccine has been estimated as 0.30 USD (25). The resources that can be mobilized for PPR eradication are not unlimited and need to be utilized effectively in line with the program goals. Routine, institutionalized vaccination that is not targeted to viral elimination leads to suppressed endemism and is an impediment to eradication (26). Prior to vaccination, ground work to establish epidemiological goals and coordinated delivery mechanisms that achieve those goals are required.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical approval was granted, approval numbers: IRB201701701 (University of Florida), IRB1707030 (Tufts University) and by the institutional research board of Makerere University (Research proposal SBLS/REC/17/001), University of Florida (Study #; 201701701) and Tufts University (Study #: 1707030). Institutional Animal Care and Use Committee (IACUC) was obtained from the University of Florida (Protocol #: 201709832).

AUTHOR CONTRIBUTIONS

JN participated in field investigations and development and optimization of laboratory analysis plan, performed spatial and phylogenetic analysis, and writing the manuscript. JC-S conducted sight assessment interviews, investigated and sampled outbreaks, facilitated risk mapping, and contributed to writing the manuscript. SO supervised development and optimization of laboratory protocols. FM supervised development and optimization of laboratory protocols. AP supported surveillance and detected, field diagnosed, and sampled the Kamion outbreak. CN participated in laboratory and phylogenetic analysis. EI facilitated focus groups, supported surveillance, and outbreak sampling. NN contributed to the design of the research and surveillance system. PN participated in field investigations. RA participated in field assessments and establishing the surveillance system. SH participated in the design of the research. JM led research and manuscript preparation and contributed to the site assessment, risk mapping, surveillance system, and outbreak investigation and sampling.

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PPR Control in a Sahelian Setting: What Vaccination Strategy for Mauritania?

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Peste des Petits Ruminants (PPR) is a viral disease affecting domestic and small wild ruminants. Endemic in large parts of the world, PPR causes severe damages to animal production and household economies. In 2015, FAO and OIE launched a global eradication program (GCSE) based on vaccination campaigns. The success of GCSE shall depend on the implementation of vaccination campaigns, accounting for husbandry practices, mobility and the periodicity of small ruminants' population renewal. In Mauritania, PPR outbreaks occur annually despite ongoing annual vaccination campaigns since 2008. Here, we developed a mathematical model to assess the impact of four vaccination strategies (including the GSCE one), the importance of their timing of implementation and the usefulness of individual animal identification on the reduction of PPR burden. The model was calibrated on data collected through *ad-hoc* surveys about demographic dynamics, disease impact, and national seroprevalence using Monte Carlo Markov Chain procedure. Numerical simulations were used to estimate the number of averted deaths over the next 12 years. The model results showed that the GSCE strategy prevented the largest number of deaths (9.2 million vs. 6.2 for random strategy) and provided one of the highest economic returns among all strategies (Benefit-Cost Ratio around 16 vs. 7 for random strategy). According to its current cost, identification would be a viable investment that could reduce the number of vaccine doses to distribute by 20–60%. Whilst the implementation of the identification system is crucial for PPR control, its success depends also on a coordinated approach at the regional level.

Keywords: PPR, West Africa, mathematical modeling, vaccination, cost-benefit analysis, global strategy for control and eradication (GSCE)

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INTRODUCTION

Peste des Petits Ruminants (PPR) is a viral infectious disease affecting domestic (goats and sheep) and small wild ruminants (1, 2). The virus can infect camels (3–5), cattle, and buffalos (3, 6) although their role in the transmission remains unclear. PPR virus (PPRV) is transmitted through close contact between infected and susceptible animals. Common signs of the infection are high fever, ocular and nasal discharges, erosive lesions on different mucous membranes, particularly in

the mouth, diarrhea and respiratory distress. Because these symptoms are similar to those of other diseases such as rinderpest, pasteurellosis, and bluetongue (7), the clinical diagnosis is taken as provisional until confirmed by a laboratory. Depending on age and species (sheep are clinically more resistant than goats) the disease may be hyper-acute (mortality at 98% among 4–7 months old animals), acute (mortality at 60% among all population), mild (no mortality), or sub-clinical (8, 9). The sub-clinical form is frequent in Sahelian ruminants, in particular among sheep: the infected animal, although not showing any clinical signs, may shed the virus and transmit it to other animals by close contact (10).

Due to the severe impact of PPR on animal production, and following the successful rinderpest eradication, FAO and OIE have developed a strategy for PPR eradication by 2030 relying on vaccination campaigns and disease surveillance (11). Indeed, as for rinderpest, there are a very efficacious attenuated PPR vaccines that provides lifelong immunity and efficient PPR specific diagnostic tools for disease surveillance (12–15). Despite the similarities with rinderpest, the PPR eradication strategy should take account of some characteristics of small ruminant production that could hinder the process: the small ruminants population is much larger and grows faster than that of cattle; small ruminants have a lower socio-economic value and consequently less investments are made for their health; small ruminants can be sold more easily to cover household needs, and can be traded in large flocks (16). The PPR Global Strategy for the Control and Eradication (GSCE) is composed of 4 necessary steps: 1-Assessment, 2-Control, 3-Eradication, and 4-Post-eradication follow-up (11). In stage 2, mass vaccination (100%) of all animals older than 3 months of age is suggested in a first phase, followed by a phase of targeted vaccination of animals between 4 and 12 months of age. Previous work (16) has shown that, at worldwide level, the eradication programme would be highly beneficial economically, with an average benefit-cost ratio of 33.8, providing a compelling argument for PPR eradication. On the other hand, other works (17–19) showed that other costs, like the logistic (fuel for vehicles, maintenance of the cold chain etc.) and the personnel (time and missions to vaccinate animals) ones, and the vaccine wastage (doses given to already vaccinated animals) could have a relevant impact on the vaccination campaign, accounting for, in some cases, up to 70% of the campaign costs. To be effective, GSCE should be tailored to country epidemiological situation and take account of small ruminants production system dynamics.

Small ruminant production plays a major role in Mauritania economy. Indeed, goat and sheep production ensures (an almost) self-sufficiency for the country's red meat consumption and their trade represents a major source of income contributing to almost 70% of the agricultural GDP[1]. PPR is endemic in Mauritania, with outbreaks reported yearly during winter time (January-March) and during the Tabaski period[2].

[1]GDP, Gross Domestic Product.

[2]Tabaski is the Muslim religious festivity of Aid-el-Kebir, during which each family sacrifices a sheep. The date of tabaski depends on the lunar calendar and every year is anticipated of 11 days.

Livestock mobility and population turnover are two of the main factors contributing to the propagation and persistence of the virus in the Sahelian region (20, 21). In West Africa, animals, mainly adult ones, are moved in search of better grazing areas (i.e., transhumance) (21–23), to be sold alive at markets (i.e., for commercial reasons and at religious festivities such as *Tabaski*) (24, 25), or to be exchanged among families and relatives (i.e., *confiage*) (25, 26). Because of these movements, infected and susceptible (e.g., naïve) herds can get in contact, thus allowing virus transmission.

On the other hand, population renewal sustains endemicity of the virus. Depending on husbandry practices and agro-ecological systems, births are concentrated in 1 or 2 periods of the year. Newborn animals from mothers with PPR antibodies (i.e., naturally immunized or vaccinated), can inherit maternal antibodies, through colostrum, and be protected from the infection for the first 2–4 months of their life. After this period, animals become fully susceptible to PPR (27, 28) thus ensuring the regular re-introduction in the population of fully susceptible animals that could feed the disease cycle (29).

PPR represents a huge constraint to the development of Mauritania, affecting the economies of middle-low incomes families. Symptomatic animals are treated with antibiotics for a week (30) and vitamins. These treatments are done at the disease onset, aiming to prevent secondary bacterial infection, reduce severity of the disease and minimize economic losses. A retrospective study in Mauritania. El Arbi (10) reported that the practice of giving antibiotics to animals is widespread among herders and livestock owners, although this is not recommended by OIE. Vaccination remains the only viable and practical tool to control the disease as it will be impossible to implement drastic sanitary measures, stamping out policy and restriction of animal movements in Mauritania. Small ruminants vaccination campaigns against PPR are implemented since 2008 but the coverage rate remains low (ranging from 2 to 8% between 2008 and 2010; and in 2018 reaching 15.6% of the population) (10). The low vaccination coverage can be explained by several factors, such as: (i) vaccination is not compulsory, except in case of outbreaks; (ii) there is a lack of information about vaccine benefits (10), and most importantly, (iii) logistics issues, such as the cold chain for maintaining the vaccine, constrain the distribution of the vaccines. Nevertheless, for small ruminants' owners, vaccinating an animal costs 0.10 USD against 1.40 USD for giving antibiotics treatment (10).

To stop the epidemics spreading the GSCE (11) requires the post-vaccination immunity coverage to reach at least 70% (PVIR threshold), 80% to consider the country PPR-free. The PVIR threshold depends on the basic reproduction ratio R_0 that could vary depending on the characteristics of the geographical area and epidemic setting. For example, the authors of Fournié et al. (31) estimated a lower value of the PVIR threshold, around 61.7% for the Ethiopian small ruminant population. Moreover, as shown in Hammami et al. (29, 32) for sub-Saharan Africa herds, the immunity coverage is strongly dependent on the month of vaccination.

Effective and efficient use of public funds is considered as necessary in the context of limited resource availability.

In the Mauritanian context, the economic evaluation of PPR eradication scenario options through a cost-benefit analysis is therefore of great interest as it would inform the government about the most cost-effective choice, at community level, between financing of the vaccination campaign and the management of disease outbreaks by breeders. In this work, we used a dynamic model to estimate the impact of PPR in Mauritania and economic benefits of different vaccination strategies, some of them already being in place, others to be implemented, for the period 2018–2030. Based on recent epidemiological and socio-economic data collected on the field, our model takes account of both transmission and demographic dynamics of the Mauritanian national herd. Dynamical models are commonly used in human and animal health, and have been applied to study cost-effectiveness or cost benefits of vaccination strategies (33–35) mainly for their capacity of assessing indirect effects of vaccination (36, 37). A similar model was developed for the Ethiopian national herd (31). We also used the model to assess if and under which conditions identification and "identification and screening" could be viable procedures to reduce the number of vaccine doses to distribute by minimizing vaccination wastage.

MATERIALS AND METHODS

Study Area

Mauritania is located on the African Atlantic coast, confining with Morocco, Western Sahara, Algeria, Mali, and Senegal. The northern part of the country is hyper arid, while the rest is arid (38). The country is divided in 15 Wilayas (i.e., regions), subdivided in 44 Moughataas (departments). Most of the population is concentrated along the coast, mainly in Nouakchott accounting for almost a quarter of the population, and along the river Senegal in the South. In 2016, Mauritanian small ruminant national population counts around 6.2 million goats and 9.6 million sheep (http://www.fao.org/faostat/), mostly located in the Eastern (50% of national herd) and Southern (35%) Wilayas along the Senegal River. According to the recent demographic survey done by ONARDEL[3] and Mauritanian Veterinary Services, small ruminant herds are mixed (sheep and goats) with a higher proportion of sheep, reaching 70% of the herd.

The first documented occurrence of PPR dates back to 1982 in the Gorgol Wilaya (39). Since then, the disease has been considered endemic in the country. According to the 2010 PPR national serosurvey, conducted under the frame of the AU-Ibar project VACNADA (http://www.au-ibar.org/vacnada), the estimated seroprevalence rate among small ruminants was 39% (95% C.I. 37–41%) (40).

Data

Data on herd demography, PPR seroprevalence and disease impact were collected by ONARDEL officers through *ad-hoc* national surveys to calibrate the epidemiological model. Data on herd demography, which include deaths, births, purchases, and sales of small ruminants were collected in 2015 through a survey among all the Wilayas, except the Nouakchott district (investigated Wilayas are the colored ones in **Figure 1**). During the same year, a retrospective study was conducted to retrieve information on the impact of PPR outbreaks, number of cases and deaths, in the 12 previous months. The study was done in 10 Wilayas located in the three major pastoral areas of Mauritania: Hods, Assaba, and Senegal River valley (patterned Wilayas in **Figure 1**). Finally, in 2010 a national serosurvey campaign was conducted as part of the VACNADA project activities to estimate PPR prevalence in 10 Wilayas (circles in **Figure 1**).

Demographic Data

A total of 2,892 small ruminant herds were surveyed among 12 Wilayas in the pastoral area. Information were collected about herd size, their composition in terms of sex (male and female), species (goats and sheep) and age (weans, younger than 6 months, and animals older than 6 months), and the demographic events which had occurred over the previous 12 months (births and deaths, animal entry and exit, see **Table 1**).

Serological Data

Sheep and goats older than 3 months and coming from 21 villages in 10 Wilayas were sampled for a total of 1,897 small ruminants (711 goats and 1,186 sheep). The collected sera were tested for the presence of IgG antibodies against PPRV. For each animal, information about species, sex, and age (based on teeth counting) were also collected. The results show a significant difference according to species, with sheep presenting a higher prevalence level than goats (**Table 2**).

Disease Impact Data

Seven hundred and eight herders were surveyed using a semi-structured questionnaire over the events of the last 12 months, in particular: PPR knowledge; PPR cases and related deaths in the herd; intervention costs and the impact of the disease on the animal production, and epidemiological and economic data collected for more than 9,200 animals. Herders were chosen according to husbandry practices: transhumant or sedentary. No distinction was made between species in the premises, their gender and age. **Table 3** reports some of the survey results that have been used to calibrate the model. The fatality rate has been evaluated as the ratio of PPR-related deaths over cases counted in a year.

Model Structure and Calibration

The small ruminant population (sheep and goats) demographics and transmission dynamics were simulated using a deterministic age-stratified compartmental model, without differentiating animals according to their species or their spatial location. A pictorial representation of the model is given in **Figure 2** (to simplify, only the first and the i-th age-group are presented). The model considered a population stratified in seven age-groups (0–3 months-old, 3–6 months-old, 6–12 months-old, 12–24 months-old, 24–36 months-old, 36–48 months-old, and

[3]ONARDEL (Office National de Recherche et Développement de l'Elevage), it is the competent body for animal health in Mauritania

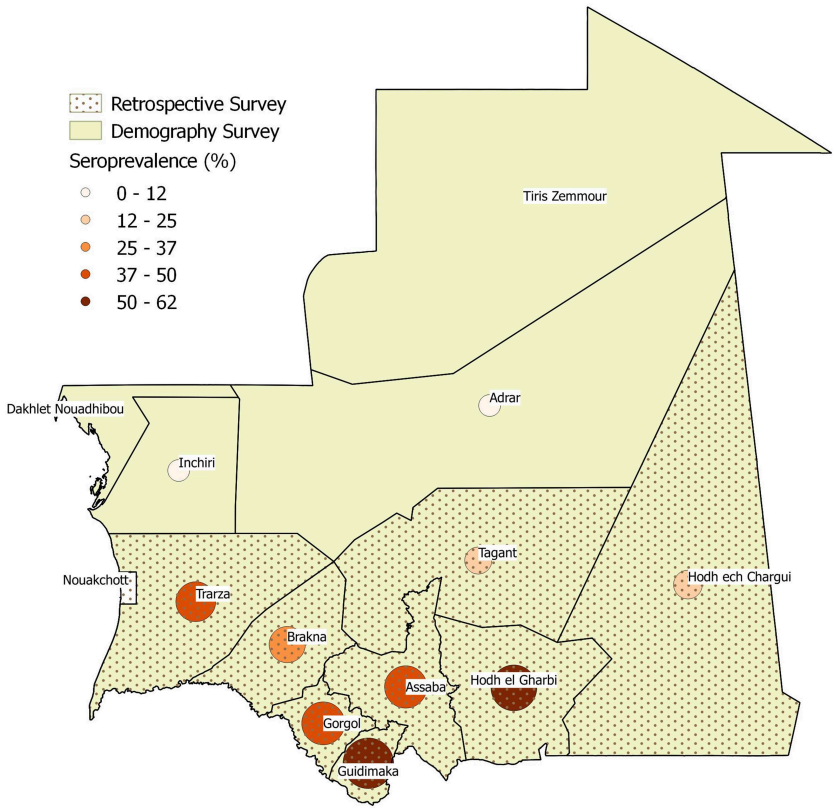

FIGURE 1 | Wilayas included in the demographic (color), impact (dotted pattern) and seroprevalence (circles of darker color and increasing size by positive percentage) surveys.

TABLE 1 | Data from national demographic survey conducted in 2015.

Species	Weans (<6 months old)	Others	Population	Births (last 12 months)	Entries	Deaths (last 12 months)	Exit
Goats	43,729	113,387	157,116	38,046	1,730	9,998	12,629
Sheep	287,869	107,975	395,844	97,814	7,114	36,673	43,973
Total	331,598	221,362	552,960	135,860	8,844	46,671	56,602

Entries and exits indicate the total number of animals entering or leaving the herd, respectively, due to purchases, sales, festivities and loans.

TABLE 2 | Number and percentage (in brackets) of seropositive PPR animals in each age group, by species.

	Goats		Sheep		Small ruminants	
Age (month)	Population	Positive (%)	Population	Positive (%)	Population	Positive (%)
3–6	16	6 (37.5)	34	9 (26.5)	50	15 (33.3)
6–12	136	44 (32.4)	233	102 (43.8)	369	146 (39.6)
12–24	156	58 (37.2)	285	117 (41.1)	441	175(39.7)
24–36	145	49 (33.8)	260	103 (39.6)	405	152 (37.5)
36–48	128	42 (32.8)	212	79 (37.3)	340	121 (35.6)
48+	130	44 (33.9)	162	90 (55.6)	292	134 (45.9)
Total	711	243 (34.2)	1186	500 (42.2)	1897	743 (39.2)

TABLE 3 | Summary table of disease impact survey by type of rearing.

	Sedentary	Transhumant	Total
Herds	178	530	708
Population (*n*)	7,645	89,570	97,215
PPR Cases (z)	1,147	7,167	8,314
PPR-related Deaths	459	1,792	2,251
Fatality rate	40%	25%	27.0%

48 months and older), the age structure being fixed a priori to match the age stratification of the serological survey. The youngest age-group (0–3 months old) accounts for the fact that a large fraction (around 92%) of newborn animals can be protected from the disease over the first 3 months of their life due to the potential inheritance of maternal antibodies against PPRV (27, 29). Because of this, and only for the first group, an extra compartment "Imm" is added to account for animals protected by maternal antibodies. In each age-group, susceptible animals (S) move to the latent state (E) after effective contacts with infectious animals (I), and subsequently become infectious (I). Infectious animals (I), after the infectious period, may recover (R) with a probability (1-p), or die for disease related causes (D) with a probability (p). The epidemiological dynamics is coupled with the underlying demographic one, with animals dying (with natural mortality rate μ), aging (with rate ε), leaving or entering the population due to trade exchanges to and from other countries (with rate *outgoing* and *incoming*), and reproducing (with rate α). We supposed that only animals older than 1 year could be exchanged and give birth. In Mauritania, births are concentrated in two specific moments of the year (August–September and December–January) and movements of small ruminants are concentrated in two periods: between April and June and around Tabaski (26) whose occurrence is anticipated every year of 11 days. The Tabaski-related peak of movements accounts for one fifth of the annual volume of animals traded and outbreaks are reported during this period. We adapted the transmission model to account for these characteristics. The list of parameters and their values is shown in **Supplementary Table 2**.

Demographic Parameters' Estimation

We considered a disease-free population, where the population in each age class (N_a) was susceptible (no infected animal) to study the demographic dynamics of the population. At each time, each age class could change due to death, birth, aging, sale, and purchase of animals. We calibrated the model to estimate natural mortality, fertility, entry, and exit rates due to commercial exchanges. We supposed that the mortality rate was the same for all age groups (μ) except the last one (μ_5). Fertility rate (α), entry (*incoming*), and exit (*outgoing*) ones were null for the first 3 age groups, and constant for all the other. The rates (α,μ,μ_5, *incoming, outgoing*) were estimated by fitting model results to data in **Table 1** using a Bayesian Framework (41). The model ran for a set of parameters to simulate the equivalent of 100 years, with a time step of 1 day. At the equilibrium, we estimated the proportion of deaths, births, entries and exits during the last 12 months, i.e.,

$$p_x = \frac{x}{\sum_a N_a}$$

Where x indicates the annual number of one of the events (death, birth, entry and exit) as simulated by our model. We sampled from the posterior distribution of the parameters $(\alpha, \mu, \mu_5, incoming, outgoing)$ using Metropolis-Hastings algorithm, assuming uniform priors. The numbers of deaths, births, entry and exits (n_x) reported in demographic survey data, **Table 1**, followed a binomial distribution.

$$n_x \sim Binom(Population, p_x)$$

Where *Population* is the number of small ruminants estimated during the survey. We ran 50 independent chains of 1,000 iterations. Results of the calibration procedure are provided in the **Supplementary Material**.

Transmission Model Calibration

Due to the age structure of the model, we introduced the transmission matrix T whose elements T_{ij} are the rate of transmission from infected animals of age group j to susceptible animals in age group i (42, 43). We imposed some transmission patterns, to reduce the number of parameters to estimate. Preliminary analysis of serological data showed that the percentage of seropositive steadily increases for the age-groups (3–6; 6–12 months) and subsequently flattens for older groups. This indicates that the force of infection (λ), the rate at which the susceptible population is infected changes drastically for animals younger and older than 1 year of age: the bulk of infections occurs among the youngest groups whilst new infections among the oldest groups seldom occur. We assumed that:

$$\begin{cases} T_{ij} = \beta_0 & i,j = 1,2,3 \\ T_{ij} = \beta_1 & i,j = 4,5,6,7 \end{cases} \qquad (1a,b)$$

with $\beta_1 \ll \beta_0$. Elements in Equations (1a) and (1b) are the matrix elements for the within-young (both i,j ≤ 3) and within-old (both i,j > 3) groups, respectively, and correspond to the block diagonal elements of the transmission matrix. The other elements of the transmission matrix, indicating transmissions between young (<1 year old) and old groups (>1 year old), we impose to be equal to one of the two (β_1 , β_0). We also considered the case that the transmission parameter is constant across the age groups ($\beta_1 = \beta_0$).

Symptoms appear after 4–6 days (31, 44–46), so we considered an average latent period of 5 days, whilst death can occur after 5–10 days from the onset of symptoms (9, 44, 45) and we considered an infectious period of 5 days. The PPR-related mortality rate, or fatality rate (p), varies with age. Young animals (3–12 months old) are more likely to experience acute or super-acute infections with fatality rate ranging from 70 to 100% (31, 47, 48). Among older animals, more likely to experience a sub-acute form, the fatality rate is negligible, and was set between 0 and 2%. Through the calibration procedure, we estimated the values of the fatality rates for the youngest age-groups.

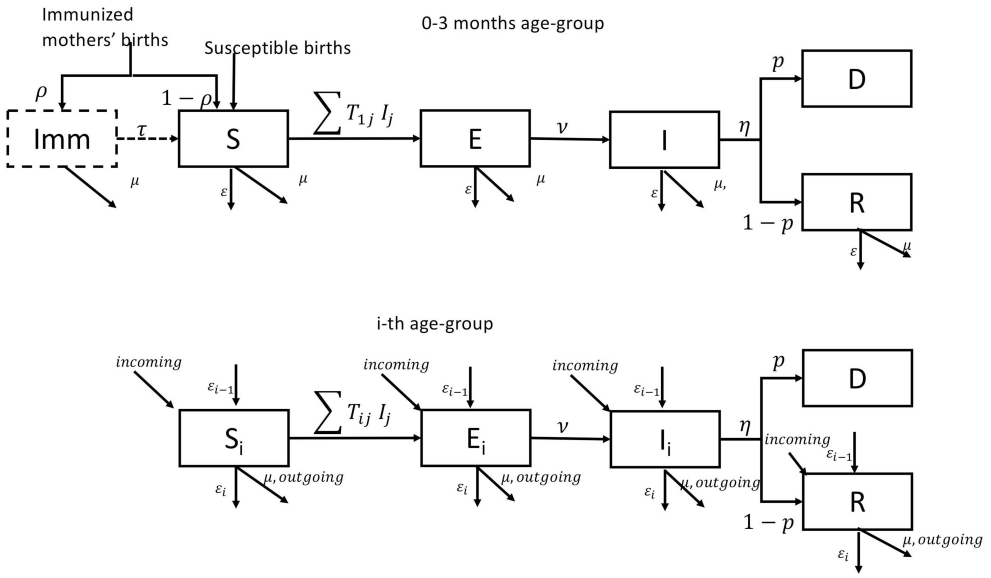

FIGURE 2 | Pictorial representation of the epidemiological model for the first and i-th age group.

The transmission parameters β_1, β_0 and the fatality rates p_{inf}, p_0, for animals of age 0–3 months and 3–12 months, respectively, were estimated through calibration by fitting the model to serological and PPR-related death data in **Tables 2**, **3** and choosing the set of parameters minimizing the Deviance Information Criterion (DIC) value (49). To calibrate the transmission model, we consider that <1% of the population was initially infectious and let the system run for 100 years. At the equilibrium, we estimated, for each age-group the number of recovered animals (R_a) and the total number of deaths caused by the infection in the last year (*D)* among the infected animals in the last year (*Z)*. Parameters estimation was done by fitting the fraction of the immune animals and the fraction of fatal cases to the serological data of **Table 2** and the fatal cases of **Table 3**.

$$\begin{cases} p_a = R_a/N_a \\ p_d = D/Z \end{cases} \qquad (2a, b)$$

where N_a is the population in the a-th age-group. The number of seropositives (pos_a) and PPR-related deaths (*deaths*) follow a binominal distribution:

$$\begin{cases} pos_a = Bin(N_a, p_a) \\ deaths = Bin(Z, p_d) \end{cases} \qquad (3a, b)$$

For all forms of the transition matrix T, we ran 50 Markov chains Monte Carlo (MCMC) Metropolis-Hastings algorithm of 1,000 iterations length and sampled from the posterior distribution of the parameters $Pars = (\beta_1, \beta_0, p_0, p_{\text{inf}})$. The best model had the lowest information criterion (DIC) (49) value. Results are shown in **Supplementary Table 2**.

Forecasts and Impact of Four Different Vaccination Strategies

Baseline Case and 16 Tested Scenarios

We initially run the baseline scenario, where no vaccination is implemented. Then we considered 4 vaccination strategies that could be applied for the period 2019–2030:

- National Strategy (SR): half of the population is vaccinated. This is the current strategy implemented as a containment measure in Mauritania in case of appearance of new cases: only half of the animals of herds in the vicinity of outbreaks herd are vaccinated.
- Targeted scenario (ST): all animals between 4 and 12 months of age are vaccinated. This is the strategy planned for the next years in Mauritania.
- Mixed scenario (SM): National Strategy (SR) for the first 5 years, and targeted vaccination (ST) for the remaining years. This scenario has been introduced to take account of the delay for building up an identification system.
- Global Strategy for Control and Eradication (GSCE): all animals older than 3 months are vaccinated during the first 2 years, followed by a targeted vaccination (ST) of animals between 4 and 12 months until 2030. This is the procedure recommended by the Global Strategy (11) to be implemented for the first 4 years of the program.

For each strategy, the vaccination was implemented once a year but simulated on four different months of the year (March, July, October, and December), corresponding to specific demographic events (before transhumance, before the first peak of births, current period of vaccination, period around second peak of births) and periods of population renewal. Delayed vaccination could miss targeted population with long terms consequences on the population health status. In total, we simulated 16

different scenarios: 4 months of implementation for each of the 4 strategies. In all scenarios, vaccine is given to animals older than 3 months of age, since younger age animals might be protected by maternal antibodies and still have an immature immune system (11, 28). We also assumed that the vaccination is fully successful (all the animals vaccinated end up immunized) and confers a lifelong immunity. All scenarios start in 2018 with vaccination in October and 15.6% of animals vaccinated, according to information provided by Veterinary Service. We assessed the effectiveness of vaccination strategies by assuming that the higher the cumulative number of cases/deaths averted, the "better" the vaccination strategy. To further characterize the benefits of the different strategies, we introduced the notion of effective vaccine doses (E). Every year a certain quantity of vaccine doses (Q) is administrated to small ruminant population. Among them, due to the absence of an identification system, certain number of doses is given to already immunized animals either because they were previously vaccinated either because have already experienced the disease. We indicated these doses as wasted doses (W). The number of effective vaccine doses is the quantity of vaccine that is given to susceptible animals:

$$E = Q - W \tag{4}$$

The quantity of effective doses varies according to the strategy but also depending on the period of the year and the health status of the population.

Cost-Benefit Analysis

Disease-Related and Vaccination-Related Costs

Disease-related costs were distinguished from vaccination-related ones. The former consists of only treatment expenses (antibiotics + vitamins) for each infected animal, incurred by the owner. The treatment usually consists of antibiotics for 1 week and vitamins and, in average, it amounts at $c_{tr} = 1.40\$$ for each infected animal. Consequently, the total disease-related cost is estimated as follow:

$$D = c_{tr} * Cases \tag{5}$$

Two types of costs intervene in the cost of vaccination: the public and the private contribution. Administrating a dose of vaccine costs to the State $c_{adm} = 0.3\$$ including the cost of the vaccine dose and logistic expenses, like the cold chain, equipment, personnel and carburant. Each herder pays a contribution of $c_{pri} = 0.1\$$ for each animal vaccinated. Therefore, the vaccination-related costs can be estimated as follow:

$$V = \left(c_{adm} + c_{pri}\right) * Q = c_V * Q \tag{6}$$

where $c_V = \left(c_{adm} + c_{pri}\right)$ is the total cost associated to each vaccine dose.

A way to reduce vaccination costs is to reduce vaccine wastage (W), consequently administering only the effective number of doses (E). This can be achieved through individual identification and screening of animals: identification will avoid vaccinating animals that have been vaccinated during previous campaigns; whilst screening will allow to identify animals that have already experienced the disease and are already immunized. Excluding those animals from vaccination will reduce the required number of vaccine doses to administer the desired quantity of effective doses (E). In this analysis we are interested in assessing the viability and economical usefulness of the "identification and screening" procedure.

Identification and screening come with costs. We considered that animal identification is done during the vaccination. Consequently, identified animals are also vaccinated ones. As long as the cost of vaccinating all animals is higher than the one of identifying and vaccinated only un-identified animals, the identification is a viable cost:

$$cV^{*}\, Q \geq (c_V + c_{id}) * (Q - W) \tag{7}$$

$$\frac{c_{id}}{c_V + c_{id}} \leq \frac{W}{Q} \tag{8}$$

Where the left side of Equation (7) corresponds to the cost of vaccinating all the animals (identified and not) while the right side corresponds to the cost of vaccinating (and identifying) only the un-identified animals (Q-W).

Vaccine wastage can be further reduced by identifying and vaccinating only the susceptible animals among un-identified animals via an "identification and screening" procedure. We consider that during the vaccination campaign, animals are checked for identification marks: those already marked will not be vaccinated, whilst the un-marked ones will be marked and tested for the presence of PPR antibodies. Only those animals with negative results will be vaccinated. A pictorial representation for the "identification and screening procedure" is given in **Figure 3**. Animals excluded from vaccination are what we indicated with W, among them a fraction (1-p) is already marked, from previous vaccination, and a fraction p is seropositive. Besides the cost of dispensing doses, this procedure should account for the costs of identifying animals and screening. Some estimates of identification cost (c_{id}) for animals are already available and we are interested in estimating the maximal acceptable cost for screening (c_s). The "identification and screening" procedure is economically advantageous until its cost is $<$ the cost of vaccinating all animals (c_V*Q). This condition can be expressed mathematically as:

$$c_V * Q \geq (c_V + c_{id} + c_s)(Q - W) + (c_{id} + c_s)\, pW \tag{9}$$

$$c_s \leq \frac{c_V - \left((c_V + c_{id}) * (1 - W/Q) + c_{id} * p * W/Q\right)}{p * W/Q + (1 - W/Q)} \tag{10}$$

The maximal cost depends on the fraction of seropositive as well as the fraction of total wasted vaccine.

Benefits

The benefits evaluation involves two levels: the public and the private one. In the first case, benefits are mostly indirect: because of vaccination, less animals die from PPR and consequently animal production increases together with related products (milk, leather etc.). An increase in animal production means less importation and avoiding currency weakening. At the same time,

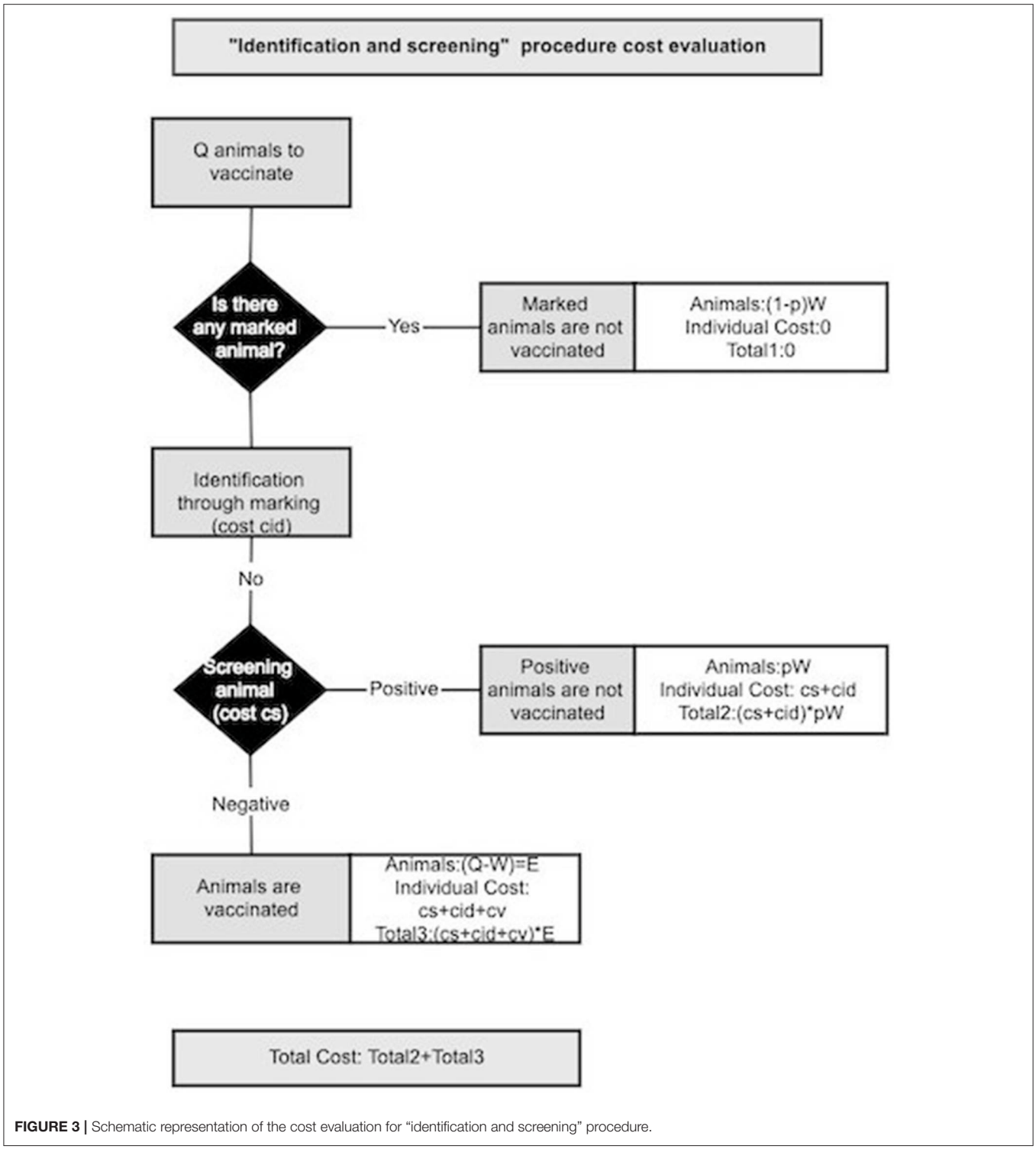

FIGURE 3 | Schematic representation of the cost evaluation for "identification and screening" procedure.

improvement of household socio-economic conditions due to avoided mortality means higher taxes revenue. Private benefits could be both direct and indirect. Through vaccination, owners avoid medical expenses for treatments of infected animals. Furthermore, more animals, in better health, can be sold at markets increasing household income and providing some means to face emergency. Furthermore, a higher income could lead to improved social and health conditions of household members. A schematic summary of benefits is presented in **Table 4**.

TABLE 4 | Summary of direct and indirect benefits from vaccination.

	Direct	Indirect
Public	N/A	• Improve food security by increasing animal production • Taxes return • Reduce import • Avoid currency weakening
Private	• Increase in animal production • Increase production of milk, dairy products, and leather • Higher revenue • Avoid medical expenses to treat infected animals	• Improve socio economic status • Improve health condition

In this analysis, we focus on direct benefits coming from the avoided losses due to PPR related deaths (BS) and avoided treatment expenses (BM) to assess the economic impact of the vaccination. The market values of young and old animals are different, with young ones, the more susceptible, sold at lower price than older ones ($r_{young} < r_{adult}$). The BS can be estimated from the number of averted deaths in both groups as:

$$BS = r_{young} * YoungDeaths\_Averted + r_{adult} * AdultDeaths\_Averted \quad (11)$$

Where *YoungDeaths_Averted* and *AdultDeaths_Averted* indicate the number of PPR-related deaths averted in the young and adult groups. The avoided treatment expenses (BM) can be estimated from the number of cases prevented as

$$BM = c_{tr} * (YoungCases\_Averted + AdultCases\_Averted) \quad (12)$$

Where *YoungCases_Averted* and *AdultCases_Averted* indicate the number of PPR cases averted in the young and adult groups.

The total benefit can then be evaluated as:

$$BT = BS + BM \quad (13)$$

All the analysis, simulations, calibrations and plots were done using the software R v 3.4.3 (50) and the packages deSolve (51), fitR (52), and ggplot (53).

RESULTS

Calibration Results

Based on the lowest value of the DIC (49), the transmission matrix optimizing the fit of the model can be written as:

$$T = \begin{pmatrix} \beta_0 & \beta_0 & \beta_0 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_0 & \beta_0 & \beta_0 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_0 & \beta_0 & \beta_0 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 & \beta_1 \end{pmatrix}$$

where $\beta_1 < \beta_0$.

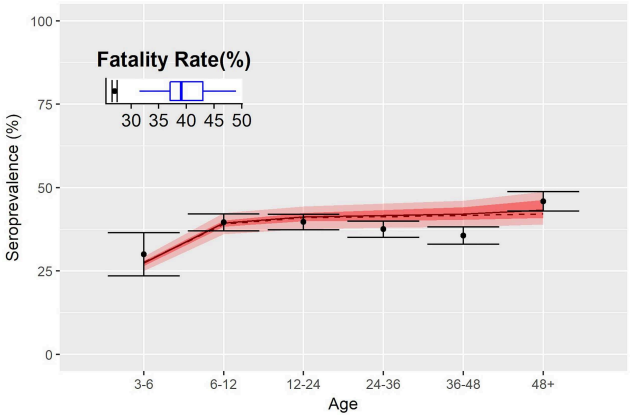

FIGURE 4 | Fatality rates and seroprevalence estimated over the calibration of the transmission model. Dots represent the percentage of seropositive by age group, and shaded red area indicates 50 and 95% confidence interval of simulations. Inset shows the fatality rate estimate of the disease as from data (dots) and model (blue boxplot).

The fraction of immunized animals by age group, estimated by the model, matched well with sero-survey results (**Figure 4**) especially in the youngest and oldest groups. Nevertheless, the model predicts a slow increase of the seroprevalence with age, as expected for an endemic disease, whilst data show a decrease in the group between 3 and 4 years of age. The inset of **Figure 4** shows the percentage of infected animals that subsequently die: dots correspond to the estimate of the fatality rate from data and the boxplot the estimates from the model. Despite the good agreement on the serological aspects, the model predicts a higher fatality rate relative to PPR (almost 10% above).

The calibration provided estimations for the demographic and epidemiological parameters. We sampled from the posterior distributions of the parameters to evaluate the basic reproductive ratio R_0 using the Next Generation Approach as in Diekmann et al. (54). As reported in **Supplementary Table 2**, we found that the median value of R_0 is around 2.9 (95% C.I. between 2.7 and 3.35). Consequently, the fraction of animals that should be vaccinated to reach the herd immunity threshold ($HIT = 1 - 1/R_0$) is around 66% (95% C.I 64 and 71%).

Vaccination Scenarios

We simulated the evolution of the disease from 2018 until 2030 considering an initial population composed of 15.8 million heads. We sampled from the parameter's distribution and for each combination, we ran the model for 100 years to estimate the equilibrium distribution of the population in the epidemiological compartments. The equilibrium distribution has been used as the initial state for all the simulation of the baseline (no vaccination) and vaccination scenario.

Demographic and epidemiological results of simulations for the baseline scenario, i.e., when no vaccination is considered are illustrated in **Figure 5**, distinguishing animals of <1 year of age (young) from the older ones (adult). The daily trend of population is provided in **Figure 5A**, with peaks corresponding

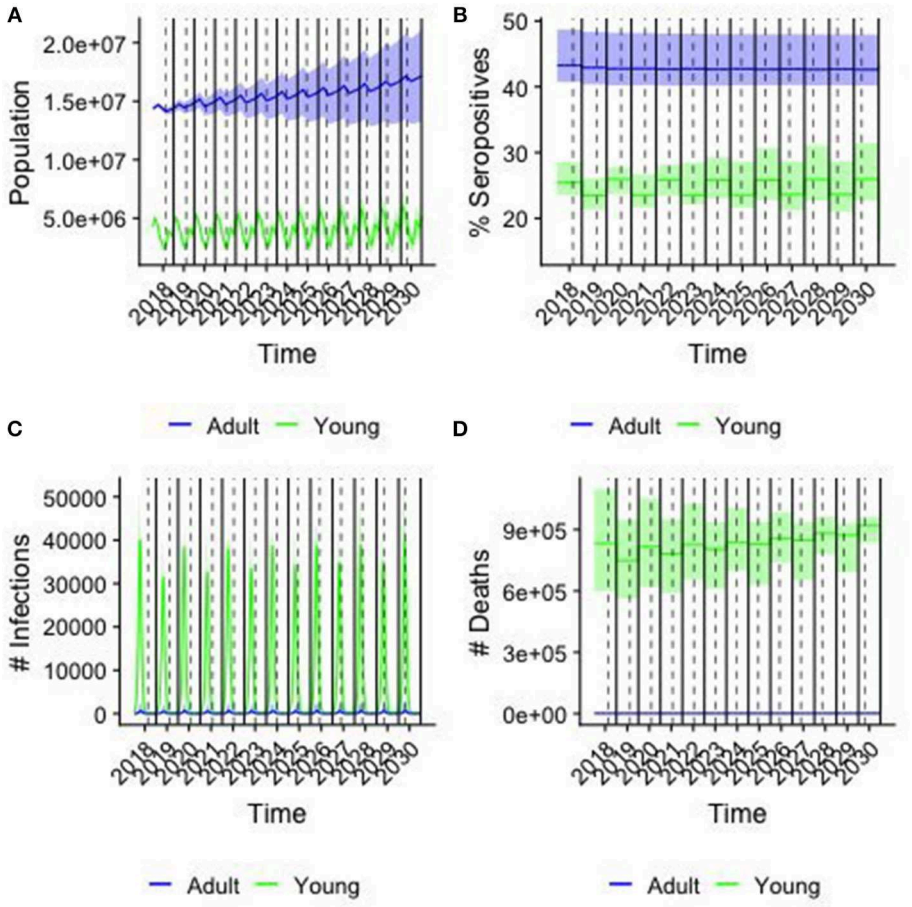

FIGURE 5 | Results from the baseline case. colors correspond to young (<1 year old) and adults (>1 year old), solid line corresponding of the median and shaded area the 95% confidence interval of the simulations over a sample of 250 parameter values. Solid lines indicate the end/beginning of the year, while dashed line indicates Tabaski date. **(A)** The population in each age group by day **(B)** the percentage of seropositive animals in each group **(C)** the number of new infections by day **(D)** the cumulative number of PPR-related deaths by year.

to the two birthing periods. Population grows over time, almost doubles in 10 years, following a trend similar to that predicted by FAOStat. **Figure 5B** shows the yearly average percentage of seropositive animals by age group. For adults the seroprevalence is constant (43%, C.I.[42.6,43.2]) along the years, while it is oscillating around the value (24.6 %, C.I[21,26.0]) for young. On average, the total seroprevalence is around 39.2% C.I[38.3,39.7]), comparable with the expected one from VACNADA data (10, 46). **Figure 5C** shows the daily number of new infections. The epidemics show a recurrent pattern with a peak of new infections occurring every year during the first few months, mostly among young animals. Finally, **Figure 5D** shows the year-cumulative number of PPR-related deaths. On average, every year, almost 2.5 million small ruminants would be affected by PPR and among them almost 8.5×10^5 die of the disease. Few cases and deaths were registered in the adult class.

Figure 6 shows the cumulative number of infections (**Figure 6A**) and deaths (**Figure 6B**) averted along the 2019–2030 period by vaccination strategy (color) and month of vaccination (plot). In 2018, the number of cases and deaths averted is the same for all vaccination strategies, since we assumed the same quantity of vaccine was distributed for all scenarios, and accounted for around 2,700 infections and 650 deaths averted, on average. Starting from 2019, the effects of the different vaccination strategies are becoming distinct, and from 2020 we can see two different trends: on one side the GSCE and targeted (ST) strategies on the other the national strategy (SR) and the mixed one (SM). GSCE-vaccination appears to be the most effective strategy in terms of deaths and case reduction. The difference between targeted strategy (ST) and GSCE is essentially the vaccination coverage at the beginning, the latter considering the double of vaccine doses. As expected, the mixed strategy's (SM) effects become more evident with time. Since the first 5 years there is no difference from a random vaccination, whilst in the last few years the number of cases and deaths averted increases. The gap in cases and deaths averted between the SR and the GSCE strategy is that of a few million at the end (around 10 for the infections, and 3 for deaths). We notice that for each

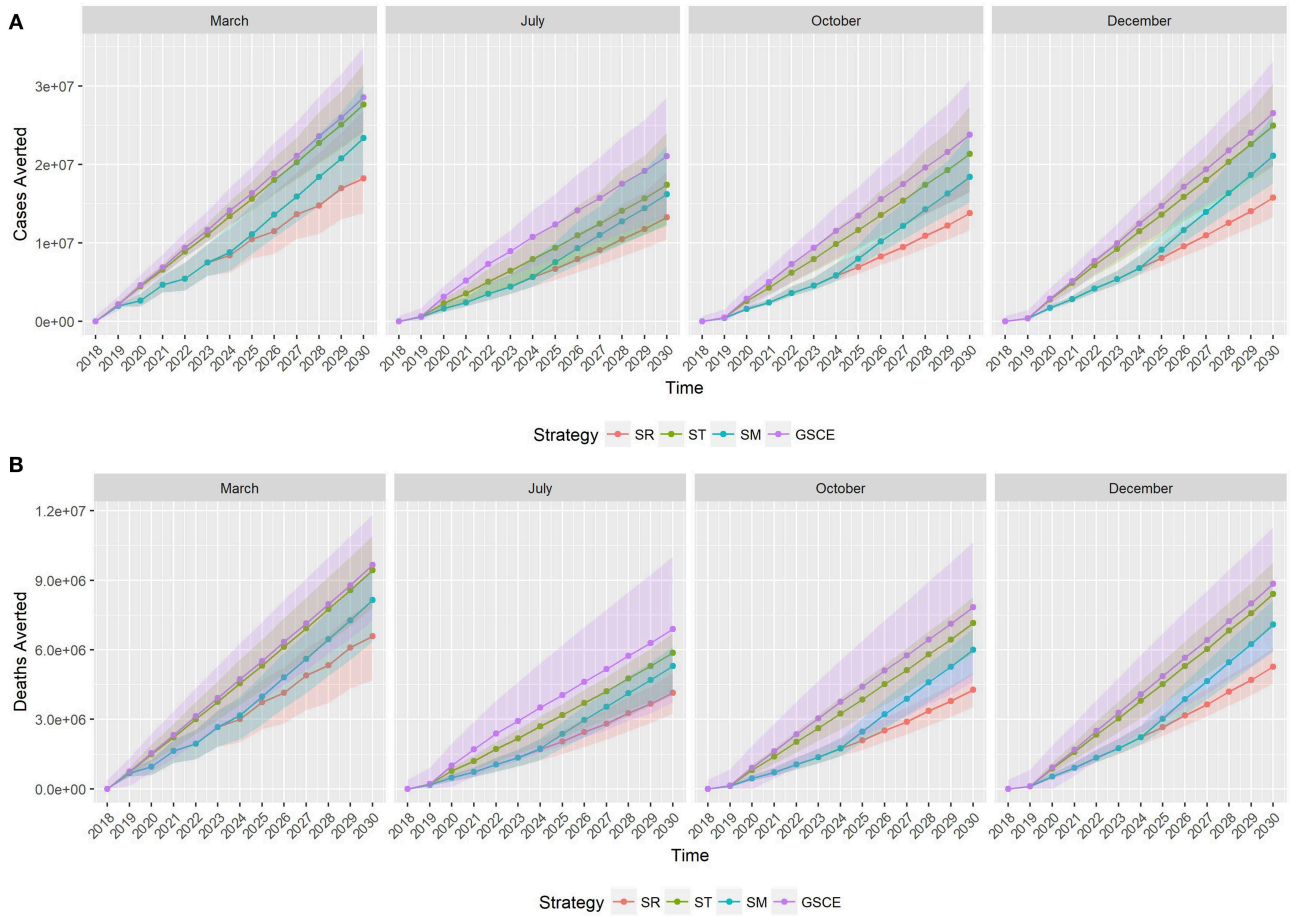

FIGURE 6 | Median cumulative number of cases **(A)** and deaths **(B)** averted by vaccination. Colors correspond to the vaccination strategy, while line type to the month of vaccination. SR, National Strategy; ST, Targeted scenario; SM, Mixed scenario (SM) and GSCE, Global Strategy for Control and Eradication.

vaccination strategy there is a strong dependency on the month of vaccination, with vaccination done in March and December being the most effective ones.

Targeted vaccination (ST) is the most effective in terms of doses distributed. In **Figure 7** we report the quantity of vaccine distributed (Q) each year according to the different strategy and vaccination month, and the corresponding effective doses (E). Each year of the simulation (position on the y-axis), for each vaccination strategy (color) and month of implementation (type of line), we draw a segment whose ends correspond to the quantity of vaccine distributed (Q, right end) and the effective one (E, on the left). The segment's length quantifies the number of wasted doses (W). As can be easily seen the quantity of doses distributed each year by targeted and GSCE vaccination after 2020 is much smaller compared to a random allocation. However, for the first 2 years the quantity of vaccine allocated according to GSCE strategy is much higher than the others. Moreover, we notice that the quantity of vaccine wasted (W) is much smaller for targeted (ST) vaccination than any other vaccination strategy: less vaccine is wasted. For the first 2 years of implementation, the quantity of vaccine wasted for GSCE is higher than the other allocations and in 2020 the quantity of vaccine wasted by the GSCE strategy almost doubles. This is an effect of the previous mass vaccination campaign. According to our model, vaccination month has an effect on the quantity of vaccine to be distributed. For targeted vaccination (ST), for example, vaccination in March requires a slightly higher number of doses than for the other months. This is due to the presence of animals born during the second period of births, around December, which has become eligible to be vaccinated (older than 3 months).

Costs and Benefits Analysis

Figure 8 shows, for each scenario, the cumulative costs of the vaccination campaign (i.e., the cost of administrated? doses—red line), the costs of the effective vaccination (i.e., the cost of vaccinating only susceptible animals—blue line) and the total benefit from the averted death and averted treatment expenses (green line). For all scenarios, the estimated revenue is around one order of magnitude higher than the cost for vaccination. For SR strategies, independently of the month, the cost of vaccination campaign is always increasing. Except for vaccination implemented in March, for the SR case the benefits,

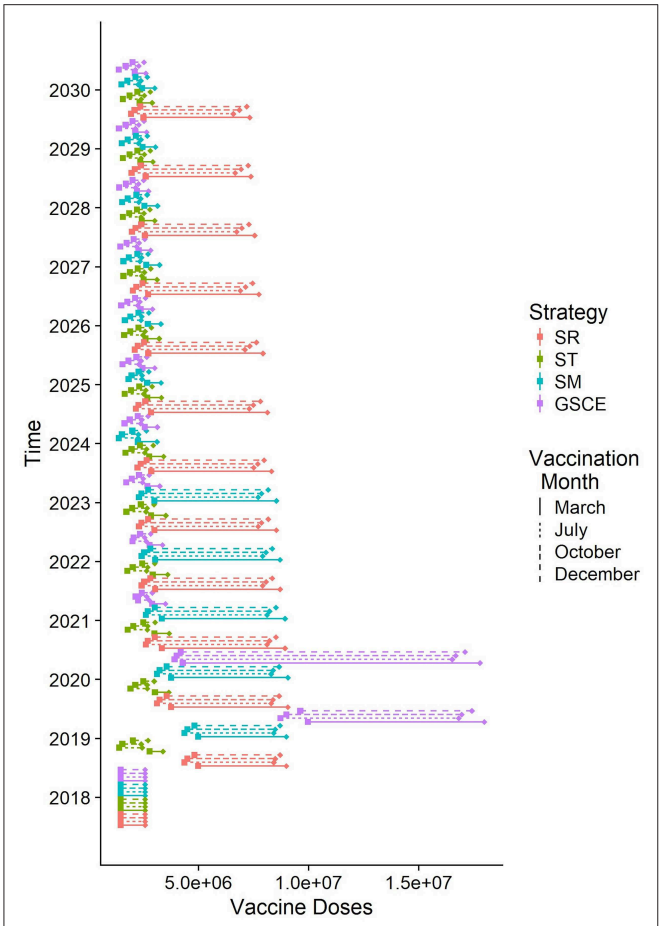

FIGURE 7 | Quantity of vaccine distributed each year according to different strategies (median). For each line, on the right the total number of doses distributed, on the left the effective doses given to susceptible individuals. The length of the rod corresponds to the number of doses wasted because given to already infected individuals.

during the first years, are comparable to vaccination costs. For ST strategies, effective and total vaccination costs (blue and red line, respectively) are comparable, mainly due to the fact that new born animals can be easily identified thus reducing vaccine wastage, and are in all cases lower than those of SR. The cumulative vaccination costs for ST monotonically increase indicating that an (almost) fixed quantity of vaccines is used every year. In the first 2 years, benefits suddenly increase. For the other two strategies (SM and GSCE), the vaccination costs are slightly higher than the targeted ones due to the massive vaccinations at the beginning. For SM and CSCE strategies implemented in months different from March, the benefits are comparable to the costs and steadily increase in the first 2 years. For all strategies, benefits from vaccination in March are immediately evident.

The total administration costs, the economic impact of vaccine wastage and the costs for the effective vaccination at the end of the period 2018–2030, together with the cumulative benefits were summarized in **Table 5**. We indicate with BCR the Benefit Cost Ratio, the amount of monetary gain realized by a single vaccination dose. The random (not targeted) strategies are the most expensive in terms of vaccine-administration costs and vaccine wastage: the more vaccine doses are distributed randomly, the more are wasted. Moreover, the benefits of SR strategies are the lowest among all the strategies. Targeted interventions, on the other hand, have the lowest administration costs and wastage, and, at the same time, the highest fraction of effective vaccination and economics benefit. The analysis of BCR shows that ST strategies are the most effective, whilst SR are the least ones. In **Table 5**, we identified in bold, for each strategy, the most effective month of vaccination. The effectiveness is estimated as the economic benefit by single dose distributed, as an example 1 USD invested in SR strategy in December returns 7.15 USD more. For all strategies, the most effective month of vaccination is March, except for the target one where it is December. In terms of BCR vaccinating in March is the most cost-effective period, except for ST, for whom December is the best period.

For SR strategies, the percentage of vaccines wasted is between 62 and 66 % depending on the month of vaccination, whilst for targeted strategies the figure lies between 20 and 35%, Reducing the wastage, through animal identification, could further increase the benefits. Identification cost (c_{id}) amounts to 0.10$ per animal, thus contributing to 20% of the cost for vaccinating and identify animals ($c_{id}+ c_V$) that is, in most of the cases (not for the target strategies), less than the fraction of wastage. Finally, the estimated maximal cost for the screening procedure (c_s) according to the scenario and percentage of seropositives in the population were presented in **Figure 9**. The maximal screening cost (c_s) depends on the total vaccination cost (c_V), the PPR prevalence and also the fraction of wastage. The latter two could change along the years. For each strategy we have considered three periods (2018–2020; 2020–2025; 2025–2030) to take account of possible variations in vaccine wastage. In **Figure 9** each line corresponds to the maximal screening cost for a specific value of the prevalence, while the shaded areas correspond to the range of vaccination wastage in the period. Intersection between the line and the shaded area indicate the maximum affordable screening cost for the period. A negative or null value of (c_s) indicates that identification screening procedure is not economically viable and then not worthy implementing. We notice that the higher the prevalence the lower is the maximal screening costs. For most of the strategy the maximal screening cost varies between 0 and 1 USD, except for the ST that is almost null. The maximal screening costs for strategy, decrease during the three periods, except for the SR strategy. In the late period for this strategy, the screening option is still viable till a cost of 1 USD. This is mainly due to the fact that SR strategy has the highest fraction of vaccine wasted. For the SM strategy, we notice that during the second period the vaccination wastage widely changes, due to switch from mass to targeted vaccination.

DISCUSSION

PPR is a major constraint to small ruminant production in Mauritania with serious negative impacts to the livelihoods of

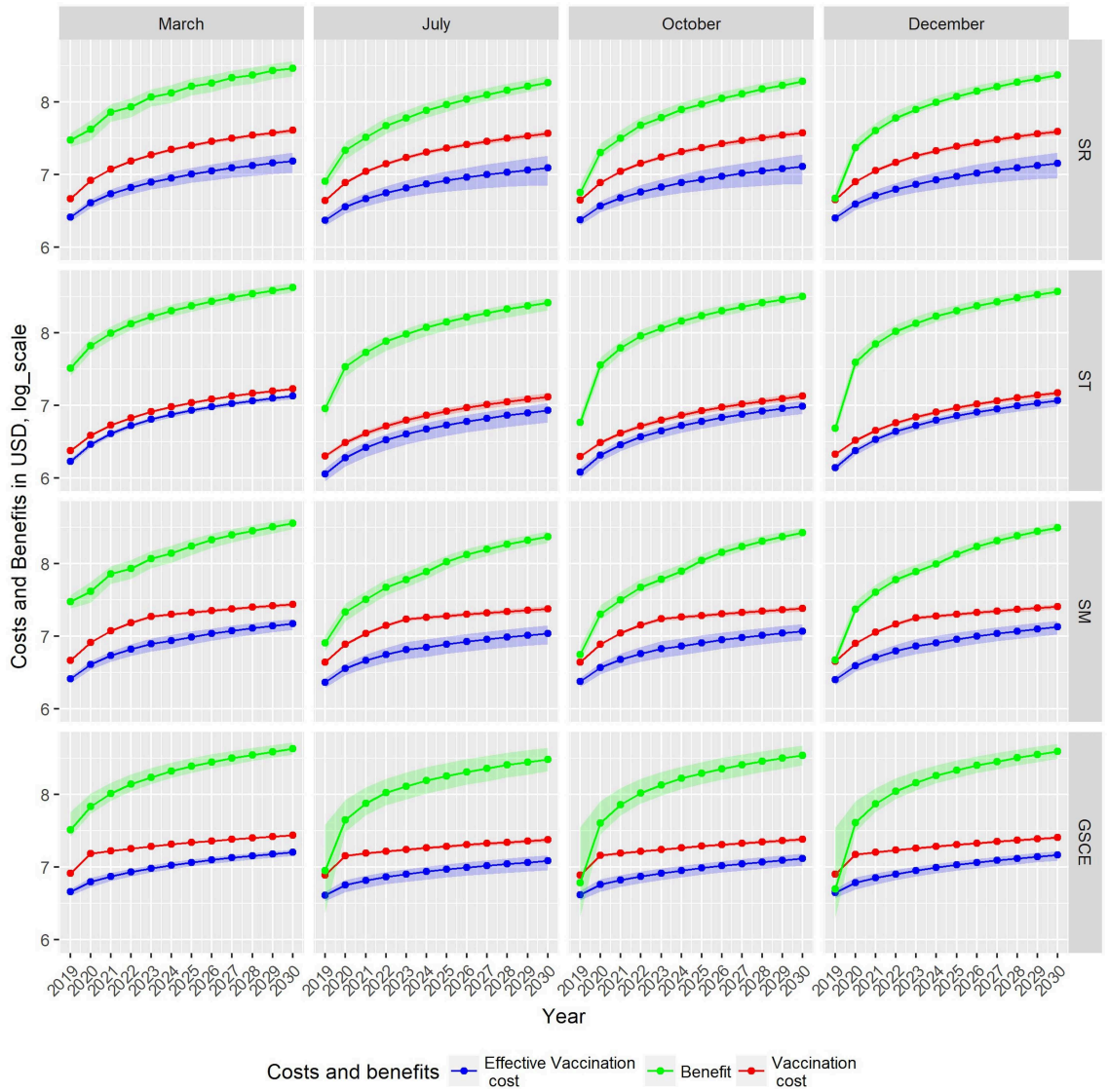

FIGURE 8 | Cumulative cost and benefit for each strategy (row) and month of vaccination. Green indicates benefits from averted mortality, red the vaccination cost, and blue the loss due to wasted vaccination, all expressed in U.S. Dollars. Due to different scales of costs and benefit, estimates are given in Log_{10}.

small farmer households. Several factors contribute to maintain the disease endemic in the area, among them population renewal and animal mobility. Safe and very effective vaccines are available for the control of the disease, which is now targeted for global eradication by year 2030. In this work, we presented a dynamical model for the transmission of PPR in Mauritania. Our model considers an undistinguished population of small ruminants, divided by age group, and takes account of some demographic factors (birth seasonality, movements, and renewal dynamics) ruling small ruminants' dynamics. Calibrated on serological data collected during the 2010 national serosurvey campaign and data from national surveys on herd's demography and disease impact, our model predicts a higher fatality rate for the disease than estimated from the data (37% against 27% from data). However, outbreaks investigations in three Wilayas during 2012 epidemics suggest a case-fatality rate close to our estimation (range [39; 58]%) (40, 46). This discrepancy could be related to the fact that estimation of PPR-related deaths wasn't confirmed by diagnostic control but based on surveyed recollection of previous year's PPR-related events. Due to this, the number of cases or the number of deaths related to PPR could have been easily miscalculated.

Our model predicts a value of R_0 around 2.9, consequently the PVIR threshold is fixed around 66.6% a value in-between the GSCE PVIR estimate (70%) and those predicted by Fournié et al. (31).

In the baseline scenario, where no vaccination is applied, the model predicts around 16 million deaths due to PPR before

TABLE 5 | Cumulative costs and benefits from the different vaccination scenario.

Vaccination	Administration costs (million $)				Effective doses (million $)				Vaccination wasted (million $)			
	March	Jul	Oct	Dec	March	Jul	Oct	Dec	March	Jul	Oct	Dec
SR	40.5	36.7	37.6	39.0	21.7	18.4	19.1	20.4	18.8	18.3	18.5	18.6
ST	16.9	13.1	13.4	14.9	14.3	9.7	10.6	12.5	2.6	3.4	2.8	2.4
SM	27.6	23.7	24.1	25.6	18.1	14.1	14.8	16.5	9.5	9.6	9.3	9.1
GSCE	27.3	23.7	24.1	25.5	18.9	15.0	15.9	17.5	8.4	8.7	8.2	8.0
Benefits	**BS (million $)**				**BM (million $)**				**BT = BS + BM (million $) (BCR = BT/cost)**			
	March	**Jul**	**Oct**	**Dec**	**March**	**Jul**	**Oct**	**Dec**	**March**	**Jul**	**Oct**	**Dec**
SR	264	166	171	211	25.5	18.5	19.3	22.1	**289.9 (7.15)**	184.5 (5.0)	190.3 (5.1)	231.1 (5.9)
ST	378	235	240	337	38.7	24.3	29.9	34.9	416.7 (24.6)	259.3 (19.4)	269.9 (20.1)	**371.9 (24.9)**
SM	326	212	240	284	32.7	22.7	25.8	29.5	**358.7 (12.9)**	234.7 (9.9)	265.8 (11.02)	313.5 (12.2)
GSCE	387	276	314	354	40.0	29.4	33.3	37.2	**427 (15.6)**	305.4 (12.9)	347.3 (14.4)	391.2 (15.3)

SR, National Strategy; ST, Targeted scenario; SM, Mixed scenario (SM) and GSCE, Global Strategy for Control and Eradication. Top part of the table Vaccination information; bottom part benefits. Administration Costs indicate the total amount spent between 2018–2030, while Vaccination Wasted indicates the cost of the vaccine given to already vaccinated or immunized animals, with Effective doses we indicated the total costs of vaccinating only susceptible animals. Benefits are classified as those related to the market value of the animals (BS) and those related to the avoidance of medical treatments (BM). BT indicates the total benefit as the sum of the previous ones. Bold cells indicate those strategies with highest Benefit cost ratio (in parenthesis).

2030. Four different vaccination strategies have been considered and their implementation simulated in four different periods of the year. The use of a dynamical model allowed us to monitor the population distribution across the different epidemiological compartments at each time step of the simulation, but also to estimate the wastage of vaccine doses (W) due to re-vaccination of animals and vaccination of naturally immunized ones. Random strategies (SR) are the less effective in terms of the number of vaccine doses distributed (Q), wastage (W), and reduction of PPR-related deaths, whilst the GSCE strategies are, in the long term, the most effective in terms of cases and deaths reduction. Targeted strategies (ST) are the most convenient in terms of doses distributed, effectiveness of vaccination (higher ratio of effective vaccine doses), due to the targeting of young and probably non-immunized animals. On the other hand, the GSCE strategies, independently of the month, prevent the largest number of cases and deaths. The targeted strategies and the GSCE ones rely on the targeted vaccination of young animals, thus reducing the number of doses to distribute. As pointed out by Hammami et al. (32), it looks safer to implement at least 2 mass vaccination campaigns, firstly because GSCE strategy provides highest reduction in deaths and cases; secondly a mass vaccination could overcome the reticence of some herders. Strategies involved partial mass vaccination, like SM and SR, despite the large number of doses deemed less effective.

In terms of economic benefits, a GSCE strategy, independently of the vaccination month, has a much higher economic return compared to other strategies, whilst the target ones (ST) had the lowest costs associated. The cumulative vaccination costs for GSCE strategy, over the period 2018–2030, are higher than other strategies, mainly because of the mass campaign implemented at the beginning. Moreover, in this work we have compared only the cost of vaccination against those of administering antibiotics and vitamins, the common practice among herders. In the long term the abuse of antibiotics could lead to development of antimicrobial resistance with catastrophic consequences. Vaccination campaigns should be accompanied with sensibilization activities on the use/abuse of antibiotics.

The strategy choice and its implementation month have important effects on both costs and benefits at long term. For all strategies, vaccination should be implemented those months with highest presence of immunocompetent animals, i.e., animals older than 3 months of age and in good shape. In Mauritania these months correspond to the months of December and March. The end of March marks the beginning of the hot dry season, during which an animal's body and health conditions deteriorate, thus affecting their immune response, and herders begin leaving for transhumance. In our model, for all strategies, the best months for vaccinating animals are December and March. For vaccination implemented in these months the number of deaths and cases prevented and the BCR are the highest. Our model considers that vaccination is implemented in 1 month only, whilst Veterinary Service takes around 6 months to cover all the national territory (between October and April). BCR values for vaccination campaigns implement in the period December-March fluctuate between the two values reported in this article. Consequently, implementing a vaccination campaign in this period has the highest benefit. Mauritania encompasses several climatic areas (from hyper-arid in the North, to sub-humid in the South along the river Senegal) and demographic trends and transhumance's schedules depend on the natural resources available along the year, and could vary between years. To improve their efficacy and covering the largest fraction of animals, the vaccination schedule should take account of the resource availability in the different areas and prioritize those areas where resources could be depleted earlier (mainly from the north of the area). In our model we have considered that all

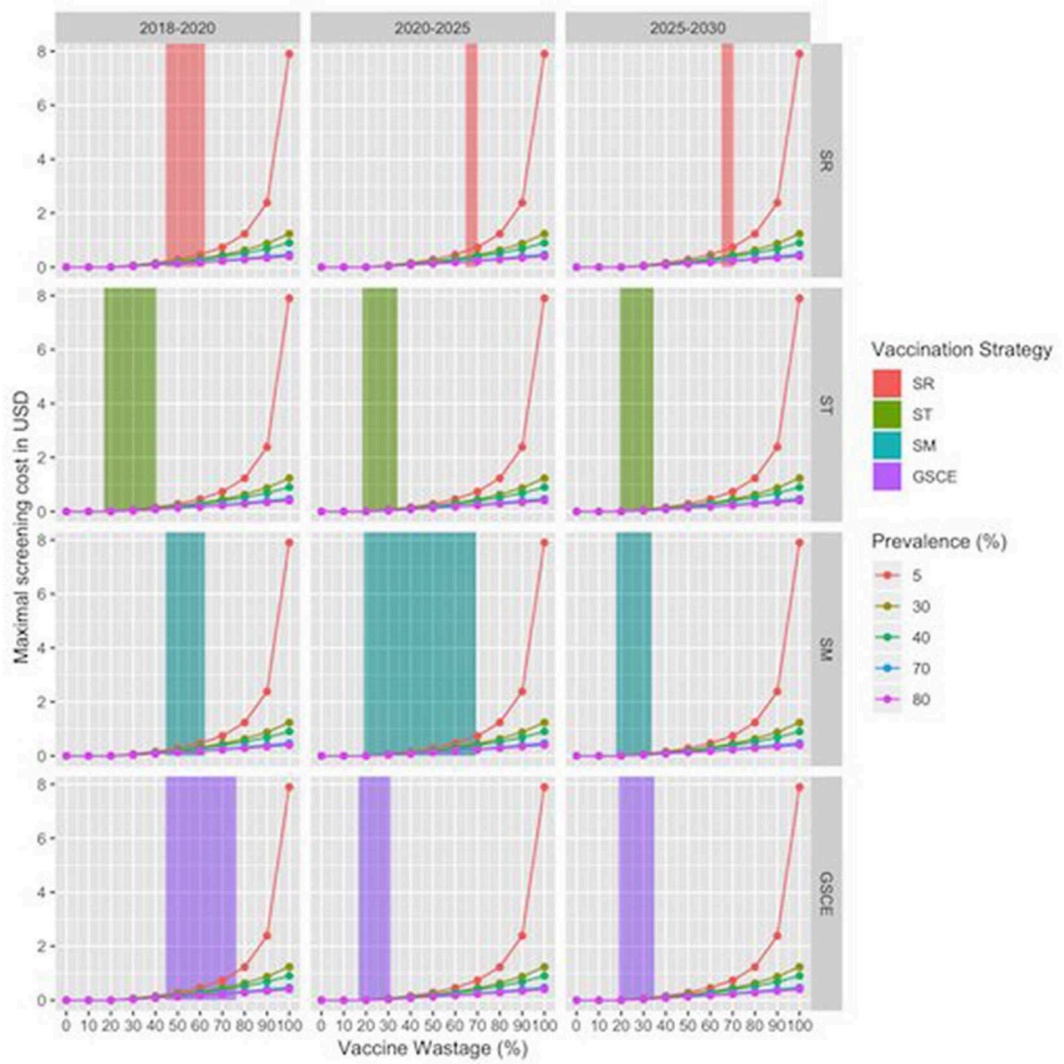

FIGURE 9 | Maximal Screening cost per animal by vaccination strategy and period. X-axes correspond to the vaccine wastage, while y axis corresponds to maximal screening cost, zero value indicating that the procedure is not convenient. Line colors correspond to the evaluation for different sero-prevalence values. Shaded areas correspond to range of vaccination wastage in that period by vaccination strategy.

neighboring countries have implemented the same vaccination strategy and the same vaccination coverage rate. Preliminary study, not reported in this article, has shown that vaccination coverage in neighboring countries could have a dramatic effect on Mauritania's national herd. We considered several scenarios in which the percentage of vaccinated animals among imported animals could vary from 0 (no vaccination) to 100% (all the animals are vaccinated). Focusing on the GSCE scenarios, if other countries are not implementing any vaccination campaign (vaccination coverage = 0%), the number of PPR-related deaths in Mauritania will be between 4 and 20% higher depending on vaccination month. On the other hand, when imported animals are all vaccinated (vaccination coverage = 100%) the number of deaths drastically reduces to almost 0. Reaching this level of vaccination coverage would be possible vaccinating animal at the border.

The BCR estimated for GSCE strategies in our model varies between 19.4 and 24.9 depending on the month of implementation. These values are far from those predicted by Jones et al. (16) (median 33.8 varying between 18.5 for low mortality area and 60.0 for high ones), with the benefit for treatment avoidance accounting for 10% of the total BCR. The discrepancies between our estimates and Jones' ones could be imputed to the small ruminants' market values used in our model.

Reducing the vaccine wastage could increase the economic benefits of vaccination. Vaccination wastage impacts the vaccination costs for a percentage varying from 20% (ST March) to 66.6% (SR in July). Wastage reduction can be achieved through the identification of the animals to avoid multiple vaccinations, a strategy recommended by FAO and OIE and sought to be implemented by Mauritania Veterinary

Services. Our analysis provided strong arguments in favor of the identification procedure whose contribution to the final vaccination cost (administration + identification cost) is around 20%. Identification might then be considered as a viable option for all the strategies, in particular for the random ones. For targeted strategies (ST) the fraction of wasted vaccine is comparable to the contribution of identification to the total costs. However, due to the high BCR, the identification should be implemented. We also tested the possibility of adopting a two stage procedure, "identification and screening," to increase the amount of effective vaccine doses and reduce the final number of animals to vaccinate. The possibility of deploying this type of procedure is hindered by many factors, among them the knowledge of the actual epidemiological situation, the type of vaccination strategy and the costs related to the screening test. The maximal cost for screening c_s depends on the prevalence and the vaccination strategy. A low value of c_s indicates that the implementation of the screening is not economically viable. In our cases we found that for most of our scenario the identification screening is not a viable solution. Moreover, depending on the particular test used, results couldn't be immediate thus complicating the vaccination procedure.

In our model, logistic costs were not detailed. However, considering that a single dose is 0.10 USD, almost 80% of the vaccine costs (0.40 USD) are related to logistic expenses. Mauritania geographical extension and the distribution of supporting infrastructure for maintaining the vaccine cold chain, constrain the number and the duration of field missions by Veterinary Services. The use of a thermostable vaccine could greatly reduce the logistic costs. Future studies should consider a detailed description of the logistic costs as part of costs benefits analysis of vaccination campaign as previously done for the Senegalese case (17).

Our model includes some characteristics of the Mauritania husbandry practices, like births and movement's seasonality. At one-year coarser temporal scale, the serological estimates are comparable to collected data. However, the model fails to predict the outbreaks occurring around Tabaski (reported by veterinarian services). These outbreaks are related to the rapid concentration of animals in urban areas, and the consequent burst of transmission. A model including multiple patches of population, linked by animal movements, could better describe the spatio-temporal patterns of disease propagation and reproduce the Tabaski peaks of infections.

In our model we have considered that GSCE strategy is applied all along the period 2018–2030 a period longer than suggested by OIE. Disrupting the vaccination could cause the re-insurgence of PPR, due to the re-introduction of the virus by transboundary movements, with catastrophic effects on small ruminants' production, as it has occurred in Morocco during 2016. Mauritanian commercial movements are mostly directed toward neighboring countries and import accounts for only 2% of the volume of animal traded. Moreover, due to the permeability of the borders and the lack of an integrated control and surveillance system in the area, PPR cannot be fully eradicated from Mauritania. In fact, because of these transboundary movements, infected and susceptible animals could be regularly introduced in Mauritania and re-ignite PPR outbreaks. The severity of these outbreaks would depend on the level of vaccination coverage of neighboring countries. Either Eradication requires a coordinated action at regional level with all countries in the region implementing vaccination policies aiming at covering 70–80% of the population of small ruminants and/or vaccinating imported animals at the border. In this case, this will mean adding extra vaccine doses, equivalent to the fraction of imported animals in Mauritania, for each vaccination campaign and create structures (vaccination parks) for the administration of the vaccine. Also, in this case to better assess the effect of vaccination in different countries a spatially structured model is required that takes in account the seasonality of mobility and the diffusion of immune animals.

In our model we have considered PPRV as the only pathogen circulating in the area and affecting small ruminant's production. However, other pathogens circulating in the region, like Pasteurellosis, could resurge after PPR eradication and disrupt the production chain. Because of this, PPR vaccination should be done during a joint campaign against other viruses and bacteria.

Results of our model suggests that vaccination campaigns done following the GSCE guidelines coupled with identification procedure could be an economically viable option to control PPR in Mauritania. However, eradication can be achieved only through a coordinate approach at regional level.

DATA AVAILABILITY

All datasets analyzed for this study are included in the manuscript and the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

AE, YK, and RL supervised the data collection and performed the preliminary data analysis. AA, RM, PH, and MC developed and implemented the dynamic model. AB, AA, and AE performed the cost-benefit analysis. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

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OPINION
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A Global PPR Network for Field Staff

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INTRODUCTION

Among the lessons learned from rinderpest eradication was that networks developed for laboratory testing for diagnosis and for serological assays for rinderpest virus antibody proved very valuable to the final success of the Global Rinderpest Eradication Programme. The Joint Division of the Food and Agriculture Organization of the United Nations (FAO) and the International Atomic Energy Agency (IAEA) co-ordinated perhaps the best known of these networks across Africa. This network successfully built and supported a team of skilled laboratory staff across the continent who knew, trusted and collaborated with one another, and from which many individuals progressed to important positions in national, regional, and global animal disease control.

The value of such networks for PPR control and eradication, as well as collaboration between laboratories in general, encouraged two meetings of the Global PPR Research Alliance (GPRA) after which the FAO and the World Organization for Animal Health (OIE) established a Global Research and Expertise Network (GREN) as an integral part of the PPR-Global Eradication Programme. The background and potential of GREN was explored and developed during an electronic conference held in February to April 2014 and GREN was launched at the IAEA headquarters in Vienna in April 2018.

The author contributed to the first meeting of the GPRA, and subsequently, as moderator of the e-conference in 2014, had first-hand access to individual inputs and ideas and drafted the final report. He presented a summary of these and additional findings at the launch of GREN in 2018. This paper re-caps some of the findings and concepts in those presentations and reports. It then makes the case that whilst GREN should actively encourage and develop technical networking at the laboratory level it should not miss the opportunity to establish an equivalent programme for staff involved in field operations.

EARLY STEPS: 1—THE GLOBAL PPR RESEARCH ALLIANCE, 2012–2013

Following the official confirmation of global rinderpest eradication in 2011, the Pirbright Institute and others established a forum, GPRA, for greater collaboration amongst scientists studying PPR. The GPRA met twice, in London and in Nairobi. The outcomes were clear; substantial research was being carried out on PPR, much of this was at a sophisticated technical level, and there was perhaps insufficient collaboration and study in the field. The author gave a brief presentation attempting to highlight the advantages that might come from more involvement with and coordination of field workers (1). The suggested potential benefits included a better understand of local patterns of disease (endemic areas, main factors behind spread of infection, seasonality, the dynamics of herd structure, and recruitment of susceptibles, etc.) and the chance to maximize efforts for better control (best opportunities to interrupt chains of virus transmission, minimum immunity rates to break transmission, use of different vaccines), and defining the true role of other susceptible species in the overall epidemiology of PPR. Several of these issues have or are now being addressed by

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established research teams (2–5) but the opportunity for more observational and practical research in the field is still there, as is the potential for increased awareness and willingness to search for and report possible cases of PPR.

The Take-Away Message

There is considerable human interest and potential for studying PPR in the field as well as the laboratory.

EARLY STEPS: 2—THE GREN E-CONFERENCE, 2014

Participation

The moderated, part-time e-conference was held over a period of 5 weeks in early 2014. An immediate difference to the earlier rinderpest eradication research networking, was that GREN would not work just with laboratory-based scientists but would encourage policy and operational level staff to contribute their expertise into the discussions. Over 300 participants registered with 90 making at least one contribution. There was a strong laboratory-based bias to participants ranging from internationally recognized scientists in the accredited laboratories, to national labs through to aspiring researchers and their students in small veterinary colleges and provincial diagnostic laboratories. However, there were also many participants who were not laboratory-based and who were working in administrative and operational positions in national and regional programmes, including a considerable number contributing in the field through vaccine delivery and disease investigation, several of whom were newly qualified veterinarians. Geographic participation covered most countries where PPR was a problem, as well as some where PPR is yet to occur and may never occur. The potential for the e-conference was under-realized with 40 would be participants asking to be registered on the final day of the conference, and individual requests to join the conference still being received as recently as July 2019.

Ideas and Concepts From the e-conference

The proposed purpose of the GREN was "to accelerate the progressive control of PPR through a forum that distributes new knowledge about the virus, the disease, and improved methods for its control." The conference concluded that the concept of GREN as a forum for information exchange was (and still is) very welcome. Whilst it was not the purpose of the e-conference to decide exactly what format the GREN should follow—it did propose that a moderated global network with an open system for reports and queries and possible monthly structured "seminars" and question times would help keep the momentum for eradication going. In view of language issues and regional programmes, it might also want to consider global, regional, and national components.

The e-conference was successful and well-received by most participants. One shortcoming however was that the rigid framework provided by the organizers focused predominantly on scientific and technical subjects with the result that crucial issues such as motivation, resourcing, promotion, and general awareness were not discussed or only briefly.

The Take-Away Message

It was impossible to ignore the enthusiasm and interplay between participants with different backgrounds and expertise: the willingness of several internationally acclaimed scientists to engage with and answer questions from recent graduates was noticeably positive. Many of the questions being asked were very perceptive and open requiring careful answers, and a few were completely off the wall, which proved equally challenging and stimulating. This ability of the GREN to foster exchange of ideas between senior scientists and inexperienced field and lab staff was a powerful example of how the "experience" component of GREN might work and could be a strong source of motivation for staff joining the PPR eradication community (6).

THE LAUNCH OF GREN, 2018

PPR-GEP GREN was officially launched in April 2018 at a meeting in Vienna. The presentations at the meeting were predominantly institutional and laboratory-science focused. However, the author was given the opportunity to recount his experience with the e-conference and argued for a wider base for GREN: "Whilst the inaugural emphasis is largely laboratory-based the network should aim to include field workers and programme managers who, by reporting what they are experiencing in the field, including clinical signs and pathology, and their successes and difficulties in achieving control, will stimulate discussion and sharing of the best methods for disease surveillance and immunization. By harnessing and guiding this widespread enthusiasm to share knowledge about PPR, GREN can be the tool to effectively promote and harmonize the global effort against the virus making the 2030 target for its elimination more feasible" (7).

The final communique of the meeting (8) presented the Terms of Reference for GREN which includes nine specific roles and functions of the network. First on this list is that the GREN shall "Serve as a communication and technology sharing gateway for the PPR GEP to coordinate inclusive field collaboration across the PPR-GEP community." If the gate to the gateway is permanently open, operating in both directions to allow coordination and knowledge of new technology to pass outwards, and information from the field to flow inwards—this could be a very powerful tool for PPR-GEP management and for gathering epidemiological information.

The Take-Away Message

The GREN intends to promote field collaboration across the PPR-Community.

DISCUSSION AND CONCLUSION

As with rinderpest, the PPR-GEP strategy will concentrate on eliminating clinical PPR followed by intensive clinical and serological surveillance to confirm eradication of infection with the virus. The main source of evidence to support clinical

elimination is the field through routine reports, outbreak reports, participatory epidemiology, specific targeted disease searching, etc. Unfortunately, these channels are not always used to their maximum advantage but might be more effective if the field staff generating the information was more highly motivated. Other than a massive pay rise, what might induce such motivation? The three take-away messages from the sections above combine to strongly suggest that a network as outlined will be well-received and likely to increase field workers sense of inclusion in the overall global eradication process. The 2014 GREN e-conference showed a clear desire for knowledge about PPR at all levels of participation including the field front-line. Publishing all PPR-GEP newsletters and appropriate reports on the GREN would be of widespread interest to the PPR community. Many field staff would be interested in new developments in PPR control but, unlike staff in most established laboratories, do not have easy access to new reports and papers. PPR-GEP could consider using GREN to disseminate the OIE's "PPR Watch" list of recent PPR publications to the wider PPR community. Providing this monthly list to all members of a field-based GREN would be much appreciated—especially if donor funds could ensure that there was open access to all papers for GREN members. Such inputs could be easily repaid in terms of information flowing back from the field. A network where front line staff from Bulgaria to Bangladesh and Burundi, from Tunisia to Tajikistan and Tanzania could share their ideas and descriptions of disease, share their photos of clinical signs between themselves and with PPR-GEP would allow them to feel more involved, especially where their efforts are appreciated and acknowledged, and possibly acted upon. Raising staff interest, moral, and sense of participation in the global programme should increase disease reporting, feedback about control programmes, and early warning of problems and difficulties. With virtually all staff now possessing powerful smart phones the technology is already available in the field, all that is required is the network, and its coordination and management. Make a brief field visit anywhere in the world where there is plenty of PPR and you will probably be shown more good photos of the clinical signs and even the pathology of PPR than exist in any textbook or training manual. The same is also true of what is known about the epidemiology of PPR at local levels and of what "works best" to stop the disease in such locations. How useful it would be to share and discuss this untapped experience. If greater motivation in the field could hasten the global eradication of PPR by just one year, how much time, resources, and funding might be saved?

The details of how such a network should be run will require further deliberation, checks, and balances to ensure that information in the network does not by-pass national and regional programmes and reporting structures. Therefore, the proposal initially concentrates on veterinary front-line staff in the public or private sector under the overall direction of the DVS but in the field there are many more actors and stakeholders who can contribute to disease reporting. These include community animal health workers, local government, and NGO service providers, as well as farmers and herders themselves. Many of these, especially herders, greatly outnumber front-line field staff which could make receiving, assessing, and responding to information from them a time-consuming job requiring the possible recruitment of extra staff to cope with this workload. Consequently, it might be practical to begin the field network with veterinary front-line staff alone in order to keep it manageable. If successful, the next step could be to enlarge the network at country level incorporating other actors and methodologies deemed appropriate in that location—and ensuring the flow of information is always accessible to the national veterinary services.

The proposed network could also provide other opportunities for GREN. In addition to collaboration in the field, the final communique of the inaugural meeting of GREN highlighted closer interaction between epidemiology and socio-economics as a "thematic area" and a "Priority Research Need." The field network could be a valuable entry point for socio-economic input. The involvement of socio-economists in the development and management of the network would increase its value especially where this leads to better understanding of some of the constraints to disease reporting and how these can be removed to increase the flow of useful epidemiological information. In addition, socio-economic involvement from the outset could help to provide the data to show, at a later date when examining the progress of PPR-GEP, whether field networking actually improves disease reporting, resulting in earlier eradication of PPR and consequent economic savings. If the proposed network could be shown to do this, it would significantly help PPR-GEP GREN "to accelerate the progressive control of PPR."

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Genetic Evidence for Transboundary Circulation of Peste Des Petits Ruminants Across West Africa

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Peste des Petits Ruminants (PPR) is a viral disease affecting predominantly small ruminants. Due to its transboundary nature, regional coordination of control strategies will be key to the success of the on-going PPR eradication campaign. Here, we aimed at exploring the extent of transboundary movement of PPR in West Africa using phylogenetic analyses based on partial viral gene sequences. We collected samples and obtained partial nucleoprotein gene sequence from PPR-infected small ruminants across countries within West Africa. This new sequence data was combined with publically available data from the region to perform phylogenetic analyses. A total of fifty-five sequences were obtained in a region still poorly sampled. Phylogenetic analyses showed that the majority of virus sequences obtained in this study were placed within genetic clusters regrouping samples from multiple West African countries. Some of these clusters contained samples from countries sharing borders. In other cases, clusters grouped samples from very distant countries. Our results suggest extensive and recurrent transboundary movements of PPR within West Africa, supporting the need for a regional coordinated strategy for PPR surveillance and control in the region. Simple phylogenetic analyses based on readily available data can provide information on PPR transboundary dynamics and, therefore, could contribute to improve control strategies. On-going and future projects dedicated to PPR should include extensive genetic characterization and phylogenetic analyses of circulating viral strains in their effort to support the campaign for global eradication of the disease.

Keywords: virus spread, peste des petits ruminants, phylogeny, eradication, morbillivirus, small ruminant

INTRODUCTION

Peste des petits ruminants (PPR) is a viral disease affecting predominantly small ruminants, such as sheep and goats. PPR is classified as a Transboundary Animal Disease (TAD) due to its rapid spread in large parts of Africa, the Middle East and Asia, associated with animal trade and human movements (1, 2). PPR is transmitted mostly through direct contact, spreading rapidly

among immunologically naïve flocks with mortality rates reaching 90% (OIE Terrestrial Manual). Compulsory notification to the World Animal Health Organization (OIE) of the presence of PPR in a country leads to restriction on movements of livestock and animal products. Due to its impact on the livelihood and food security for smallholders farmers, the OIE and the Food and Agriculture Organization (FAO) have launched a campaign for the global eradication of PPR (3). For this transboundary disease, regional coordination of control strategies will be key to the success of the campaign. The re-emergence of PPR in Morocco, due to transboundary movement of infected animals, few years after complete eradication from the country stresses the importance of this aspect (4).

The extent of transboundary movements of PPR may be difficult to appreciate. Risks analyses based on animal mobility and animal trade data could guide the development of efficient national and regional surveillance and control strategies (5). In addition, viral genetic data from PPR-infected animals could provide direct evidence of the extent, location, and direction of the movements of the pathogen across borders, supporting data obtained from modeling analyses.

The virus causing PPR is a non-segmented, negative-sense RNA virus of the genus *Morbillivirus* in the family *Paramyxoviridae*. Recently, the International Committee on Taxonomy of Viruses (ICTV) has changed the name of the virus from *peste des petits ruminants virus* to *small ruminant morbillivirus* (6). Here, the abbreviation PPRV will be used throughout the text for the PPR virus to avoid confusing non-specialist readers interested in the global PPR eradication campaign. The PPRV genome has a length of 16 kb and encodes for 8 proteins: the nucleocapsid protein (N), the phosphoprotein (P), the matrix protein (M), the fusion protein (F), the haemagglutinin protein (H), the polymerase protein (L) and the two non-structural proteins, C and V (7). RNA viruses evolve rapidly, with a mutation rate between 10^{-4} and 10^{-5} mutations per base per replication cycle, accumulating genetic changes fast enough to be used to study epidemiological processes, notably thanks to the rise of high-throughput sequencing technologies (8). Based on genetic data, PPRV can be classified in 4 genetic lineages: lineages I and II in West Africa, lineage III in East Africa, and a lineage IV rapidly spreading in Asia, Middle East and in many parts of Africa (1, 9, 10). Interestingly, even simple phylogenetic analyses based on a short nucleotide segment of the N gene, obtained from a reverse transcription Polymerase Chain Reaction (RT-PCR) diagnostic method commonly-used for PPR detection and lineage identification (11), can provide some insights on transboundary movements of the disease. Notably, such analysis was used to follow the extension of lineage IV into West Africa (9). Similar analyses also provided some insights into the origin of the PPR emergence in Georgia (12). However, it has never been used to get insight into regional transboundary dynamics of PPR transmission in an endemic region.

Here, we aimed at exploring the extent of transboundary movement of PPR in West Africa using phylogenetic analyses based on partial N gene sequences. There are more than 160 million small ruminants in West Africa, with extensive livestock trade mostly from countries in the Sahel region toward southern West African countries (13, 14). PPR is endemic in West Africa, where it was first described in 1942 (15). Countries in the region implement vaccination against PPR but with limit success due to lack of funds and coordination (13). However, the implementation of regional projects such as the Regional Support Project Pastoralism in the Sahel (PRAPS, http://praps.cilss.int/) may improve the situation.

Due to transhumance and poorly controlled movement of animals across the region, we expect to find evidence of close phylogenetic relationship between PPRV strains in West Africa. We collected samples and obtained partial N gene sequences from PPRV-infected small ruminants across countries within West Africa. This new sequence data was combined with publically available data from the region to perform phylogenetic analyses and test this hypothesis.

MATERIALS AND METHODS

Sampling and Laboratory Analysis

This study took advantage of sampling effort realized in the frame of previous projects or as part of routine control efforts carried out by veterinary services. Samples were collected from small ruminants showing clinical signs suggestive of PPR infection in the main markets of Dakar, Senegal in 2013, and in villages and markets in Burkina Faso, Ghana, Mali, and Mauritania in 2014 (**Table 1**). Veterinarians of national veterinary services conducted the field studies in accordance with local legislation, with no specific ethical approval required. Still, the tissues used in the study were sourced ethically. The study was conducted in animals in contact with outdoor environments with natural exposure to diseases (PPR is endemic in the region). Ocular or nasal swabs were collected on live animals by aseptic means and/or by non-invasive methods, and tissues (lung, lymph node and/or spleen) were sampled from animals that died of infection or were euthanized humanely if symptoms of acute PPR infection were observed (mucopurulent ocular/nasal discharges, diarrhea, fever, loss of weight, respiratory distress). The samples were kept at 4°C during the time of transport to the national veterinary laboratories. In addition, two positive samples collected in Mali in 1999 and in Burkina Faso in 2008, respectively, and stored at the FAO and OIE reference laboratory for PPR (CIRAD, Montpellier, France) were included in the study.

All samples collected were sent to CIRAD, Montpellier, France. Once there, the samples were processed in a biosafety level 3 containment laboratory.

At CIRAD, the tissue samples were cut to pieces and ground in 3 ml of Minimum Essential Media (MEM) by vortexing with 0.2 µm glass beads. The swabs were placed in 1 ml MEM and vortexed. In all cases, the sample suspensions were centrifuged 3 min at 1,000 g to collect the supernatant. Total RNA was extracted from the supernatant using the NucleoSpin RNA virus extraction Kit (Macherey-Nagel, France), according to the manufacturer's instructions.

A RT-PCR was performed using the qScript XLT One-Step RT-PCR Kit (Quantabio, VWR, France) to amplify a 351 base pair (bp) segment of the PPRV N gene with the

TABLE 1 | List of samples used in this study.

Location	Type	Species	Sample	N	Year	Accession number
Burkina faso						
Binde	flock	sheep	Ns	2/5	2014	MK777897 MK777901
Ouindigui	flock	goat	Ns, Lg	0/3	2014	-
	flock	sheep	Ns	0/2	2014	-
Pibaore	flock	sheep	Ln	2/3	2014	MK777902
Sabou	flock	sheep	Ns	2/2	2014	failed
Toece	flock	sheep	Lg, Ln, Sp	0/3	2014	-
Zeguedeguin	flock	goat	Os	1/1	2008	MK777898
Ghana						
Atta Bagbe	flock	goat	Lg, Sp	2/3	2014	MK777904 MK777905
Ayensudo	flock	goat	Lg,Ln	1/2	2014	MK777904
Enyitsewdo	flock	goat	Lg, Ln, Sp	2/3	2014	MK777899
Wyamoah	flock	goat	Lg, Ln, Sp	4/4	2014	MK777905
Wyomoah	flock	goat	Lg, Ln, Sp	1/4	2014	MK777905
Mali						
Bamako	market	goat	Lg	1/1	1999	MK777896
Dialafara	market	goat	Os	1/1	2014	MK777888
Kolondieba	market	goat	Os	10/11	2014	MK777903 MK777894 MK777895
Tousseguela	market	goat	Os	3/3	2014	MK777892 MK777893
Samako	market	goat	Os	8/8	2014	MK777889 MK777890 MK777891
Sekou	market	goat	Os	5/5	2014	MK777887
Mauritania						
Atar	flock	goat	Os	1/8	2014	MK777900
	flock	sheep	Os	0/3	2014	-
Senegal						
Dakar	market	goat	Os	8/39	2013	MK777907
	market	sheep	Os	1/1	2013	MK777906
Total				57/115		21

Location indicates the town where samples were collected or the main town closest to sampling site. Type indicates if samples were collected from flocks or in a market. N, number of positive samples/total samples tested. Lg, lung; Ln, lymph node; Os, ocular swab; Sp, spleen; failed, sequencing attempts failed; Accession number, GenBank accession number. Multiple accession numbers are given for one location when multiple non-identical sequences could be obtained from PPRV-positive samples. Accession numbers are repeated when the same sequence was obtained from several locations. Total of accession number is the number of non-identical sequences obtained.

NP3/NP4 primer pair modified from Couacy-Hymman et al. (11) (Forward NP3: 5′-GTC-TCG-GAA-ATC-GCC-TCA-CAG-ACT-3′ and Reverse NP4: 5′-CCT-CCT-CCT-GGT-CCT-CCA-GAA-TCT-3′) at a final concentration of 0.6 μM. PCR was set up under the following programme: 50°C for 30 min; 95°C for 15 min and 40 amplification cycles (10 s at 95°C, 30 s at 60°C and 30 s at 72°C) and a final extension step at 72°C for 5 min. The PCR products were resolved on 1.5% agarose gel to reveal the expected band size.

Sequencing and Phylogenetic Analysis

The clean-up and sequencing of positive PCR products in both forward and reverse directions were carried out by Cogenics (France) or Genewiz (United Kingdom). The sequences were submitted to GenBank (**Table 1**). Forward and reverse DNA sequences were assembled using Geneious v. 8.1.6, and trimmed to remove poor-quality portions of the sequences (final size = 255 bp). Corrected sequences were aligned with 27 PPRV N gene sequences publicly available in GenBank using MEGA 6 (see **Supplementary Material**). This dataset contained representatives of the four genetic lineages, including 18 sequences of the lineage II, dominant in West Africa. A phylogenetic tree was constructed using the Neighbor-Joining and the Maximum Likelihood methods as implemented in MEGA 6, with node supports evaluated by bootstrap analyses (1,000 replicates).

RESULTS

A total of 115 samples from goat ($N = 96$) and sheep ($N = 19$) with suspicion of PPR infection were collected for this study (**Table 1**). Among the samples tested, 57 gave positive results by RT-PCR: 7 from Burkina Faso, 10 from Ghana, 28 from Mali, 1 from Mauritania, and 9 from Senegal. A partial N gene sequence was obtained from all samples except two samples from Sabou in Burkina Faso (**Table 1**). A total of 21 different partial N gene sequences were identified (Genbank accession numbers: MK777887-MK777907; **Table 1**).

Phylogenetic analyses showed that all the sequences obtained belonged to the lineage II (LII) of PPRV (**Figure 1**). The sample collected in Mali in 1999 was positioned at the base of all the LII samples collected in 2000–2014. Despite the short length of the sequences aligned (255 bp), multiple genetic clusters could be observed in the phylogenetic trees, with moderate (54–66%) or good (70–87%) bootstrap support for one or two inference method used **(Figure 1)**. All sequences obtained in this study, except three samples from Mali, were placed within one of five genetic clusters regrouping samples from multiple West African and Central African countries (C1-C5 in **Figures 1**, **2**). Cluster 1 included samples from Mali and Burkina Faso obtained in this study and samples from Liberia and Ivory Coast. Within this cluster, close phylogenetic relationship was observed between two samples from Burkina Faso and Liberia (Cluster 1a). One sample from Dakar belonged to Cluster 2 with other samples from Senegal and Benin. Samples from Mali, Senegal and Mauritania formed Cluster 3. The sample collected in Burkina Faso in 2008 clustered with a sample from Ghana (Cluster 4). Finally, sequences obtained in this study from Ghana and Burkina Faso formed the Cluster 5 with samples from Benin and Nigeria **(Figures 1**, **2)**. Bootstrap support was highest for Cluster 1b (87%) and 5 (70%).

DISCUSSION

A small region of the N gene (11) of PPRV is used to follow the changes in distribution of the four lineages across continents

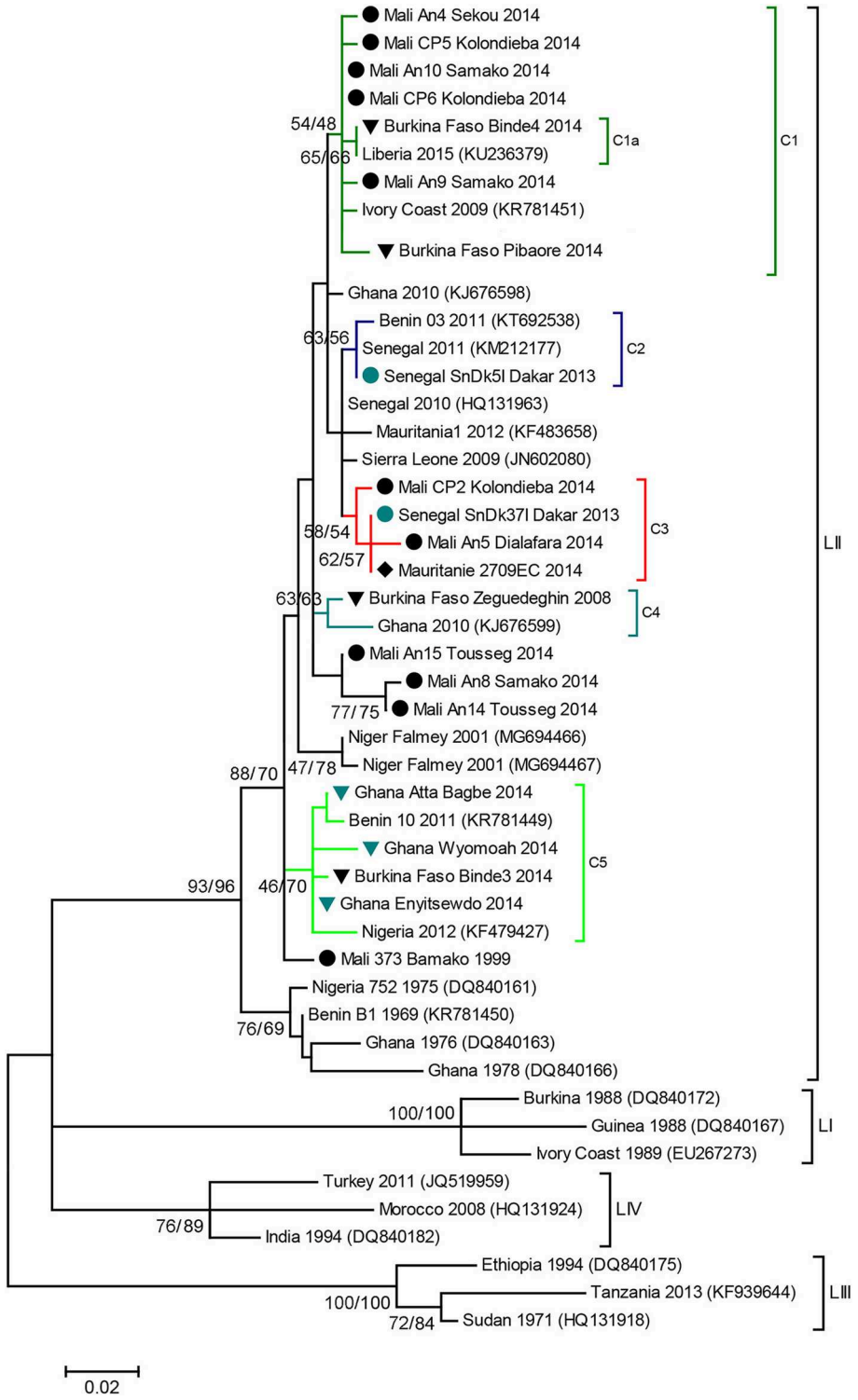

FIGURE 1 | PPR N gene phylogenetic analysis. Phylogenetic tree constructed using a Maximum Likelihood inference method and showing the relationship based on N gene sequences of peste des petits ruminants virus (PPRV) samples, with a special focus on West Africa. Samples collected in this study are indicated by icons according to sampling location (▲Burkina Faso, ▼Ghana, ●Mali, ◆Mauritania, ●Senegal). Genetic clusters of interest to this study are indicated with colored branches, and named C1 to C5. The numbers at the nodes are bootstrap values obtained from 1,000 replicates (Neighboring-Joining/ Maximum Likelihood methods). Bootstrap values are shown if >50% for at least one inference method.

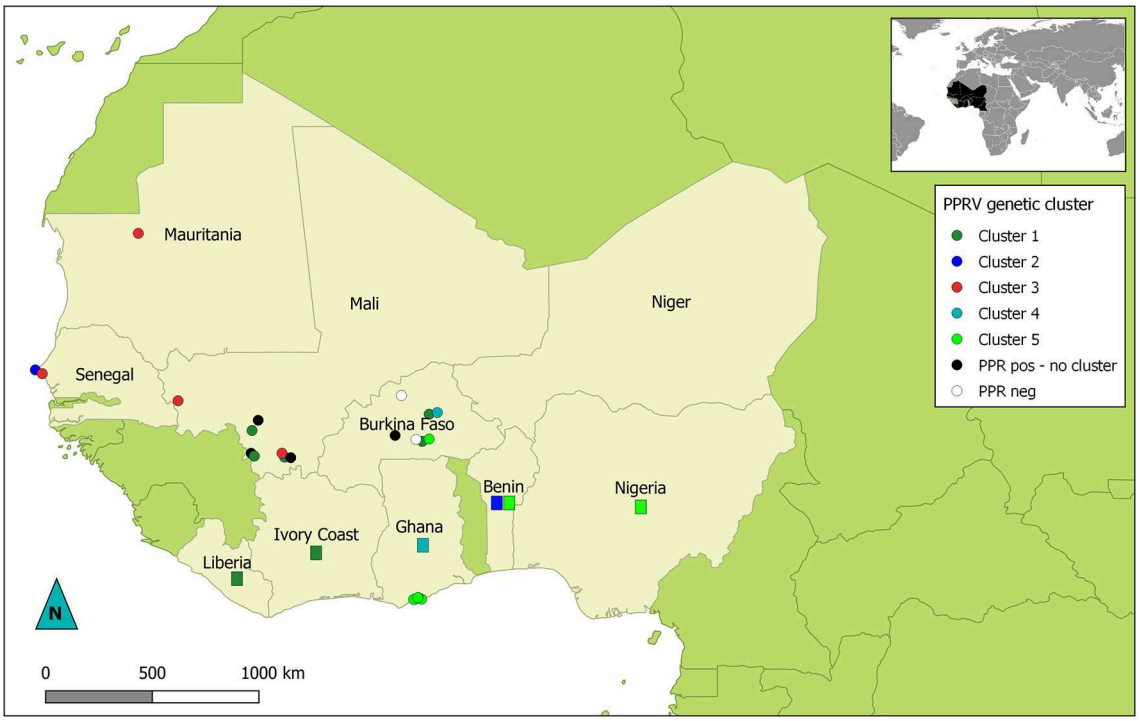

FIGURE 2 | Map of West Africa showing sampling location according to their PPRV lineage II genetic cluster. Dots represent location of samples obtained for this study. Rectangles indicate countries of origin for publically available sequence data used in this study and belonging to genetic clusters of interest in this study. Dots and rectangles are colored according to the genetic cluster (C1 to C5) they were placed in by phylogenetic analysis (see **Figure 1**). Black dots represent PPRV positive samples with no specified genetic cluster. White dots indicate sampling sites where no PPRV positive samples were obtained.

(1, 16, 17). Phylogenetic analyses based on this short (250–300 bp) sequence has been corroborated consistently by those defined on partial or full PPRV genome sequences in the recent years (18–20). A large amount of partial N gene sequence data are publically available because it is produced from one of the most common PPRV diagnostic method used worldwide (11) comparatively to the F gene (21). Therefore, this wealth of data could be used to further our understanding of the epidemiology and transmission dynamics of this important transboundary animal disease.

In this study, we focused on West Africa, aiming at exploring the extent of transboundary movement of PPRV in the region using phylogenetic analysis. PPRV sequences were obtained from fifty-fivesamples collected during this study, with a total of twenty-one new partial PPRV sequences identified in a region still poorly sampled. Most sequences were obtained from samples collected from goats, possibly because goats are usually more affected by PPR than sheep (7). All sequences obtained belonged to PPRV lineage II. Based on the limited number of samples available, it is hard to assess whether the Asiatic lineage IV, currently spreading into West Africa (9), was present in the countries sampled in 2013 and 2014. Further sampling, notably at the borders between Burkina Faso, Mali, Nigeria, Niger and Benin would be necessary to follow closely the progression of the lineage. In the same way, sampling size is too limited to evaluate if the lineage I, not reported since 2001 in Niger (9), was circulating in the regions sampled. Another potential bias is that sampling based on disease report may miss strains circulating silently without provoking any clear symptoms in the animals. Still, our results suggest that lineage II was the most dominant genetic lineage in the region at the time of sampling, as it has been observed before (1). The current distribution of PPRV genetic lineages in the region may be very different, notably because of the risk of rapid spread of the lineage IV in West Africa (9).

Phylogenetic analyses based on sequence data from this lineage can be used to study transboundary PPRV dynamics in the West African region, characterized by complex transboundary movements of animals through transhumance and trade. Indeed, our results showed that we could identify different genetic clusters within lineage II containing samples from more than one West African country, although good statistical support was obtained for only two of them. Some of these clusters consisted of samples from countries sharing borders (for example cluster 5 with samples from Ghana, Burkina Faso, Benin and Nigeria; **Figure 2**). In other cases, clusters grouped samples from very distant countries. This is the case for cluster 1a, which suggest virus circulation between Burkina Faso and Liberia (∼1,500 km). Livestock trade between West African countries is extensive, with movement generally going from producers in the Sahel region toward southern West African countries (14). Our results corroborate previous studies highlighting the risk of intraregional trade for disease emergence (22).

The short sequences used in this study do not provide enough resolution to ascertain the relevance of some clusters identified or to perform complex phylogeographic and phylodynamic inferences that would inform us on the direction and intensity of the movement of PPRV. Some sequences included in the phylogenetic analyses could not be grouped within specific clusters, because of lack of resolution or the paucity of sequence data form the region. Still, our results clearly suggest extensive transboundary movements of PPRV within the region. The genetic clusters contain samples collected from 2004 to 2014 (**Figure 1**). It suggests that extensive movements are recurrent and not extraordinary events, although it is well-known that risk of virus spread may increase during specific religious events such as Tabaski (5). Our results support the call from the FAO and OIE for a regional coordinated strategy for the surveillance and control of the disease in order to eradicate it from West Africa (3). If vaccination campaigns are not coordinated in West Africa, it is likely that local efforts may be wasted due to the high risk of PPRV re-emergence through highly porous national borders, as happened in Morocco (4). Fortunately, the support for PPRV control efforts has increased, notably through regional projects such as the Regional Support Project Pastoralism in the Sahel (PRAPS, http://praps.cilss.int/) in West Africa. Such project should put emphasis into ensuring coordination among participating countries.

Risk mapping analyses based on national and regional animal trade and mobility data are important in the development and implementation of efficient surveillance strategy at national borders and at PPRV transmission hotspots. Our study shows that simple phylogenetic analyses based on readily available data can provide further information on PPRV transboundary dynamics and, therefore, could contribute to improve control strategies. On-going and future projects dedicated to PPRV should include extensive genetic characterization and phylogenetic analyses of circulating PPRV strains in their effort to support the campaign for global eradication of the disease.

DATA AVAILABILITY

The datasets generated for this study can be found in Genbank, MK777887-MK777907.

ETHICS STATEMENT

Veterinarians of national veterinary services conducted the field studies in accordance with local legislation, with no specific ethical approval required. Still, the tissues used in the study were sourced ethically. The study was conducted in animals in contact with outdoor environments with natural exposure to diseases (PPR is endemic in the region). Ocular or nasal swabs were collected on live animals by aseptic means and/or by non-invasive methods, and tissues (lung, lymph node and/or spleen) were sampled from animals that died of infection or were euthanized humanely if symptoms of acute PPR infection were observed (mucopurulent ocular/nasal discharges, diarrhea, fever, loss of weight, respiratory distress).

AUTHOR CONTRIBUTIONS

AmB, ABE, AS, ASE, AL, BD, CA, EI, GM, HH, HS, JS, LO, MG, MDi, ML, MN, and YB organized and carried out field examination of animals and sample collection. AA, KT, HS, MDa, and OK performed laboratory analyses. ArB, KT, OK, and HS performed phylogenetic analyses. ArB wrote the manuscript. ArB and GL designed the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00275/full#supplementary-material

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CORRECTION
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Corrigendum: Genetic Evidence for Transboundary Circulation of Peste Des Petits Ruminants Across West Africa

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A Corrigendum on

Genetic Evidence for Transboundary Circulation of Peste Des Petits Ruminants Across West Africa

by Tounkara, K., Kwiatek, O., Niang, M., Abou Kounta Sidibe, C., Sery, A., Dakouo, M., et al. (2019). Front. Vet. Sci. 6:275. doi: 10.3389/fvets.2019.00275

In the original article, there was an error. A sequence was mistakenly labeled as originating from the Central African Republic (GenBank accession number HQ131960) but was actually a duplicate of the sequence Burkina Faso Pibaore 2014, obtained during this study.

A correction has been made to the **Abstract**:

"Peste des Petits Ruminants (PPR) is a viral disease affecting predominantly small ruminants. Due to its transboundary nature, regional coordination of control strategies will be key to the success of the on-going PPR eradication campaign. Here, we aimed at exploring the extent of transboundary movement of PPR in West Africa using phylogenetic analyses based on partial viral gene sequences. We collected samples and obtained partial nucleoprotein gene sequence from PPR-infected small ruminants across countries within West Africa. This new sequence data was combined with publically available data from the region to perform phylogenetic analyses. A total of fifty-five sequences were obtained in a region still poorly sampled. Phylogenetic analyses showed that the majority of virus sequences obtained in this study were placed within genetic clusters regrouping samples from multiple West African countries. Some of these clusters contained samples from countries sharing borders. In other cases, clusters grouped samples from very distant countries. Our results suggest extensive and recurrent transboundary movements of PPR within West Africa, supporting the need for a regional coordinated strategy for PPR surveillance and control in the region. Simple phylogenetic analyses based on readily available data can provide information on PPR transboundary dynamics and, therefore, could contribute to improve control strategies. On-going and future projects dedicated to PPR should include extensive genetic characterization and phylogenetic analyses of circulating viral strains in their effort to support the campaign for global eradication of the disease."

A correction has been made to the **Introduction**, paragraph five:

"Due to transhumance and poorly controlled movement of animals across the region, we expect to find evidence of close phylogenetic relationship between PPRV strains in West Africa. We collected samples and obtained partial N gene sequences from PPRV-infected small ruminants across countries within West Africa. This new sequence data was combined with publically available data from the region to perform phylogenetic analyses and test this hypothesis."

A correction has been made to the **Results**, paragraph two:

"Phylogenetic analyses showed that all the sequences obtained belonged to the lineage II (LII) of PPRV (**Figure 1**). The sample collected in Mali in 1999 was positioned at the base of all the LII samples collected in 2000–2014. Despite the short length of the sequences aligned (255 bp), multiple genetic clusters could be observed in the phylogenetic trees, with moderate (54–66%) or good (70–87%) bootstrap support for one or two inference method used **(Figure 1)**. All sequences obtained in this study, except three samples from Mali, were placed within one of five genetic clusters regrouping samples from multiple West African and Central African countries (C1-C5 in **Figures 1**, **2**). Cluster 1 included samples from Mali and Burkina Faso obtained in this study and samples from Liberia and Ivory Coast. Within this cluster, close phylogenetic relationship was observed between two samples from Burkina Faso and Liberia (Cluster 1a). One sample from Dakar belonged to Cluster 2 with other samples from Senegal and Benin. Samples from Mali, Senegal and Mauritania formed Cluster 3. The sample collected in Burkina Faso in 2008 clustered with a sample from Ghana (Cluster 4). Finally, sequences obtained in this study from Ghana and Burkina Faso formed the Cluster 5 with samples from Benin and Nigeria **(Figures 1**, **2)**. Bootstrap support was highest for Cluster 1b (87%) and 5 (70%)."

A correction has been made to the **Discussion**, paragraph three:

"Phylogenetic analyses based on sequence data from this lineage can be used to study transboundary PPRV dynamics in the West African region, characterized by complex transboundary movements of animals through transhumance and trade. Indeed, our results showed that we could identify different genetic clusters within lineage II containing samples from more than one West African country, although good statistical support was obtained for only two of them. Some of these clusters consisted of samples from countries sharing borders (for example cluster 5 with samples from Ghana, Burkina Faso, Benin and Nigeria; **Figure 2**). In other cases, clusters grouped samples from very distant countries. This is the case for cluster 1a, which suggest virus circulation between Burkina Faso and Liberia (∼1,500 km). Livestock trade between West African countries is extensive, with movement generally going from producers in the Sahel region toward southern West African countries (14). Our results corroborate previous studies highlighting the risk of intraregional trade for disease emergence (22)."

Lastly, corrections have been made to **Figure 1** and **Figure 2**. The corrected figures appear below.

The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

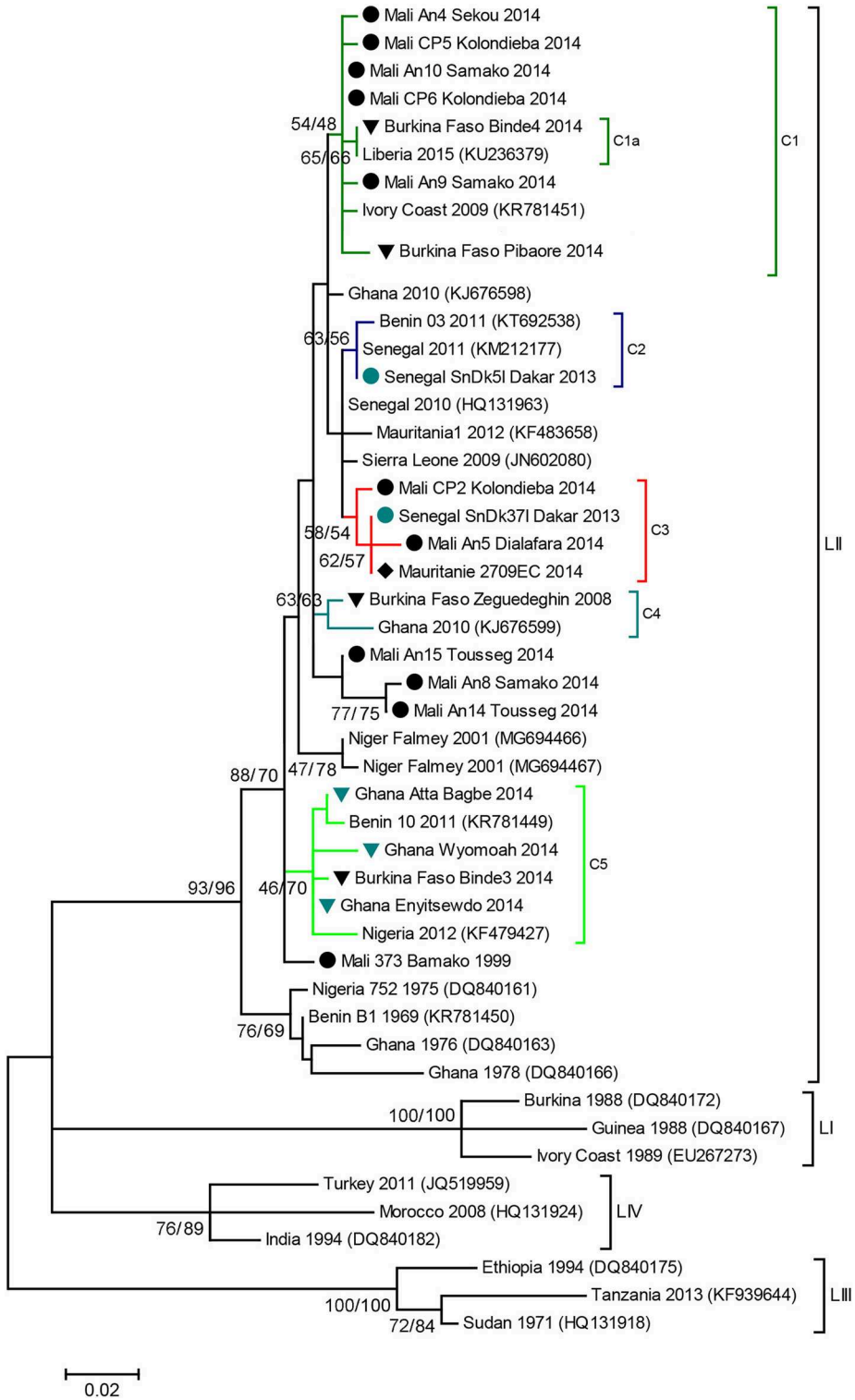

FIGURE 1 | PPR N gene phylogenetic analysis. Phylogenetic tree constructed using a Maximum Likelihood inference method and showing the relationship based on N gene sequences of peste des petits ruminants virus (PPRV) samples, with a special focus on West Africa. Samples collected in this study are indicated by icons according to sampling location (▲ Burkina Faso, ▼Ghana, ●Mali, ◆Mauritania, ●Senegal). Genetic clusters of interest to this study are indicated with colored branches, and named C1 to C5. The numbers at the nodes are bootstrap values obtained from 1,000 replicates (Neighboring-Joining/ Maximum Likelihood methods). Bootstrap values are shown if >50% for at least one inference method.

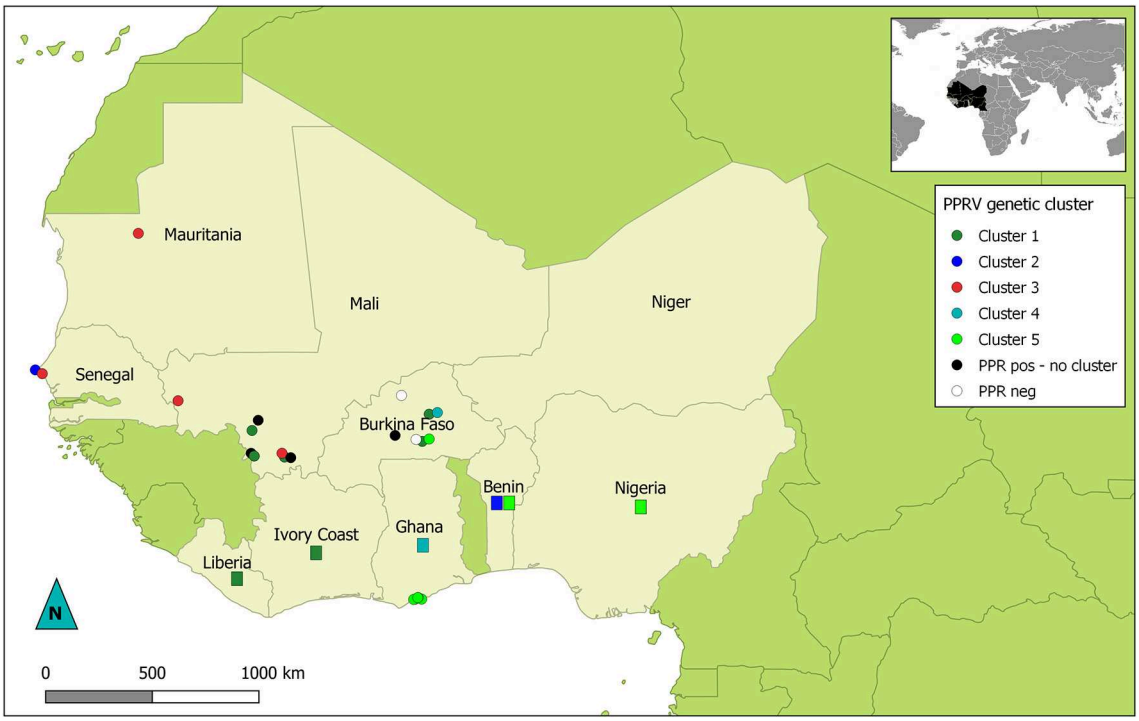

FIGURE 2 | Map of West Africa showing sampling location according to their PPRV lineage II genetic cluster. Dots represent location of samples obtained for this study. Rectangles indicate countries of origin for publically available sequence data used in this study and belonging to genetic clusters of interest in this study. Dots and rectangles are colored according to the genetic cluster (C1 to C5) they were placed in by phylogenetic analysis (see **Figure 1**). Black dots represent PPRV positive samples with no specified genetic cluster. White dots indicate sampling sites where no PPRV positive samples were obtained.

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ORIGINAL RESEARCH
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Epidemiological Survey of Peste des Petits Ruminants in Ethiopia: Cattle as Potential Sentinel for Surveillance

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Peste des petits ruminants (PPR) is a highly contagious viral disease of small ruminants; it emerged in countries previously free of the disease following the eradication of rinderpest. PPR is classified by international organizations as the next priority animal disease for global eradication campaign. Assessment of the local situations is the first step in the eradication efforts. The objective of this study was to investigate and compare the seroprevalence of PPR in cattle, sheep, and goats under two livestock production systems in Ethiopia: North Shewa zone of Amhara region represents a highland sedentary life style characterized by mixed livestock-crop production system; Zone Three of Afar region represents a lowland nomadic life style characterized by pastoral livestock production system. N-competitive ELISA PPR test was performed on sera from 2,993 animals ≥6 months old sampled at watering and grazing points. Multivariable logistic regression models comparing the seropositivity between the two production systems were built by classifying doubtful results as positive, negative, or excluding them from the data. The odds ratio (OR) comparing overall PPR seroprevalence in the sedentary North Shewa Zone compared to the nomadic Zone Three ranged from 19 to 27 ($P < 0.001$), depending on how doubtful results were classified, which contrasts with what has been reported in the literature. This is not likely to be related solely to vaccination, since seroprevalences in cattle and small ruminants were similarly high or low in the respective zones (0–4% for Zone Three and 20–40% for North Shewa Zone), and cattle were not likely to be vaccinated. The OR of seropositivity for goats compared to cattle ranged from 1.9 [95% confidence interval (CI): 1.3–2.7; $P < 0.001$] to 2.2 (95% CI: 1.5–3.1; $P < 0.001$) when doubtful results were excluded or classified as negative, respectively. When doubtful results were classified as positive, association between seropositivity and animal species was not significant ($P > 0.05$). Our results suggest to further investigate cattle as sentinel animals for PPR surveillance.

Keywords: peste des petits ruminants, cattle, sheep, goats, agroecology, seroprevalence

INTRODUCTION

Peste des petits ruminants (PPR) is a highly contagious viral disease of small ruminants. Since it was first identified in Ivory Coast in 1942, its geographic distribution has been expanding within Africa, and spread to the Middle East and Asia (1). PPR gained international attention following the detection of PPR virus in Turkey in 1996 with the fear that the disease can spread to the rest of Europe and other developed countries (1). PPR is the next priority animal disease targeted for global eradication campaign by Food and Agricultural Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) (2, 3). The disease is characterized clinically by high fever, pneumonia, necrotic lesions of the oral cavity, and diarrhea; and epidemiologically by high morbidity and mortality rates in small ruminants (4, 5). Although cattle, swine, camels, and buffaloes can be infected with the PPR virus (6–8), the role of these species in the epidemiology of the disease is still unclear (1, 4).

In Ethiopia, the first clinically suspected case of PPR was reported from goat herds in Afar region in 1977 and later was confirmed through the isolation of the virus in 1991 (9, 10). Since then, PPR has been reported from various parts of the country with seroprevalences varying between 12% in 2001 similarly to that of the national serological survey conducted in 1999 and 31% in 2009–2010 in pastoral flocks (11–14). The disease is considered endemic in the country and control relies solely on immunization of small ruminants as an efficacious live attenuated vaccine producing lifelong immunity against all PPR virus serotypes after a single administration is available (15). The strategy is mass vaccination in lowlands and ring vaccination following PPR outbreaks in the highlands considering the different production systems in the two agro-ecological zones. Animal movements in the lowlands are more frequent and commonly involve large number of animals which puts them at a higher risk for PPR infection. In addition, vaccination fees may not be affordable in the pastoral communities (15, 16). The objective of this study was to investigate and compare seroprevalences of PPR in cattle, sheep, and goats in two different but contiguous zones of Ethiopia representing on one hand a highland sedentary livestock farming system (North Shewa Zone in Amhara Region) and on the other hand a lowland pastoral nomadic system (Zone Three in Afar Region) and discuss the implication of the findings for the design of surveillance and control activities.

MATERIALS AND METHODS

A cross-sectional study was carried out from December 2005 to June 2006. Blood samples were collected from as many as possible number of cattle, sheep, and goats in two different agroecological zones. North Shewa Zone in the Amhara Region is situated in the highlands (>1,200 m above sea level) of Ethiopia where mixed livestock and crop production prevails; Zone Three of Afar Region is in the lowlands and is characterized by pastoral nomadic husbandry system (**Figure 1**). Farmers were asked for their consent to participate in the study at watering and grazing points and were purposively selected because of logistics for field sampling and time constraints. In the affirmative, animals believed to be over 6 months old in the herd were sampled, to avoid seropositivity due to maternal antibodies. Blood samples were collected from the jugular vein into plain vacutainer tubes and were kept overnight at room temperature to clot. Serum was separated from the clot by simple decantation or by centrifugation when necessary. Sera were transferred into cryovials and kept at −20°C until analyzed in the laboratory.

Serum samples were tested for the presence of specific PPR antibodies by using N-competitive enzyme linked immunosorbent assay (N-cELISA) kit according to the manufacturer's instructions (CIRAD/EMVT, Montpellier, France), at National Veterinary Institute (Bishoftu, Ethiopia). The cELISA kit was based on recombinant N-protein of PPR virus as the capture antigen and a monoclonal antibody against the N-protein as the competitive antibody (17). The optical densities (OD) were measured with an ELISA reader with an inference filter of 492 nm. The percent inhibition (PI) values were determined according to the following formula:

PI (%) = 100–[OD of control or test serum/OD of monoclonal control]*100. The PI values were categorized as negative (PI < 45%), doubtful (PI = 45–49%) or positive (PI ≥ 50%).

Multivariable logistic regression models for the outcome seropositive for PPR (0 or 1) were run separately by classifying doubtful results as (i) negative, (ii) positive, or (iii) excluded, and including the explanatory variables Zone and species. Two-way interactions between the variables were tested. Statistical analyses were performed with R version 3.2.3 using the glm function (18). Results were considered statistically significant when $P < 0.05$.

RESULTS

The proportion of positive results by species and by Zone when doubtful laboratory results were classified as positive, negative, or excluded is presented in **Table 1**. The odds of seropositivity for the combined results of the three animal species in North Shewa Zone compared to Zone Three ranged from 19 to 27 (**Table 1**), for the three scenarios of how doubtful results were classified. The odds of seropositivity for goats compared to cattle was 2.2 [95% confidence interval (CI): 1.5–3.1], 1.3 (95% CI: 0.9–1.8), and 1.9 (95% CI: 1.3–2.7) when doubtful results were classified as negative, positive, or excluded, respectively. Zone by animal species interaction (data not shown) was not statistically significant ($P > 0.05$) in the three scenarios considered for the doubtful values; results reported here therefore represent the main effects of zone and animal species adjusted for the effect of the other in the multivariable logistic regression models.

The proportions of seropositive and doubtful results in the two zones and the three livestock species is presented in **Table 2**. The proportions of laboratory doubtful results for cattle and sheep (15.5% each) were considerably higher in North Shewa Zone compared to Zone Three (0.0% in cattle and 0.2% in sheep) (**Table 2**). Similarly, the proportions of test positive results for cattle and sheep (20 and 22%, respectively) were much higher in the North Shewa Zone than in Zone Three (0.3% in cattle and 0.5% in sheep). For goats the doubtful results were relatively

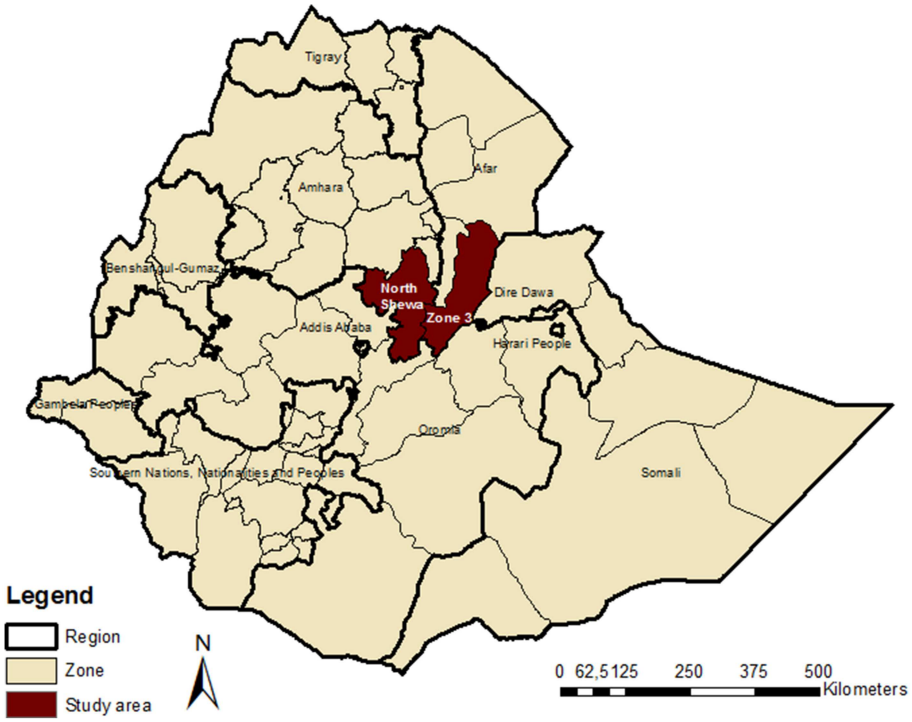

FIGURE 1 | Map of Ethiopia showing the study Zones for serological survey of Peste des petits ruminants in cattle and small ruminants.

considerably lower (4.8% in the North Shewa Zone and 0.4% in Zone Three) than that of sheep and cattle in both zones. However, we note that in both zones the highest seroprevalence (considering the proportion of test classified positive results) was observed in goats (3.6% in Zone Three and 31% in North Shewa Zone).

DISCUSSION

Similar seroprevalences for cattle and small ruminants have been found in some other studies (7, 11). This can be explained by the fact that mixed herds of different animal species likely transmit PPR virus to contact animals. Since the turn-over rate of cattle is lower (10%) than that of small ruminants (30%) (particularly in goats), and since goats are more likely to succumb to PPR disease than sheep and cattle the seroprevalence rates in sheep and cattle may occasionally be higher than that of goats (2, 19) as observed in the present study.

The results showed a significantly higher PPR seroprevalence in the sedentary highland North Shewa Zone compared to the lowland pastoral nomadic Zone Three. This is in contrast with what has been reported in the literature where lowland pastoral nomadic practices have been associated with higher PPR seroprevalence due to large number of animals in continuous movement in search of fodder and water, whereas animal mixing is less frequent in the highlands with small sedentary herds (14, 20). However, more recently, Fentie et al. (21) reported that small ruminants reared in the lowland and highland areas were more affected than those reared in midland (25, 14.58 vs. 7.5% respectively, $P < 0.05$). The difference between the present results and literature may be due to different sampling procedures in the different studies that affect their representativeness. Field collection of data and the use of probability sampling designs are challenging in Ethiopia because of poor infrastructure, cultural differences that may result in a lack of co-operation from livestock owners and periods of hot climatic conditions (22). The field data from our study did not allow a detailed evaluation of the role of the herd size, species composition of the herds and the production system (sedentary highland and lowland pastoral nomadic) on the seroprevalence rates in the two regions which may also explain the difference between results of our study and the literature. Seasonality of the disease also might have affected the results as the time period of the study was limited and outbreaks are more frequent during the main rainy season which typically lasts from March to October in Ethiopia (21). Thus, presence of active PPR outbreaks at the time of serum sample collection in one or both zones studied also could have affected our results. However, samples were obtained from apparently healthy animals and there was no indication of PPR outbreak during the field sampling. It may also be due to differences in prior vaccination status of the animals. The higher seropositivity observed in the highland zone in the present work can reflect a higher prior vaccination rate in the zone that are generally more accessible as several mass vaccination campaigns have occurred in Ethiopia between 2005 and 2011 (16). Indeed, the

TABLE 1 | Descriptive and logistic regression analyses results comparing seropositivity (dichotomous outcome recorded as seropositive or seronegative) of peste des petits ruminants between sedentary highland (North Shewa Zone, Amhara region) and nomadic lowland (Zone Three, Afar region) livestock production systems in Ethiopia, December 2005–June 2006.

Outcome classification and variables			No. animals tested	Seroprevalence (%)	Odds ratio (OR)		
					OR	95% CI*	*P*-value
≪Doubtful≫ classified as negative	Zone	Zone Three	1,953	2.1			
		North Shewa Zone	1,040	25.7	19.4	13.8–27.9	<0.001
	Species	Cattle	6,13	10.6			
		Goats	1,325	9.6	2.2	1.5–3.1	<0.001
		Sheep	1,055	11.0	1.3	0.9–1.9	0.085
≪Doubtful≫ classified as positive	Zone	Zone Three	1,953	2.4			
		North Shewa Zone	1,040	38.2	27.1	19.7–37.9	<0.001
	Species	Cattle	613	18.6			
		Goats	1,325	10.9	1.3	0.9–1.8	0.062
		Sheep	1,055	17.4	1.2	0.9–1.6	0.146
≪Doubtful≫ excluded	Zone	Zone Three	1,948	2.1			
		North Shewa Zone	910	29.3	22.2	15.8–31.9	<0.001
	Species	Cattle	564	11.5			
		Goats	1,307	9.7	1.9	1.3–2.7	<0.001
		Sheep	987	11.7	1.3	0.9–1.9	0.082

Results are presented by classifying doubtful laboratory results as positive, negative, or excluding them. Results were considered significant when $P < 0.05$.
**95% confidence interval for the odds ratio (OR).*

TABLE 2 | Percentage of animals tested doubtful or positive for peste des petits ruminants in Zone Three of Afar region and North Shewa Zone of Amhara region, Ethiopia, December 2005–June 2006.

Zone	Species	Number of animals tested	% Doubtful	% Positive
Zone Three	Cattle	296	0.0	0.3
	Goats	1,035	0.4	3.6
	Sheep	622	0.2	0.5
	Zone Three total	1,953	0.3	2.1
North Shewa Zone	Cattle	317	15.5	20.2
	Goats	290	4.8	31.0
	Sheep	433	15.5	21.6
	North Shewa Zone total	1,040	12.5	25.7
Species total	Cattle	613	8.0	10.6
	Goats	1,325	1.4	9.6
	Sheep	1,055	6.5	11.0
	Overall total	2,993	4.5	10.3

cELISA test used cannot differentiate infected and vaccinated animals. However, because cattle are not likely to be vaccinated, and because the proportion of seropositive animals is higher in North Shewa Zone in the three animal species (**Tables 1**, **2**), the difference in the seropositive proportion between the two zones is not likely to be due solely to vaccination and may rather result from natural infection. The higher prevalence in the highland zone may also indicate the expansion of the disease into parts of the country previously free of the disease.

The N-cELISA test used is reported to be a highly specific and sensitive test when compared to virus neutralization test (17) but exact corresponding performances and cut-off values have not been published. Couacy-Hymann et al. (19) using N-cELISA considered PI ≥ 50% as positive and PI > 65% as "high percentage of inhibition" when cattle were experimentally infected with virulent PPR virus strains and showed seroconversion. If the threshold of 50% appears reasonable to consider in the field for interpretation of positive or negative results, we looked at the effect of classifying the laboratory results considered doubtful as positive, negative, or excluding them, as it is the way they are recorded by the laboratory and that no clear instructions have been published to date. When laboratory doubtful results were classified as negative (OR = 2.2) or excluded (OR = 1.9), goats were twice more likely to be seropositive than cattle. Although not significant (OR = 1.3; $P = 0.062$), the same trend was observed in the model when doubtful results were classified as positive. Despite significantly higher odds of seropositivity in goats when doubtful results were classified as negative or excluded, crude seroprevalences were similar for goats (9.6–9.7%) and cattle (10.6–11.5%). On the other hand, considerable differences were found between cattle (18.6%) and goats (10.9%) when doubtful results were classified as positive although statistical analysis did not reveal significant association (**Table 1**). This might be due to stronger effect of zone than the animal species on the seroprevalence (OR = 27) when doubtful results were classified as positive compared to OR ranging from 19 to 22 when the doubtful results were classified as negative or excluded. Nevertheless, the highest seroprevalence in goats in both zones (31% in North Shewa vs. 3.6% in Zone Three; **Table 2**) is consistent with the fact that goats are maintenance hosts for the disease whereas cattle appear to be dead end hosts in the epidemiological cycle (19, 23).

Despite differences in the odds of seropositivity between goats and cattle, the difference in the prevalence between the two Zones (the three species combined) suggests that cattle may be used as sentinel animals for surveillance purposes particularly in areas at higher risk for introduction of PPR. The use of cattle as sentinel is also recently suggested by others (23, 24), and is consistent with the fact that cattle are usually considered dead-end hosts for PPR and not normally vaccinated against PPR. Detection of PPR antibodies in the cattle may indicate the exposure of cattle to infected small ruminants during housing, grazing, and watering which is typical of small holder livestock production system in Ethiopia (11).

The fact that 15.5% of cattle and sheep sampled from North Shewa zone were classified as doubtful compared to 4.8% in goats cannot be explained by any differential performance of N-cELISA that may be present in different animal species. The test was first developed and validated using goats and cattle sera at 94.5% sensitivity and 99.4% specificity by using virus neutralization test as a gold standard test (17). A recent study, Bodjo et al. (25) similarly reported 96.4% sensitivity and 97.1% specificity for sera obtained from sheep and goats using virus neutralization as a gold standard. However, any species difference in the test performance, if exists, does not diminish the utility of testing cattle as an indicator of PPR virus circulation or seroprevalence in small ruminant herds. However, under very low prevalence, as observed in Zone Three, results should be interpreted with caution. The fact that 15.5% of sheep from the North Shewa zone were classified as doubtful, similarly to cattle, remains unexplained and needs further investigation particularly cELISA test outputs need to be revised. Since the seropositive results in cattle and sheep were also higher in the North Shewa Zone (20.2–21.6%) than in Zone Three (0.3–0.5%), it is also more likely that the doubtful results would be similarly higher in the North Shewa Zone compared to the Zone Three. So, it is unlikely that the higher percentage of doubtful results is due to higher percentage of doubtful results in the zone but more likely due to the generally higher seroprevalence in the North Shewa Zone which would result in higher positive percentage and therefore also more doubtful results. We speculate the shifting of PPR occurrence toward the highland zone since doubtful and test positive results were higher in the North Shewa Zone compared to Zone Three. It may also be due to the non-random sampling of the study animals performed in the present work due to practical constraints. We also note that the doubtful results were not re-tested or verified by other methods.

Many heterogeneities in the population structure and husbandry practices in Ethiopia could not be captured in this study. The limitations are partly due to lack of variables to be included in the analysis and if new studies will be performed in the future, efforts should be made to include at least timing of successive vaccination campaigns and age of the animals to be sampled as already mentioned by Fournié et al. (26). Results of seropositivity are probably influenced by non-probability sampling method used but, in our opinion, this does not affect the finding that cattle can be used as potential sentinels for the serosurveillance of PPR.

CONCLUSION

The present work reports an unexpectedly higher PPR seroprevalence in the sedentary highland North Shewa Zone compared to the lowlands pastoral nomadic Zone Three. Goats were twice as likely to be seropositive compared to cattle. Our results suggest that cattle can be used as sentinel species for PPR surveillance in cattle-small ruminant mixed farming areas, and to monitor the impacts of interventions and disease freedom in high risk areas. This is very important since FAO and the Ethiopian Ministry of Livestock and Fisheries reaffirmed their commitments to eradicate PPR from Ethiopia by 2027. No DIVA vaccine is available to date that can help differentiate infected and vaccinated animals.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

According to EU law (Directive 2010/63/UE), procedures which use farm animals according to common veterinary practice, can be done without minister permission and without an ethics committee opinion.

AUTHOR CONTRIBUTIONS

GA, FA, DS, GB, YW, KB, BT, MB, and FR conceived and designed the study. FA, DS, and GB collected and analyzed samples. GA, YW, KB, BT, and MB supervised data acquisition. GA, LW, DR, and AW-S organized the dataset and performed statistical analysis. GA wrote the first draft of the manuscript. DR, FR, and AW-S wrote sections of the manuscript. All authors helped in the interpretation of the data, revised the manuscript, read, and approved the final version.

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Strategies for the Global Eradication of Peste des Petits Ruminants: An Argument for the Use of Guerrilla Rather Than Trench Warfare

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Many historical disease eradication campaigns have been characterized by large-scale mobilization and long-term campaigns of mass vaccination. As the duration of a program increases, the total cost also increases, but the effectiveness and sustainability decrease, sometimes resulting in premature loss of stakeholder support, field team fatigue, and failure or major set-backs. In contrast to this trench warfare approach, this paper proposes an eradication strategy modeled on guerrilla tactics: use exceptionally good, locally relevant and timely intelligence; strike rapidly and effectively in small areas; achieve your goals; and keep moving. For peste des petits ruminants eradication, this means a shift away from long-term mass vaccination, focusing instead on addressing some of the challenges that have plagued previous eradication programs: ineffective surveillance and movement management. Recent developments in surveillance have shown that it is now feasible to capture information about almost all cases of disease, all movements and all control activities, from the entire population in real time. Developing powerful, effective and sustainable surveillance systems is an essential prerequisite for rapid, affordable PPR eradication. PPR can be rapidly eliminated from small populations by achieving very high levels of vaccination coverage for only a short period. The key challenge is then to prevent the re-introduction of disease as immunity wanes, and to respond rapidly and effectively in the case of further local outbreaks. A comprehensive understanding of movement patterns and their drivers will allow rapid progressive eradication to be implemented. The population can be divided into manageably small units, targeted sequentially for high-coverage short-duration vaccination, then moving to the next unit based on the distribution of disease and the direction of animal flow. This approach optimizes the use of available resources, and minimizes the challenge and disruption of managing retrograde movement from infected to uninfected areas. High levels of community engagement are required to achieve the quality of surveillance, movement management and rapid response necessary for success. Traditionally, long-term vaccination has been used to first eliminate the virus from a population, and then to protect it against re-introduction of the disease. Under the guerrilla strategy, continuous real-time information, not long-term vaccination, is the main tool for disease eradication.

Keywords: PPR, disease eradication, strategic vaccination, movement management, surveillance, user-focused

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INTRODUCTION

Following the declaration of successful global eradication of rinderpest, peste des petits ruminants (PPR) has been proposed as a candidate for global eradication (1). The World Organization for Animal Health (OIE) and the Food and Agriculture of the United Nations (FAO) released a strategy in 2015 aiming for global eradication of PPR by 2030 (2). Jones et al. (3) have developed and assessed an alternative strategy for eradication, one of the features of which is time-bound vaccination to avoid the need for long-term costly control programs (trench warfare). This paper builds on the detailed work already undertaken, incorporating recent experience in sociological approaches to user-focused surveillance (4), and a consideration of disease control theory, to present a more aggressive (guerrilla) strategy for rapid, affordable global PPR eradication. Global disease eradication is enormously complex, and requires many components. This paper focuses on specific technical areas that differ from those already developed, building on previous work.

Factors Influencing Likelihood of Eradication

In order to survive and reproduce, viruses like PPR need to be transmitted from one host to another. Control and eradication strategies are focused on interrupting transmission. The feasibility of this depends on the characteristics of the virus and the populations that it infects. A number of factors support PPR eradication:

- **Survival of the virus outside the host**. PPR is fragile outside the host as its lipid bilayer envelope is rapidly destroyed by heat and sunlight (5, 6). It is therefore mainly transmitted by direct contact (bodily secretions), local aerosol spread from coughing, or contaminated feed or water, but only to animals within close proximity.
- **Vaccine**. The currently used homologous attenuated PPR vaccine has major advantages: it protects against all lineages; it provides long lasting protection (at least 3–5 years, but probably life-long); it is safe, in that it has not reverted to virulence and does not cause abortion; and it is widely available and quality controlled (6).
- **Hosts range**. There is no prolonged carrier state after infection, and there are no known reservoirs outside domestic small ruminants (or at least none that are likely to play an epidemiologically significant role) (6).
- **Diagnosis**. Many cases demonstrate evident clinical signs that are easily detected by herders. In previously free populations, the disease takes an epidemic form, with high morbidity and mortality and acute clinical expression, making clinical detection relatively reliable. There are good laboratory and field-based diagnostic tests available.

On the other hand, there are a number of potential constraints:

- **Hosts**. There are still questions about the role of some other species in the epidemiology of PPR, including dromedaries, wildlife and bovines (7).
- **Distribution**. PPR is extremely widespread (**Figure 1**) and endemic in many countries with under-resourced veterinary services.
- **Population dynamics**. Small ruminants have a high population turnover, resulting in the rapid introduction of naïve animals into vaccinated populations (6). Local animal density within flocks is high, facilitating rapid within-flock spread. In many endemic areas, farming practices include transhumance and migratory management, increasing the opportunity for disease spread.
- **Economics**. While the total cost of disease is high, the value of individual animals (relative to cattle, for example) is much lower. This, coupled with short lifespan means that the proportional cost of vaccination is higher than was the case for rinderpest.
- **Clinical expression**. Expression varies with species and breed, and the signs are not specific making a definitive clinical diagnosis difficult or impossible. In endemic areas, virus may circulate with little clinical expression.

Proposed Strategy

This paper presents a hypothesis: that by learning from the lessons of rinderpest, building on existing ideas (2, 3, 6) and epidemiological theory, and incorporating new technological, sociological and epidemiological developments, a new approach to PPR eradication is possible—one that will be able to achieve global eradication more rapidly, less expensively and with longer term sustainable benefits than traditional approaches. The key elements of this new approach, to be expanded upon in the following sections, are:

- Aiming for **rapid global eradication**—to avoid donor and veterinary service fatigue
- Achieving effective **global coordination**—focusing disease eradication efforts on the disease, populations, ecosystems, animal movement, and other risk factors, not on national boundaries or government administrations
- Progressive eradication by dividing the population into **small units**—allowing intensive allocation of resources in a small area, to achieve very high vaccination coverage
- Using very **short-duration local control interventions**—to avoid eroding the support of producers and other local stakeholders
- Intelligent focused **movement management**, and carefully sequenced spatial and temporal progression of eradication activities—to minimize the disruption to producers and markets and avoid introducing price distortions that provide incentives for dangerous movements
- Aiming for a short period of very high vaccination coverage within each population unit to achieve virus elimination and then quickly return to a largely susceptible population—to **maximize the sensitivity of clinical surveillance** for detecting new outbreaks
- Maintain high levels of **producer engagement** in disease surveillance and control, along with rapid, effective outbreak response capacity—to detect and rapidly eliminate new outbreaks in otherwise free areas

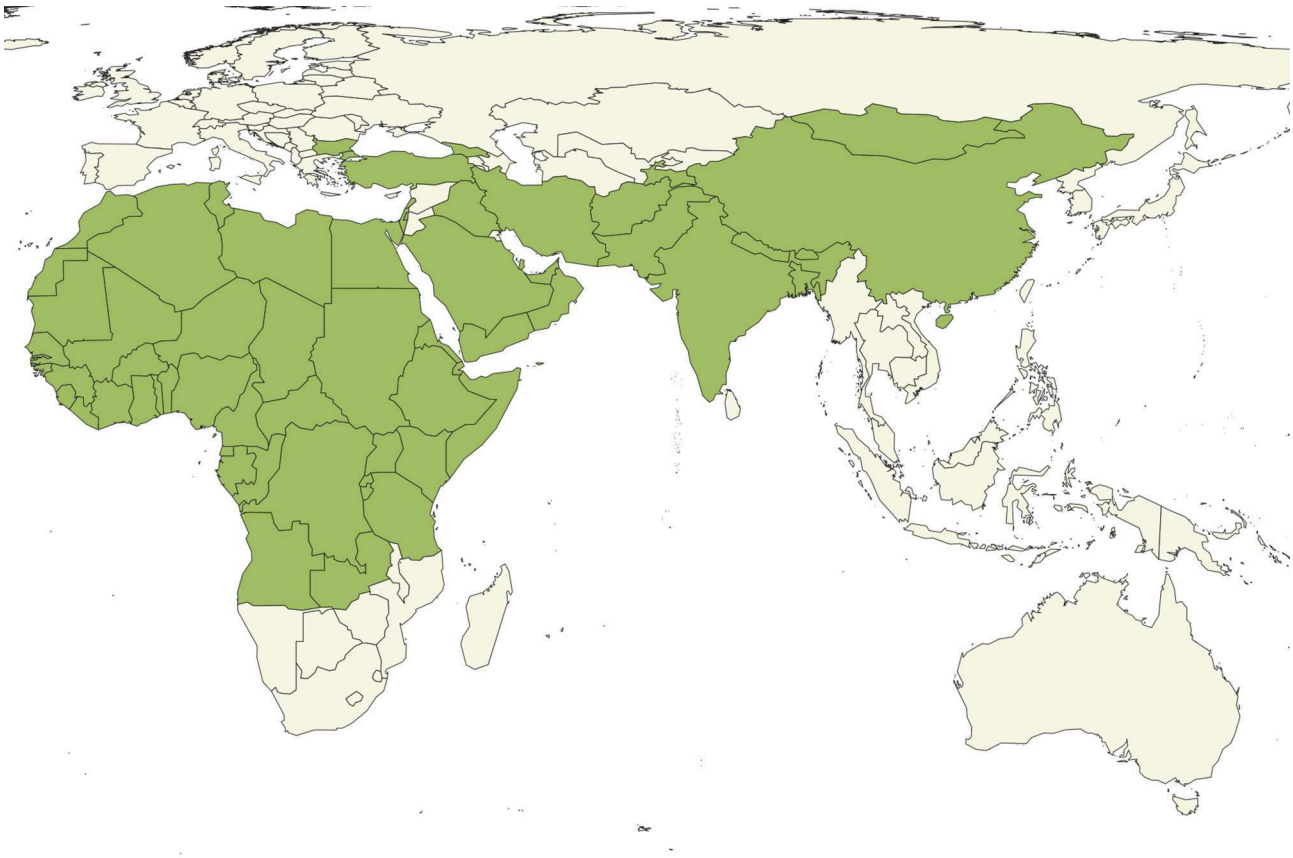

FIGURE 1 | Countries (green) reporting the presence of PPR to OIE as of April 2019 (8).

- Underpin everything with **excellent information**: sustainable, affordable, real-time, census-level, highly granular, and integrated surveillance covering all aspects of the eradication program, including animal movements and their drivers, population, vaccination, veterinary infrastructure and resources available, control activities, disease occurrence, and outbreak response.

This hypothesis has been developed on the basis of epidemiological theory and evidence from previous eradication programs. While other authors (9) have emphasized the need for more strategic vaccination based on better surveillance, this guerrilla approach to small-area intensive vaccination, and rapid planned progression through population units may be perceived as carrying higher risks. These are mitigated by a greatly increased emphasis on high quality information generated using existing approaches to effective stakeholder engagement.

The purpose of a hypothesis is to be tested, and this is often achieved by small-scale experimentation. Unfortunately, testing this hypothesis will require large scale investment and commitment, ideally at a regional level. This paper is intended to start a conversation as to whether the hypothesis has enough merit to warrant such a large-scale test.

LESSONS LEARNED

What Can We Learn From Rinderpest Eradication?

The global eradication of Rinderpest was announced in 2011 and represents a landmark for livestock disease control (10). The first major coordinated rinderpest eradication program was the 15-country Joint Program (JP15), launched in Africa in 1961. It went through several stages of evolution [Pan-African Rinderpest Campaign (PARC), The Pan African Program for the Control of Epizootics (PACE), and the Global Rinderpest Eradication Program (GREP)] and took 50 years for eradication to succeed. Without taking away from this remarkable success, it is important to ask, as we consider embarking on another livestock morbillivirus eradication program, whether we can do it better—faster, more cost-effectively, and with even greater net benefit.

The expected duration of the eradication program is perhaps the most critical factor influencing cost. It is extremely unlikely that even the most visionary donor or finance department would willingly embark on a program, knowing that it may not succeed for 50 years. Learning the lessons from rinderpest eradication may help achieve the goal more quickly, at low cost, and with greater confidence (11).

Withdrawing Support too Early

In 1979 after 18 years, JP15 had successfully decreased rinderpest in participating countries to very low levels, with only a few sporadic outbreaks. Unfortunately, the disease fought back, with extensive spread in five of the participating countries. In 1986, PARC was initiated, but faced a far greater challenge, and took 15 more years to succeed.

Lack of Access to, or Use of, Epidemiological Information

In 1999, the Intensified GREP program changed the approach to control by improving the use of surveillance information to focus on localized reservoirs of infection. This approach was first developed in Ethiopia and achieved considerable success. It was then extended to Sudan, the Arabian Peninsula, Pakistan and East Africa resulting in rapid eradication by 2001 (10).

One of the summary conclusions of the 2010 GREP symposium (11) was that "newer approaches such as immunosterilization and community-based vaccine delivery with heat-tolerant vaccine … made a valuable contribution in South Sudan. Noting that future control campaigns against PPR may require even more vaccination than did rinderpest, several participants advocated the use of more modern approaches from the start and suggest that additional innovative thinking for epidemiological targeting and vaccine delivery may be necessary."

Lack of Community Engagement

"Another lesson was that there must be communication with cattle keepers to convince them of the need for vaccination and counter other considerations that could argue against them having their animals vaccinated. As a result of not taking these and other considerations into account, JP15 controlled rinderpest but did not eradicate it, and the disease returned as a major epidemic in Africa" (9). It could be contended that our understanding of community engagement has evolved since these words were written. We should no longer seek to "convince" farmers of the need for vaccination, but instead to engage them as full partners in disease eradication, placing their needs at the center of the program (4).

Ineffective Vaccination Coverage

At times during rinderpest eradication, sufficient levels of population immunity were not being achieved to attain eradication. Indeed, it was proposed that sub-optimal vaccination could mask the presence of disease and decrease the efficacy of surveillance programs, and could be worse than no vaccination (12). In India, mass vaccination was only able to achieve coverage rates of 40–50% (13).

Mass Vaccination Strategy

"An important lesson from JP15 was that 3 years of blanket vaccination with no regard for the epidemiological significance of cattle numbers, distributions, movements and husbandry was not an appropriate strategy" (9). Taylor et al. (14) noted the success of so-called immunosterilization, which they defined as two doses within 6 months designed to eradicate disease from the population. They further noted that "… in an immunosterilization campaign the critical issue was to disrupt viral transmission through the short-term generation of a highly immunized population. Relative to the desired objective, it did not particularly matter if, in the succeeding months, the population remained cohesive and highly immune, or fragmentary and increasingly susceptible, provided that at the time a serviceable herd immunity had been generated" (15).

Inadequate Coordination

Imperfect local and international coordination hampered progress. This is linked to inadequate donor coordination and commitment.

Lack of Broad and Sustainable Benefit

"It could help motivation and prioritization in developing countries if future programmes move from the control of a single disease to a broader remit. The control of livestock diseases that affect trade, including livestock exports, may encourage developing countries' participation. Mechanisms need to be found for sustained support for surveillance, diagnosis and response to trade-related diseases and emerging infectious diseases, including zoonoses" (16).

Institutionalization

A (possibly theoretical) challenge to rapid and effective disease control is the process of institutionalization. A major and prolonged eradication project brings with it organizational infrastructure—offices, personnel, equipment—that carry their own inertia. In particular, when a person's employment is directly linked to the eradication of a disease, the successful completion of that task necessarily raises the likelihood of termination of the position, especially if it is funded through external sources. This may represent a conflict of interest—the act of working toward eradication is more lucrative for individuals than achieving it.

Conclusions

Based on the experience of rinderpest, a major constraint to successful eradication is the duration of the eradication campaign. As a campaign drags out:

- The cumulative cost mounts, decreasing the appetite of governments or donors to continue to contribute.
- Operational fatigue sets in, affecting both farmers and field personnel. The initial enthusiasm to pull together to fight a common enemy erodes until the work becomes routine and apparently endless. Vaccination coverage levels drop and the quality of surveillance deteriorates.
- Political will wanes, as other competing priorities arise, risking premature termination of the program, especially during the final stages when progress is harder to measure but costs remain high.
- Control activities risk becoming institutionalized, and lose flexibility and responsiveness.

The other main constraint has been information. While rinderpest eradication led to some major developments in surveillance methodologies, including participatory

epidemiology (17), most of the program (until only a few years before final successful eradication) was hampered by a lack of comprehensive understanding of the populations at risk, movement patterns, early detection capacity, and accurate measures of vaccination coverage. This was exacerbated by weakness in disease information systems.

Key Objective

Based on the lessons from rinderpest, it is possible to identify some simple key objectives for a future PPR eradication program: rapid eradication, based on the effective use of good information. This is likely to require a relatively high, shorter term investment, but will be able to maintain greater motivation and higher efficiency.

DISEASE ERADICATION THEORY

This discussion presents a simplified consideration of the theoretical basis for disease eradication, building on the principle already introduced (18): to persist, viruses need access to new hosts, which may be introduced to a population by movement or birth. Preventing access can be achieved through two main methods: vaccination or movement management.

Vaccination for Disease Eradication

Consider a hypothetical virus that is transmitted only by direct contact; for which there is an effective vaccine that provides life-long immunity in 100% of vaccinated animals; there is no carrier state or wildlife reservoirs; and infected animals either die or recover after which they are rapidly free from virus (within 4 weeks) and have persistent immunity. The areas in which PPRV differs from this hypothetical virus will be discussed below.

In a closed population in which infected animals are present, vaccination which generates immunity of all animals will result in rapid elimination of the virus. Infected animals die or recover, and no new animals are able to be infected. A single round of vaccination with 100% coverage should be adequate (14, 15). Why then is it so hard to eradicate disease? The answer lies in the realities of vaccination programs and population dynamics.

- **Vaccination coverage**: it is often very difficult to use vaccination to protect 100% of animals in an area. This may be related to communication with owners or herders, difficult access, lack of owner compliance, inadequate vaccine, inadequate time or human resources, or corruption (on-selling or discarding vaccine and falsely reporting that vaccination has been completed).
- **Rate of vaccination**: in large populations, all animals cannot be vaccinated simultaneously. By the end of a vaccination round, immunity in part of the population may be falling (see section Timing Considerations) or non-immune animals may be introduced.
- **Immune response**: vaccinated animals don't necessarily develop immunity to the field virus. This may be due to inappropriate choice of vaccine (unlikely to be a problem for PPR), poor vaccine quality control and potency, suboptimal handling of the vaccine during storage and transport resulting in decreased efficacy, poor vaccination technique resulting in failure to deliver an adequate dose in the right location, or poor immune response within the animal due, for example, to stress, poor nutrition, concurrent disease, or interference with maternal immunity in the offspring of seropositive animals,.
- **Reproduction**: populations are not closed and turnover is rapid. Depending on seasonal lambing/kidding patterns, a high proportion of the population may be replaced with non-immune animals in a short period.
- **Animal movements**: even if movements from an infected area are blocked, movements from free areas may result in the introduction of non-immune animals, diluting the proportion of protected animals.

This means that achieving a population that is 100% immune for long enough for the disease to be eradicated is difficult. In the past, control and eradication programs, for both rinderpest and PPR (15) have acknowledged these constraints and overcome them with longer periods of protection. Instead, the guerrilla strategy seeks to strategically address these constraints to achieve very high levels of protection for a short period.

Herd Immunity

The constraints identified above are normally partly addressed by the concept of herd immunity. The effective reproductive rate (R) is a measure of the average number of new cases of disease generated by an infected animal (19) in a partially immune population. If R is <1, the disease will, over time, die out. Herd immunity is achieved when the proportion of vaccinated animals is high enough to decrease R to below one.

Many disease control programs focus on estimating the vaccination coverage required to maintain R below one [for example, the Global Strategy targets an immunity of between 70 and 80% (2)] and aim to maintain that level of coverage for a prolonged period. This is because the time required for the disease to be eradicated due to herd immunity is influenced by R and the population size.

If $R = 1$, the disease will maintain itself at a steady state. As R decreases due to higher vaccination rates, the time to elimination of the disease becomes shorter. At the limit, if $R = 0$ (100% effective vaccination), the disease will be eliminated in the space of a single infectious period (plus the duration of survival of the agent in the environment). In very small populations, elimination is faster due to integer mathematics effects. With a population of 10, when prevalence falls below 10% (a single animal) the disease must be eradicated. With a population of 10,000, the prevalence needs to be below 0.01% for eradication.

Population Size

The rate at which a population is vaccinated also has an impact on the ability to eradicate disease. If the entire population is vaccinated simultaneously, eradication will be faster. If there is progressive vaccination, population turnover (loss of immune animals through slaughter) and the introduction of new susceptible animals (through birth or introduction) will decrease herd immunity in part of the population, leading to heterogenous R. This is illustrated in a hypothetical population in **Figure 2**. A

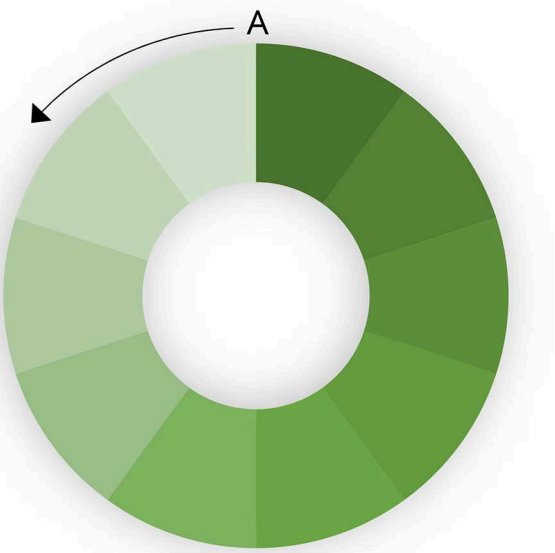

FIGURE 2 | Effect of progressive vaccination in a large population. The color intensity indicates population immunity. Vaccination starts at point A and progresses anticlockwise.

circular population is used to clarify the effect. If vaccination is started at point A and progresses in an anticlockwise direction, population turnover will mean that the vaccination coverage (indicated by depth of shading) in the first vaccinated part of the population is relatively low by the time the last part of the population is vaccinated. This means that there is a risk that infected shedding animals in the last (unvaccinated) part of the population are in contact with the first vaccinated part of the population in which immunity is decreasing. If the rate of vaccination is too slow, and the population turnover too high, it may still be possible to maintain the virus in the population despite ongoing high-coverage vaccination at too slow a rate.

The solution to these problems is to keep the population small. By dividing the population into small population units (for example a large flock, a village or a subdistrict), it is possible to achieve near simultaneous vaccination of the whole population unit. It is also much more feasible to achieve near 100% coverage of the population, by applying available resources more intensively to a smaller population. The conclusion is that viral elimination through vaccination can be achieved more reliably and more quickly if the population is divided into relatively small subunits. The size of the population unit should be small enough to achieve close to 100% coverage, rapidly enough to maintain near complete protection before non-immune animals enter the population (for example, through lambing or kidding).

Timing Considerations

A population unit should be considered free from PPRV when all animals have been vaccinated (in such a way as to provide the greatest chance for a very high immune coverage), and enough time has passed such that protective antibodies have developed and any animal infected at the time of the vaccination has either died or recovered, and is no longer at risk of shedding virus.

Protective antibodies develop within 1 week of vaccination (20). There is scant information on the period of viral shedding after infection. Parida et al. (21) found that 14 days after infection (the last sampling date), 6 out of 10 nasal swabs from infected goats were PCR positive, while only 1 and 0 were positive from saliva and eye swabs, respectively. Lui et al. (22) found PCR positive ocular secretions in one of 12 goats, 26 days after infection (in a study that ran for 40 days). In both studies, the presence of viral RNA does not necessarily mean that viable virus is being shed. In the absence of transmission studies, and on the basis of the available evidence, it would seem prudent to assume that virus may be shed for up to 4 weeks after infection.

Based on this assessment, population units in which 100% of animals are effectively vaccinated may be considered free from infection 5 weeks later, assuming a high proportion of animals develop immunity following vaccination.

The timing of vaccination also plays a role. Vaccination should be avoided shortly before lambing/kidding, to avoid a rapid decrease in the proportion of immune animals in the population unit as a result of dilution of the immune adults by a large influx of non-immune lambs or kids. It should be timed to avoid times of peak demand for animal movement (see section Theory of Animal Movement Management) in order to allow the population to be closed during the period of virus eradication. Periods of migration or when flocks are inaccessible due to remote grazing areas should be avoided to overcome problems of access and to facilitate high vaccination rates. It should also be undertaken at a time when animals are at their healthiest (e.g., have access to good nutrition) to maximize the chance of developing protective immunity in response to vaccination. It is likely that some of these conditions may be contradictory, and compromises need to be made, or that pauses in the vaccination program will be required at certain times of year. A detailed understanding of populations, reproductive patterns, husbandry and movements are required to plan the optimal vaccination strategy in specific environments. Modeling approaches have been used to address this challenge (23, 24).

Theory of Animal Movement Management

As with vaccination, it is theoretically possible that movement management alone might be used to eradicate the virus. Assume that the population is divided into small closed units such that all animals are in frequent contact with all others within the unit, and that all movement between units is prevented, so there can be no introduction of infection into uninfected units. Under this scenario, the virus would die out in all infected units, because all susceptible animals in infected units rapidly acquire natural immunity (or die). None of the uninfected units would become infected. Based on this approach, the entire population could become free from infection, within the time it takes for susceptible animals within infected units to become infected and immune (or die).

This theoretical approach is not feasible: it is difficult or impossible to impose a complete movement restriction on

TABLE 1 | Rules for movements between units of different status.

Origin	Destination		
	I	C	F
Infected	✓	✗	✗
Control	✓	✗	✗
Free	✓	✓[a]	✓

✗: *movement not allowed;* ✓*: movement allowed.*
[a]*Susceptible animals moving from free to control population units risk diluting the population immunity. Only animals known to be immune should be allowed to enter active control units.*

the entire population for long enough for the disease to die out; and there are other means of spread of the virus, such as fomites.

The reason that movement restrictions are difficult to implement and to maintain is because livestock production is based on the need for movement. Markets (demand) are generally located in different areas to production (supply); in many production systems, access to feed requires frequent, constant or seasonal movements; and in some systems, breeding is achieved by the movement of males from flock to flock.

When there is an economic imperative to move animals, imposing movement restrictions results in economic hardship for producers, as well as distorting the market, providing a strong financial incentive to circumvent restrictions. If movement from a production area to a market area is prohibited, the price differential between the two will increase, providing a strong motivation for illegal activity, especially when a family's main source of income may be at risk. Similarly, if movement for grazing is prohibited, the animals' survival may depend on illegal movement.

The challenge is therefore to understand how to prevent the spread of disease through animal movements, while avoiding distorting markets. The solution to this problem is to reduce movement restrictions to the very minimum required to prevent the spread of disease from infected to known uninfected population units, while allowing enough safe movements to avoid distorting the market.

Optimizing the Eradication Sequence

The role of animal movement networks and population sizes in disease control and extinction has been extensively studied (25–28) and this work provides a basis for detailed analysis and modeling to optimize the size of populations for disease control and the sequence of eradication. This discussion provides a simple overview of the approach, to illustrate its value in PPR eradication. Rather than impose a complete movement standstill, it is important to recognize that a large proportion of routine movements pose no significant threat to successful eradication. Population units may be classified as infected (I), and not yet part of an active eradication program, known to be free (F), either historically or due to successful eradication, or the subject of active control or eradication (C) efforts.

Table 1 shows typical rules for animal movements between units of different statuses.

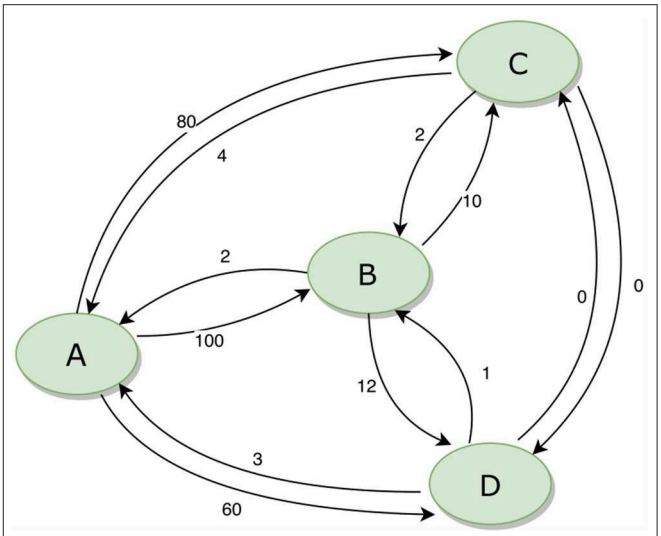

FIGURE 3 | Example of a simple animal movement network diagram for four population units. The numbers beside each arrow indicate the number of animals moving between the population units.

Different population units have different movement patterns. In a breeding area, the bulk of movements are outgoing (with strong seasonal variation), while in a consumption area (with an abattoir, for example), the bulk of movements are incoming. A fattening area may have roughly equal incoming and outgoing movements, but during different seasons. A market area may have balanced inward and outward movements on a daily basis.

The movement of animals between units can be expressed as a network. **Figure 3** provides an example of a simple network of four population units, with movements in and out (for any reason, including trade, transhumance, etc.) indicated. During disease eradication, implementation of movement restrictions will block movements between some units depending on their different statuses. The sequence in which disease eradication is carried out in the population units can have a major impact on the total number of movements that need to be restricted, as shown in **Table 2**.

If eradication starts in a breeding area (A), when most movements are outgoing, there will be minimal disruption to the market. In contrast, if eradication starts in a consumption area (B or C), many movements will need to be blocked, risking major disruption and making it much more difficult to successfully implement effective movement management. The best option (ABCD) results in only 5% of the blocked movements of the worst option (BCDA).

Real World Examples

With a small number of nodes such as those used in this example, the optimal permutation can be calculated manually. For a large number of nodes, and for seasonally varying movement patterns, the challenge is much more significant. Two examples were used to illustrate this using real world movement data: goat movements on Java Island in Indonesia, and cattle and deer movements in New Zealand. Neither area is infected with PPR

TABLE 2 | Total number of blocked movements required during an eradication program, based on all possible sequences of eradication in four population units (A, B, C, and D) as illustrated in **Figure 3**.

Sequence	Movements	Sequence	Movements	Sequence	Movements	Sequence	Movements
ABCD	35	DABC	176	DBAC	418	DBCA	728
ABDC	37	DACB	202	DCAB	422	DCBA	736
ACBD	48	CABD	205	BDAC	438	BDCA	748
ADBC	56	BACD	227	CDAB	440	CDBA	754
ACDB	79	BADC	229	CBAD	469	CBDA	762
ADCB	82	CADB	236	BCAD	474	BCDA	767

but are used because of the availability of high quality, contrasting movement data.

Goat Movements in Java, Indonesia (2016)

In Indonesia, the iSIKHNAS animal health and production information system provides a practical source of detailed individual animal movements which can be used to simulate and evaluate alternative sequences of control activities (29). Data on all recorded individual goat movements on the island of Java in 2016 was extracted from the iSIKHNAS database, as an origin-destination matrix. For the purposes of this example, the district (kabupaten) is used as the population unit, although smaller units would be likely to be used in practice. Of the 119 districts in Java, 60 recorded intra-island goat movements in or out during 2016, with a total of 54,995 animals moved.

An exhaustive analysis of all combinations of the 60 districts would require analysis of 8.3×10^{81} combinations. Dynamic programming techniques may provide a feasible approach to finding the optimal combination (30). However, for the purposes of this analysis, a simple analytical tool was developed using R (31), to calculate the total number of blocked movements based on the Java goat movement data, for a given sequence of eradication over the 60 districts. A sample of eradication sequences was generated by simulating 100,000 random sequences, and calculating total blocked movements for each. The distribution of the results is shown in **Figure 4**.

While this approach is not able to determine the single optimal sequence of eradication to minimize disruption, selecting the sequence with the minimum blocked movements will provide a "good" option. In the simulation illustrated above, the best sequence resulted in 17,279 blocked movements over the 60 eradication time periods (**Figure 5**), while the worst resulted in 1,896,292 blocked movements. While better and worse sequences are likely to exist, the use of the best simulated sequence would result in 0.9% of blocked movements relative to the worst. This is an example of a low-density matrix, where only 4.8% of cells had a movement recorded. More importantly, the Java goat matrix is very asymmetrical—only 0.19% of district pairs had reciprocal movements.

Cattle and deer movements in New Zealand (2018)

The same approach was used to a dataset consisting of all completed cattle and deer movements in New Zealand in 2018, consisting of movements between 73 cities and districts (32). In contrast to the Java data, 40.98% of movements were reciprocal. The distribution of the results for 100,000 random sequences are illustrated in **Figure 6**. In this case, the minimum number of blocked movements calculated was 40,392,916, which is 43% of the largest number observed.

The best sequence observed is illustrated in **Figure 7**.

These two examples demonstrate that, using a random sample, it is feasible to estimate a good eradication sequence that is close to the optimal, even when the number of units is large. It also shows that the movement structure has an influence on the benefits that can be gained from this approach. Where movements are largely asymmetrical, the benefits can be very large, but when most population units have both significant inward and outward units, the benefits are less marked. The scale may also play a role. What may well appear to be a source-sink dynamic at a larger scale, may not be at a smaller scale, and this should be taken into account when determining the appropriate unit size.

The optimal eradication sequence may need to take further factors into account, including seasonal variations in movement patterns, logistics and resourcing, natural geographic barriers, cultural factors etc. These may be able to be included as constraints in a dynamic programming optimization model.

Alternative Sequencing Approach

Detailed modeling and optimization depends on accurate animal movement data for every node. As discussed in section Surveillance, surveillance approaches exist that mean that it is feasible to capture this level of data in most target countries for PPR eradication. However, if such detailed movement data is not available, an alternative approach is available to optimize the sequence of eradication to minimize the impact of movement restrictions. Market price information systems exist in many countries and are feasible to establish where not already available (33). It is possible to use data on market prices to predict livestock movement patterns (34).

Figure 8 illustrates an example of a price surface plot for the average daily modal live goat market price for 2018 in and around Karnataka state, India (35). Markets were georeferenced using public sources and the price surface interpolated using an inverse distance weighted algorithm (36). Contour lines were generated at 500 rupee intervals (37). The peaks represent areas of high prices, and the troughs low prices.

In general, market forces dictate that animals are more likely to move from the lower to the higher areas. If eradication is commenced in the lowest areas (the areas where supply

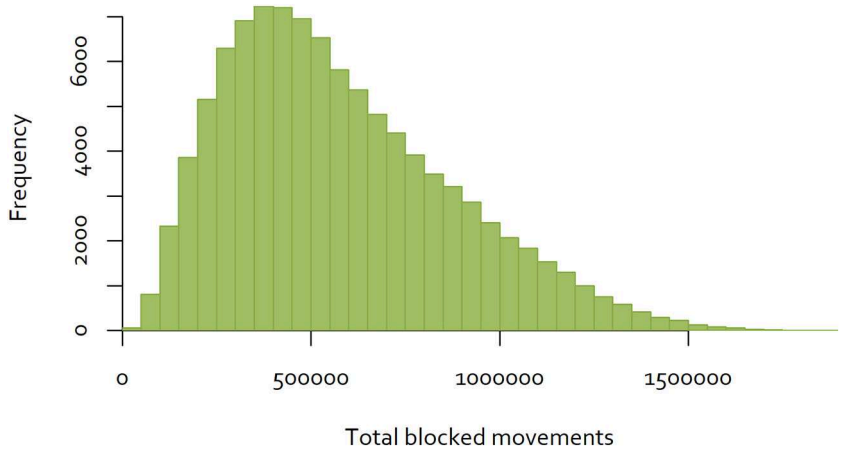

FIGURE 4 | Distribution of the number of blocked movements for goats on Java, over 100,000 random sequences of control.

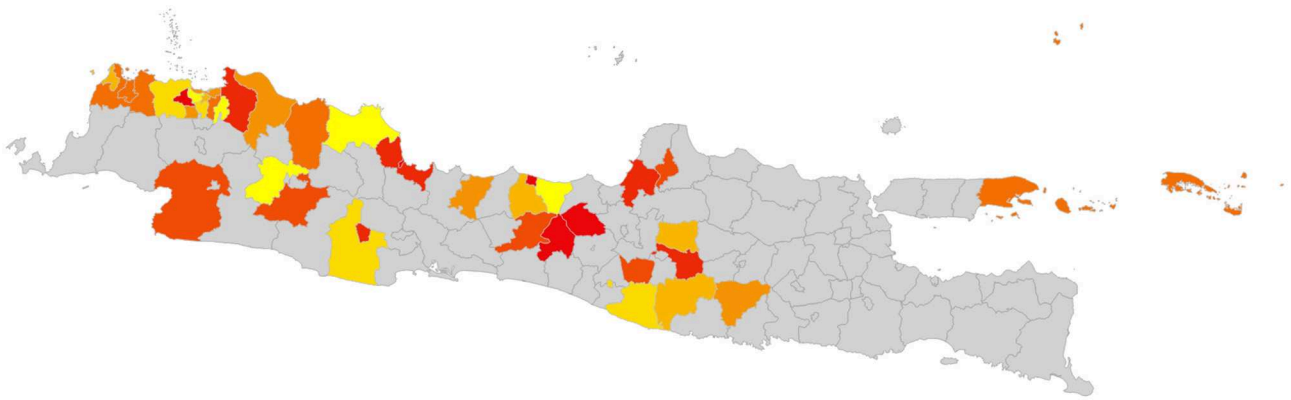

FIGURE 5 | Best identified sequence of control for goats on Java island, to minimize disruption of animal movements. Red indicates the first districts, yellow the last districts in the sequence.

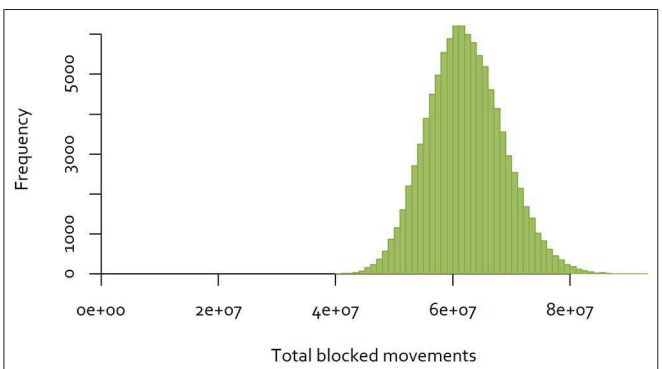

FIGURE 6 | Distribution of the number of blocked movements in New Zealand, over 100,000 random sequences of control.

is highest and demand is lowest), and progresses upwards (imagine flooding the valleys), it is likely that this approach will approximate a control sequence that has a relatively low impact on trade patterns.

Addressing Counter-Current Movements

Regardless of the approach taken, optimizing the sequence of disease eradication is unlikely to ever result in a situation where no movements need to be blocked. The risk of producers and traders circumventing movement restrictions may be further managed by the implementation of risk-based strategies to specifically address the small number of remaining movements that would otherwise be blocked. Detailed movement data will allow risk to be assessed in detail, taking multiple factors into account, including the age, sex, and purpose of the animal, production system, and nature of the movement and the nature of the destination (slaughter, market, breeding, fattening). Risk management strategies may include direct compensation, creation of short-term alternative markets (to artificially shift the price-driven movement gradient), or risk-based measures such as allowing movement after vaccination and/or quarantine, although any such strategies should be carefully examined to ensure that it does not have counterproductive or unexpected effect on the movement network. In any case, ongoing detailed surveillance of movement patterns is needed to detect and respond to unexpected changes in a highly dynamic system.

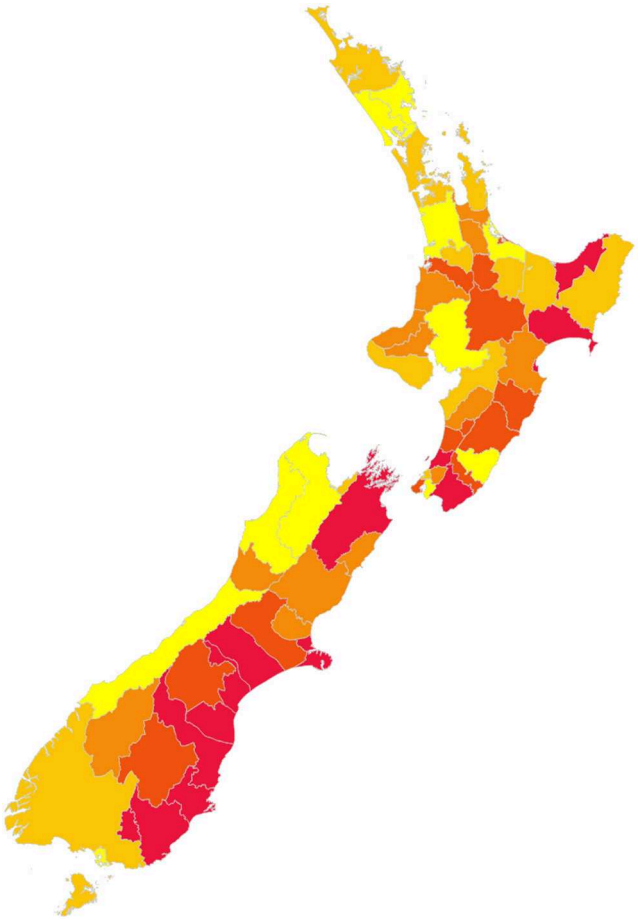

FIGURE 7 | Best identified sequence of control for New Zealand, to minimize disruption of animal movements. Red indicates the first districts, yellow the last districts in the sequence.

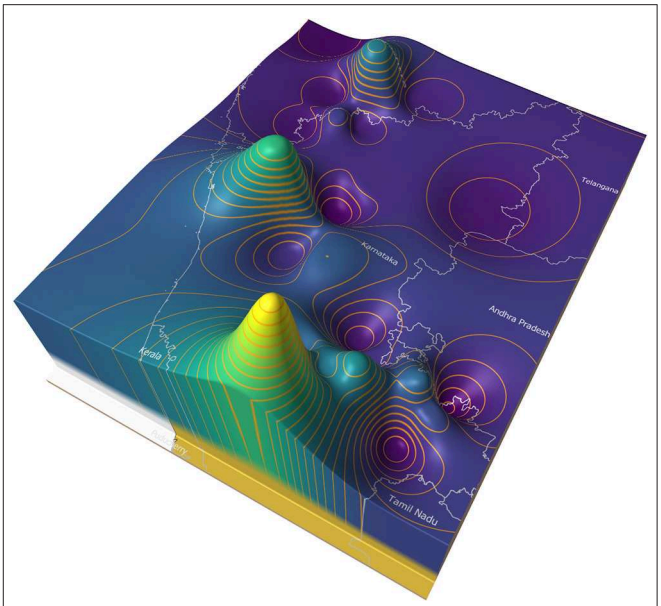

FIGURE 8 | Average goat price surface for Karnataka state in 2018 with 500 rupee contours.

Biosecurity

With PPR, the main method of transmission of the virus is through direct contact between animals. Fomite spread may occur, so precautions must be taken to address this risk. One of the advantages of an eradication strategy based on intensive short-term interventions in small population units, and with a major focus on stakeholder engagement is that there is increased opportunity to work with livestock owners and herders to develop practical and effective biosecurity measures.

Managing the Risk of Reintroduction of Infection

The strategy of rapid small-area eradication, moving quickly to other population units has the potential to eliminate PPRV after only a single vaccination round. However, after eradication is successful, the level of immunity in the population will rapidly decrease. Immunity in vaccinated animals is likely to be effectively life-long, however the rapid population turnover in sheep and goat populations means that the proportion of vaccinated animals may fall by as much as 25% per year, or even faster if susceptible animals are introduced into the population.

The movement restrictions discussed in sections Theory of Animal Movement Management and Biosecurity are intended to prevent reintroduction of infection into free populations. Naturally, in any eradication program, measures must be taken to manage these risks, but it is very unlikely that such efforts will be 100% effective.

There are two main options to deal with this residual risk of reintroduction of disease into free areas. The first (the traditional trench warfare approach) is to continue to vaccinate the free population, so that if virus is introduced, it will not spread. The problems with this approach are that it is expensive; absorbs a lot of resources that would be better spent eradicating the disease from known infected areas; must be carried on for a prolonged period; is unlikely to consistently achieve very high levels of coverage, so may allow low levels of virus circulation; and masks clinical signs making rapid detection of outbreaks much more difficult (depending on serological surveys and the use of DIVA vaccines, or antigen detection tests).

The second alternative (guerrilla warfare) is to welcome the loss of vaccine induced immunity. A non-immune population risks becoming infected and allowing disease to spread rapidly. However, it also means that, if introduced, the disease is much more likely to show easily detectable clinical signs. Clinical surveillance for early detection of new outbreaks in a non-immune population is cheaper, faster and more sensitive than using periodic surveys in a vaccinated population. However, there are two prerequisites for this approach to be successful: it requires an effective farmer-based early detection surveillance system (with near-census participation and rapid communication of suspected outbreaks—see section

Surveillance); and an effective rapid response capacity for investigating and eradicating outbreaks (be it by quarantine, vaccination or stamping out). The challenge of implementing these two prerequisites should not be underestimated. However, the task is feasible, as both have previously been successfully implemented in low- and middle-income countries. Rapid response capacity is largely a resource allocation decision: do we invest resources in trench warfare, with long term vaccination of a large part of the population, or do we use those same resources for rapid response to suspected outbreaks?

Surveillance

The proposed approach depends on timely access to complete and high quality information: an understanding of the current disease distribution, detailed information on animal movement patterns, availability of resources including personnel, transport, vaccine, market prices, and so on. The various programs to eradicate rinderpest developed surveillance and information management systems to support the effort, but these have often proven to be unsustainable (38).

The key characteristics of an effective surveillance system to support global PPR eradication (39–42) include:

- Real time data capture, with automated analysis and reporting to all relevant stakeholders
- Census-level information with complete population coverage
- High quality, reliable, clean data
- Fully disaggregated data capture
- Integrated across many data types (disease, vaccination, movement, prices etc.)
- Affordable
- Sustainable.

During Rinderpest eradication, the development of participatory epidemiology techniques (17) successfully addressed a number of these criteria. Advances in information and communication technology, cloud computing, as well as communication networks in low- and middle-income countries have all meant that solutions are now available to address the data management and communication challenges. However, technology is not able to address issues of sustainability and achieving complete population coverage. Hutchison et al. (4) describe a user-focused surveillance philosophy, applied successfully in Indonesia (29), which is based on providing an *information service* to field users. The aim is to provide immediate significant individual benefit to those that generate the data, so that they participate in the surveillance system out of self-interest, rather than compulsion. This approach has the potential to generate detailed, high quality census-level data in real time, sustainably and affordably, meeting all the requirements of PPR eradication. One key element of the approach is that it should not be focused on a specific disease. Instead, it should meet the full range of stakeholders' needs. In this way, such as system can support PPR eradication in the short term, but remain as a comprehensive and effective animal health information system long after PPR has been successfully eliminated (see section Sustainability and Multiple Utility). Such surveillance approaches, especially when coupled with rapid diagnostics, may contribute to the control of diseases such as capripox, contagious caprine pleuropneumonia and foot and mouth disease, as well as providing syndromic data to support early detection of emerging diseases.

International Collaboration

International collaboration is necessary for successful global eradication (9). Animal movement pathways in areas affected by PPR regularly cross international borders. A rapid, effective and affordable eradication strategy, such as that proposed in this paper, depends on a closely coordinated sequence of eradication, surveillance and movement control to achieve a single global program. If animal movement pathways extend between countries, the eradication strategy must as well. Collaboration in disease eradication should include coordination of activities, which requires sharing of information.

Experience from rinderpest eradication and other disease control programs has shown that international coordination is difficult to achieve, but is possible, and is a prerequisite for successful eradication (9, 43).

Sustainability and Multiple Utility

Sustainability is an important characteristic of disease control programs, from two perspectives. Firstly, the program has to be sustainable enough to achieve its primary goal of eradication. Lack of sustainable funding, field operational or stakeholder support can result in prematurely stopping the program, potentially eroding progress made to that point (as happened in 1979 with rinderpest eradication).

Secondly, budget decision-makers (whether national or international) rightly perceive the funding required for global eradication of PPR to be a major investment for a single-disease outcome. During rinderpest eradication, there was a great deal of rhetoric about capacity development in areas such as laboratories, epidemiological skills, surveillance and information systems, and coordination. While there have been a number of long-lasting benefits in participating countries, all too often many of these systems and capabilities, developed specifically to combat rinderpest, have proven to be unsustainable. While the prime objective was eventually achieved, many of the secondary benefits promised to donors and decision-makers have vanished or are seriously deteriorated.

Figure 9 provides an example of this lack of sustainability, as well as clues on overcoming it. The figure illustrates the proportion of mandatory monthly field office reports received at the national veterinary office in Cameroon from 2005 to 2009 (38).

Under PACE, field officers received payment for submission of reports. When these payments stopped, the previous reporting rate of almost 90% immediately dropped to zero. The psychology behind this is simple. Payment for information gives information providers a clear message that there is no personal benefit in generating the information beyond receiving payment. More importantly, when a new program was started for highly pathogenic avian influenza in 2008, again based on payment for information, stakeholders' trust had already been eroded, and it was no longer possible to achieve high reporting rates.

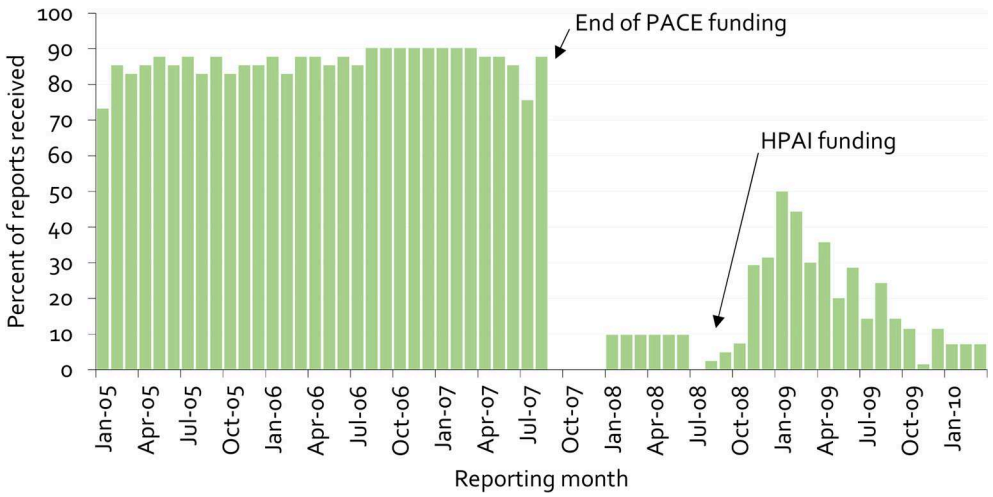

FIGURE 9 | Percentage of monthly disease surveillance field activity reports for Cameroon submitted to the national authorities from 2005 to 2009 (38).

Indonesia's iSIKHNAS (4, 29) provides a counter example. Built on the a user-focused philosophy, field officers and farmers are not paid for submitting data. Instead, the system is designed to meet their daily needs for information and to make their work easier. **Figure 10** presents real-time reports received by the system for three modules (treatment reports, livestock movement, and suspect priority disease notifications). There is no regulatory requirement to submit reports on animal treatments—field officers use this system because they want to, not because they have to. Yet between 50 and 90% of clinical cases are accompanied by treatment data (which may reflect the proportion of cases that require treatment, implying a near 100% reporting rate). Similarly, only 71,457 of the 190,536 movement reports (37.5%) are required by regulation (ruminants and groups of over 100 poultry). The rest are being voluntarily registered by owners and veterinary staff because of perceived benefits.

Donors and budget holders are likely to be hesitant to fund a large program that has no residual benefits for participating countries after PPR is eradicated, and they are also becoming less likely to accept claims of sustainability at face value. To gain their support, it is necessary to demonstrate value for money, both in the short term (PPR eradication) and the long term (sustainable improvement of veterinary service capacity to deal with other important disease problems).

Some of the key lessons regarding sustainability from Indonesia's iSIKHNAS include:

- **User-focused design**: the system is first and foremost designed to meet the needs of field users, not central decision-makers.
- **Capacity to manage any disease**: the system does not focus on a single disease, and can capture information on any disease of relevance to farmers and field officers.
- **Do not pay for information**: Payment for information undermines user perceptions of the value of the information, erodes data quality, and threatens sustainability.
- **Integrated information management**: integration of multiple data types (disease, population, movement, vaccination, disease control activities etc.) increases the value of the data and the power of analysis.
- **Capacity to rapidly evolve**: Disease evolves rapidly, as do stakeholders' needs and priorities. The information system needs to evolve rapidly to continue to meet their needs.

Some of the challenges faced in implementing the approach in Indonesia include:

- **Human resources**: developing and maintaining a dedicated management team.
- **Maintaining the principles**: flexibility means that new modules are being added regularly. There is a risk that stakeholders may stray from the core principle of focusing on user needs, and revert to top-down approaches, undermining sustainability.
- **Meeting user demands**: user expectations for immediate access to customized analyses are high, placing a strain on the management team to constantly deliver.
- **Heterogenous user groups**: it is difficult to achieve 100% participation due to variability in stakeholders perceptions of benefits, the system managers' capacity to understand these perceptions, and their ability to deliver the breadth of customized outputs to meet their needs.

PHASED IMPLEMENTATION

The previous section provided the theoretical background for the proposed PRR eradication strategy. These components need to be combined in a coordinated way to achieve the objective of rapid, affordable eradication.

A four-phase approach is proposed. This is broadly compatible with the Global Strategy (2), a step wise approach that stresses the importance of progressive and epidemiologically sound activities. This discussion intentionally omits a lot of

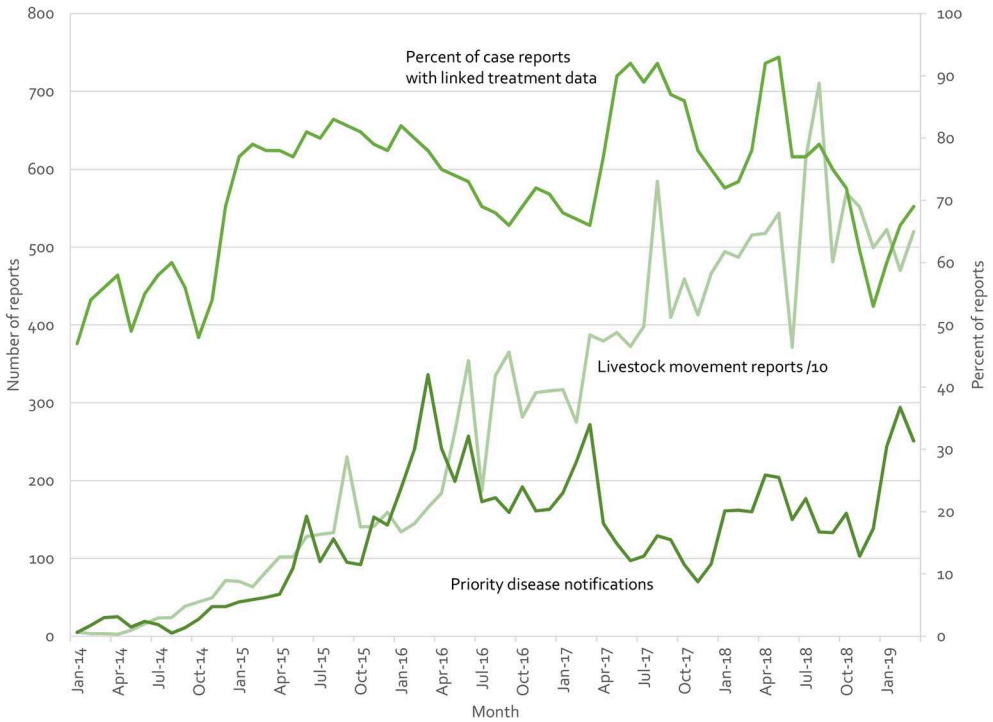

FIGURE 10 | Summary of iSIKHNAS reporting from January 2014 to March 2019 for 3 of the 30 modules: Priority disease reports (number of reports, left axis), livestock movement reports (number of reports divided by 10, left axis), and treatment reports (proportion of routine disease reports with linked treatment data, percentage, right axis).

the important detail contained in that document. The Global Strategy is built around the concept of progressive development of national capacity. Under the guerrilla approach, there should be less emphasis on national boundaries, and more emphasis on a coordinated single program. The proposed phases are:

1. Building the required foundations—funding, coordination, engagement and information
2. Detailed planning
3. Implementing eradication activities
4. Demonstrating successful eradication.

Phase 1: Foundations

It is proposed that a large part of the time spent on eradication should be spent on laying strong foundations for the program, before any specific eradication activity starts. During this phase, existing disease control activities may be continued, but their purpose is simply to prevent further spread and limit losses, not to start eradication. As with the global program, it is anticipated that this phase may last several years. It will required major investment, particularly to develop stakeholder engagement, surveillance and information systems.

Funding

There is no point in embarking on global eradication if there are not enough resources to complete the task. As was seen with rinderpest eradication, stopping too soon, and withdrawing funding can mean a delay of years, a loss of millions of animals, and dramatically increase the total cost of the program. Many (but not all) currently affected countries are unlikely to have the resources to fund eradication from their own national budgets. Eradication of PPR should be considered a global public good, so there is a strong justification for multilateral donors to fund a large proportion of the program. Jones et al. (3) have provide estimates of the benefits and costs of PPR eradication, and the process of securing these funds has already started. The guerrilla approach may make the program less expensive, but securing funds will take time and should be among the first priorities.

Coordination

Close international coordination also requires some time to establish. Planning the most effective strategy for eradication requires very good surveillance information from all participating countries. Coordination is required from the outset so that all countries involved are able to improve their surveillance and generate the information required for effective planning.

Engagement

A key feature of the proposed guerrilla strategy is the need for close and ongoing farmer and broader community engagement. Detailed surveillance information, achieving very high levels of vaccination coverage, effective movement management, and highly sensitive early detection and response to new outbreaks in free areas, all depend on strong stakeholder participation in the eradication program. Locally appropriate approaches to building this engagement are required, but adherence to

a simple core principle has been found to be effective (4): ensuring that participation provides significantly more direct, immediate, personal benefits than any costs or risks associated with the program.

Information

Successful implementation of this strategy depends on detailed, high quality information. Distinguishing features include: dividing the population into small groups; aiming for a short period of high vaccination coverage; highly strategic movement management; and highly sensitive early detection and response—but none of these are possible without detailed information.

The information requirements for effective implementation are extremely demanding and include:

- A complete knowledge of the population including, animal numbers, husbandry, spatial distribution, and reproductive, marketing and slaughter patterns
- An initial understanding of the distribution of PPR in the population, to define population units that are already free from disease
- An understanding of available resources for vaccination, surveillance, movement management and emergency response
- Information on the immune status of population units and individuals
- Detailed flock-level information on animal movements, and an understanding of the sociological and economic drivers for movements
- Accurate tracking of control activities including vaccination, biosecurity, checkpoints and outbreak response
- Extremely sensitive early detection surveillance to identify and respond to outbreaks in free areas.

Capturing this data requires census-level participation of farmers, field disease control personnel, extension officers and the broader farmer support networks. It requires fit-for-purpose communication tools and powerful integrated data management capacity. None of this is easy, but the Indonesian iSIKHNAS system (4, 29) provides a model of how it can be achieved. User-focused surveillance and production information systems have the benefit that they address the broader needs and interests of farmers and other field stakeholders, which go well beyond the requirements of the eradication of a single disease. As a result, a system that is developed to support PPR eradication may be used to sustainably support the control of a full range of other diseases, now and in the future.

Implementation of high-coverage, user-focused systems is complex, requiring a blend of sociological, epidemiological and information and communication technology skills. However, with adequate resources, based on experience of implementation in Indonesia, it may be able to be achieved within about 3 years.

In addition to information provided by surveillance and production information systems, there may be specific research questions that need to be addressed. One obvious example is whether the guerrilla strategy proposed in this paper can actually work. Pilot studies may be used to answer this and other questions (2).

Phase 2: Planning

This phase involves using the information gathered to develop a detailed comprehensive and integrated plan for eradication. It involves [in addition to elements already identified in the Global Strategy (2)] delimiting the distribution of the disease and identifying non-infected populations; defining suitable population units; analyzing movements to minimize trade disruption during eradication; planning the logistics of disease eradication including vaccination, movement management, and rapid response teams.

Phase 3: Implementation

Active eradication efforts should only start when all the requirements are in place, including funding, coordination, detailed information supporting detailed plans, trained and resourced field teams, and strong stakeholder support.

Eradication involves rapidly moving through all infected population units in the optimal sequence to minimize trade disruption. In each unit, available resources are concentrated for a single vaccination round, to achieve a very high, rapid coverage, and maintain the coverage for approximate 1 month. Livestock owner participation will have already been strengthened during the foundational phase, but will be further enhanced prior to the initiation of vaccination. During this control phase, the only inward movements permitted are of vaccinated animals from free areas. Outward movements to infected areas are possible.

After the control period, the population unit is considered to be free for the purposes of movement management: incoming movements from free units are permitted, as are outgoing movements to infected units. Farmer-based intensive clinical surveillance is used to support early detection of any new incursions, and rapid response teams are available to investigate, isolate and eradicate any new outbreaks in free units. The population units used for control can be progressively aggregated into free and control zones, as defined in the Global Strategy.

High levels of vaccination coverage and good clinical surveillance are supported by engaged farmers, and well trained and resourced vaccination and emergency response teams. If farmer support is inadequate to ensure high coverage or good surveillance, then the preparatory work on stakeholder engagement has not been adequate, and new, more effective approaches need to be adopted.

Phase 4: Demonstration of Global Freedom

The last case of smallpox occurred in 1977 in Somalia and it was declared eradicated 3 years later in 1980. The last confirmed case of rinderpest occurred in 2001 (also in Somalia), and global eradication was declared in 2011, after a major surveillance effort. Confirming global eradication is a critical step and we can't afford to get it wrong. For PPR, the eradication strategy depends on the presence of highly sensitive, sustainable, multi-disease early detection systems. Martin et al. (44–46) and Cameron (47) show how confidence in freedom from infection can be quantified and accumulate with increasing evidence, a method that was also

applied to demonstrate global freedom from rinderpest (48). It is anticipated that using such systems, the declaration of freedom from PPR could be made much sooner than the 10 years it took to build global confidence of freedom from rinderpest.

DISCUSSION

The trench warfare approach to rinderpest eradication used vaccination as its main weapon, seeking to maintain herd immunity in large populations for extended periods. Lengthy campaigns resulted in a gradual erosion of support by funders, field staff and farmers. The result was a 50 year war, that was only finally won when a more strategic approach was adopted.

When adopting guerrilla tactics, the main weapon is information and the application of epidemiological understanding of PPR. The key strategy to accessing information is the use of sociological approaches to working with field stakeholders, to build strong and sustainable engagement, and to convincingly answer their question: "What's in it for me?" Vaccination, while still an essential tool, should play a relatively much smaller role in eradication, while intelligent risk-based movement management, highly sensitivity early detection and rapid and effective outbreak response are all critical components.

Challenges and Risks

This paper has presented a hypothesis—that the guerilla approach is able to support global eradication of PPR more quickly and less expensively than the trench warfare approach. The characteristics and advantages of the guerilla approach have already been discussed. However, challenges and risks warrant consideration.

The success of the approach depends on a range of assumptions. Related to stakeholder engagement, surveillance and information, these assumptions include that:

- It is possible to use sociological and other related approaches to understand field stakeholders' needs and motivations, and to develop systems that provide meaningful immediate direct benefit, adequate to ensure sustainable, widespread support of disease eradication activities.
- Using this approach, it is possible to achieve very high coverage surveillance.
- Communication and information management technologies are suitable and available to support real-time high-volume disaggregated data capture and analysis.

Related to vaccination, they include:

- It is possible to achieve very high vaccination coverage in small population units.
- High vaccination coverage will result in high levels of protection (implying that vaccine quality, transport, vaccination technique and the ability of animals to mount an immune response are all good).
- Achieving high levels of protection for a short period (for example, 5 weeks) in a small closed population will be effective at eliminating the virus.

Related to movement management, they include:

- It is possible to largely prevent the spread of PPR from infected and/or control units to free units through epidemiologically informed management of animal movements.
- A strategic approach to movement management that minimizes disruption to trade is possible.
- It is feasible (and preferable) to implement rapidly changing, short duration movement restrictions.

Related to early detection and response, the assumptions include:

- Population turnover and movement in free areas will result in a rapid drop in the proportion of protected animals (to levels below that required for herd immunity) within a year.
- New outbreaks of PPR in free areas will exhibit readily identifiable clinical signs.
- It is possible to implement a highly sensitive farmer-based early warning system, including the communication tools required for rapid notification.
- The veterinary services have the capacity to mount a rapid response to notifications for diagnosis and, where required, local eradication (either by vaccination and movement management, or stamping out).

A number of these assumptions have been demonstrated to be invalid at various stages of rinderpest eradication (11). On the other hand, the world learnt many lessons from rinderpest, and advances in the integration of sociological techniques into disease control, as well as information and communication technologies mean that some of the challenges may now be able to be successfully addressed.

Wider Application

The strategy presented in this paper focuses on PPR eradication. It is worth considering whether the same approach may be applicable to local, national or global eradication of other diseases.

The characteristics of PPR (fragile virus with short survival outside the host, life-long immunity after a single vaccination, main method of transmission by direct contact, lack of significant reservoirs or carrier state) mean that the guerrilla approach may be well suited to this virus. Other diseases are clearly not suitable. For example, this approach would not be relevant to African Swine Fever (ASF), with no vaccine, lengthy survival outside the host, the existence of intermediate or reservoir hosts (ticks) and the potential for carrier states. Without vaccination, strict biosecurity, movement management and stamping out are the main control options available. Nevertheless, information on disease distribution, early detection and risk pathways is still critically important.

Foot and mouth disease (FMD) represents an intermediate example—not as amenable to eradication as PPR but potentially easier than ASF. In this case, a vaccine exists, but it does not provide long-lasting immunity. The virus is more resistant and infects more species, as well as being able to be transmitted by fomites, animal products as well as through airborne spread (in specific conditions). Vaccination and movement management have long been the important tools for FMD control, and it is possible that the guerrilla approach may make a useful

TABLE 3 | Selection of key challenges facing global PPR eradication, and an indication of how different components of the guerrilla strategy (phases 1–3) may be able to address them (see footnotes for clarification of the challenges and components).

	Phase 1: Foundation							Phase 2: Planning			Phase 3: Implementation			
	Farmer engagement	User-focused surveillance[a]	Information system[b]	Information[c]	International coordination	Assured funding[d]	Laboratory and vaccine[e]	Strategic implementation[f]	Comms and engagement	Resources and logistics	Small units[g]	Rapid progression[h]	Farmer reporting[i]	Rapid response[j]
ACHIEVING VERY HIGH LEVELS OF PROTECTION														
Vaccination coverage														
Inadequate communication with owners	•	•		•					•	•	•			
Physical access to flocks	•			•	•			•	•	•	•			
Owner compliance	•	•	•						•		•	•		
Inadequate supply of vaccine				•	•	•		•		•	•			
Inadequate time/human resources														
Corruption within vaccination teams	•		•	•						•	•			
Vaccination rate														
Time required to vaccinate the population	•			•				•		•	•			
Immune response														
Choice of vaccine				•			•							
Poor quality control and potency				•			•							
Poor handling and cold chain										•	•	•		
Poor vaccination technique										•	•			
Poor immune response														
Stress, malnutrition, concurrent disease etc.[k]	•	•	•	•				•			•			
Maternal immunity	•	•	•	•				•			•			
Reproduction														
New lambs/kids diluting immune population		•	•	•				•			•	•		
Movement														
Movement from infected areas	•	•	•	•	•			•	•		•	•		
Movement from free areas diluting immunity	•	•	•	•	•			•	•		•	•		
MOVEMENT MANAGEMENT														
Understanding movement pathways	•	•	•	•	•									
Flock or animal identification	•		•		•				•	•				
Market distortion due to movement management	•			•				•			•	•		
Farmer non-compliance with movement restrictions	•			•				•	•		•	•		
Transhumant or migratory production systems	•			•				•	•		•	•		
Cross-border movement patterns	•			•	•			•	•		•	•		
Rapid changes in movement patterns	•	•	•	•	•			•	•		•	•		
EARLY WARNING SURVEILLANCE														
Low disease reporting rates	•	•	•						•				•	
Low farmer awareness	•	•							•				•	
Poor field communication	•		•						•				•	
Fear of negative consequences for reporting	•	•							•				•	

(Continued)

TABLE 3 | Continued

	Phase 1: Foundation							Phase 2: Planning			Phase 3: Implementation			
	Farmer engagement	**User-focused surveillance[a]**	**Information system[b]**	**Information[c]**	**International coordination**	**Assured Funding[d]**	**Laboratory and vaccine[e]**	**Strategic implementation[f]**	**Comms and engagement**	**Resources and logistics**	**Small units[g]**	**Rapid progression[h]**	**Farmer reporting[i]**	**Rapid response[j]**
Lack of veterinary field surveillance resources	•	•	•			•				•			•	•
RAPID OUTBREAK RESPONSE														
Delay in receiving field reports of suspect outbreaks	•	•	•						•				•	
Inadequate capacity for rapid field investigation						•				•				•
Inadequate laboratory diagnostic support							•							
SUSTAINABILITY														
Lack of sustainability of systems developed for PPR eradication	•	•	•						•					

[a] *User-focused surveillance: a surveillance systems designed around users' needs, capturing data on all diseases of significance to farmers, and designed to maximize direct user benefits while eliminating any costs or risks associated with participation.*

[b] *Information system: a real-time integrated health and production information system, with field mobile data capture, automated analysis and alerts, managing (at least) disease reports, animal/flock identification, vaccination, control activities, movement management, and emergency response.*

[c] *Information: detailed, real-time information on animal populations, animal movements, disease distribution, immune status, resources and capacity, vaccination and disease control activities.*

[d] *Funding: Coordinated, adequate and sustained funding through international donors and national budgets.*

[e] *Laboratory and vaccine: Adequate laboratory diagnostic and monitoring capacity and quality control, and access to high quality adequate vaccine supplies (these issues have been well-addressed in existing PPR eradication strategies).*

[f] *Strategic implementation: Technical analysis of the appropriately sized and delimited population units, the sequence and timing of eradication.*

[g] *Small units: Definition of small population units as the building blocks for eradication, where available resources can be concentrated to achieve very high coverage, high quality vaccination for disease elimination.*

[h] *Rapid progression: Rapidly moving in an optimal sequence through all infected population units eliminating the virus and managing movement.*

[i] *Farmer reporting: an effective, highly sensitive and timely farmer-based early warning reporting system, built on effective farmer engagement and the user-focused surveillance, to achieve rapid reporting of all suspect disease events.*

[j] *Rapid response: rapid response capacity within the veterinary services working in partnership with local communities, including mobile investigation and response teams, pen-side and laboratory diagnostic capacity, and appropriate local response strategies (vaccination, stamping out, quarantine etc. as required).*

[k] *Poor immune response: Of the various reasons for failure to achieve high flock immunity, stress, malnutrition, concurrent disease and similar problems are among the most difficult to address. Working with farmers to minimize these conditions, and optimizing timing may help.*

contribution with this disease. The shorter duration of immunity after vaccination is not a problem, if effective clinical surveillance is able to detect subsequent outbreaks. However, the approach would have to be adapted, with an even greater emphasis on biosecurity, including preventing spread via fomites and animal products.

Potential Contribution

Table 3 summarizes the way in which the various aspects of the guerrilla strategy may be able to address the key challenges of rapid, affordable, effective PPR eradication.

CONCLUSION

Global PRR eradication is a grand project, requiring vision and innovation. It is hoped that elements of the guerrilla hypothesis presented here may be tested, and ultimately contribute to finding an affordable way to rapidly achieve this goal.

DATA AVAILABILITY STATEMENT

Two of the datasets analyzed for this study (32, 35) are publicly available at the URLs provided in their citations. The Java goat movement dataset is not publicly available as it has been sourced from an internal government database. Requests for access to the data should be directed to Muhammad Muharam Hidayat, mm.hidayat.andi@gmail.com.

AUTHOR CONTRIBUTIONS

AC developed the hypothesis, designed and undertook the analysis, and drafted and revised this paper.

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PERSPECTIVE
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Progress to Control and Eradication of Peste des Petits Ruminants in the Southern African Development Community Region

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In southern Africa, small ruminants are an important source of nutrition and income to resource-poor small holder farmers. After spreading from West to Central and Eastern Africa, peste des petits ruminants (PPR) emerged in the United Republic of Tanzania in 2008 and has since been reported in Angola, the Democratic Republic of the Congo, and the Comoros. The disease can cause considerable morbidity and mortality in naïve sheep and goat populations and severely impact rural livelihoods, particularly those of women. Gaps in the knowledge of PPR epidemiology still exist, particularly around the role of small-ruminant movement and the role of the abundant wildlife in southern Africa. The capacity of veterinary services to undertake surveillance and control PPR is heterogeneous within the region, with vaccination being limited. The Pan African strategy for the control and eradication of PPR mirrors the Global Strategy and provides the framework for the Southern African Development Community (SADC) region to meet the 2030 goal of eradication. Five countries and one zone within Namibia are officially PPR free according to OIE Standards. Most countries have developed national strategies for the control and eradication of PPR. To strengthen national and regional PPR eradication programme goals, there is a need for a regional risk-based surveillance adapted to infected, high-risk and lower-risk countries that will enable targeted and efficient control, rapid response to incursions and prevention of spread as well as improved preparedness. Continued international and national support will be necessary including laboratory diagnostics and enhancing surveillance capacity to prevent further spread southwards on the continent.

Keywords: peste des petits ruminants, Southern African Development Community, surveillance, risk-based approaches, small ruminants

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INTRODUCTION

Peste des petits ruminants (PPR) is a World Organization for Animal Health (OIE) listed disease (1) caused by a morbillivirus resulting in variable respiratory and enteritis associated clinical disease in sheep and goat populations. PPR can also infect cattle, camels, domestic buffaloes, and wild ruminants (2). Given the high morbidity and mortality of PPR infection in immune-naïve small ruminants, the economic and food security impact of outbreaks is large for small-holder farmers. Women's livelihoods and resilience are particularly affected by PPR as women predominately rear small ruminants primarily for income generation and food security (3). The annual cost

of PPR-associated sheep and goat deaths for worldwide infected countries is estimated between 794 million and 2.7 billion US dollars (4). This contagious viral disease has steadily expanded its geographical distribution from West into Eastern Africa and more recently to the Southern African Development Community (SADC) countries. Given the porous nature of country borders and movement of animals in many African countries, the risk of spread is high for countries bordering PPR infected ones.

Following the successful eradication of rinderpest globally in 2011, the Food and Agriculture Organization of the United Nation (FAO) and the OIE developed the Global Strategy for the Control and Eradication (GSCE) of PPR (5) to enable this plague to be the next eradicated animal disease by 2030. The control and eventual eradication of PPR will contribute significantly to achieving the elimination of poverty [Sustainable Development Goals (SDG 1)] and the end of hunger and malnutrition (SDG2) as well as contributing to other SDGs (3, 5, 8, 11, 12 and 17) (6). The global strategy was endorsed by 45 African Countries and the African Union Inter-African Bureau for Animal Resources (AU-IBAR) voiced its support for the global programme (7). The SADC region had already developed its own PPR control strategy (8). The global conference on "*Partnering and Investing for a Peste des Petits Ruminants Free World*" organized by the OIE and FAO in 2018, hosted by the European Commission was to reaffirm the political will of countries and to mobilize resources (6) to meet the 2030 eradication goal.

With the southern spread of this disease into the SADC region and issues associated with differentiating PPR from other diseases (9), national and regional approaches are urgently needed. SADC is the only region in sub-Saharan Africa with non-infected countries and therefore plays an important role in facilitating the control and eradication of PPR in infected countries which will in turn reduce the risk of disease spread further south on the African continent. An overview of the current situation is presented in this paper and the main constraints and opportunities to control PPR in the SADC regions are discussed.

SITUATION ANALYSIS

Current PPR Status in SADC

In southern Africa, PPR has spread into new areas in recent years (**Figure 1A**). Tanzania was first infected probably from imported animals from Kenya in 2008 and represents an important potential source of PPR viruses for the rest of the region (10). PPR is now considered endemic in Tanzania in small ruminants with PPR lineages II, III, and IV circulating (11). The disease has spread from Tanzania to the Democratic Republic of Congo (DRC) and Comoros (12, 13). Around 2012, Angola was infected probably with imported animals from DRC but these outbreaks have not been officially recorded (14). So far, no clinical disease has been reported in Namibia, Malawi, Mozambique, or Zambia (4). Zambia did detect PPR sero-positive goats in recent years, though in the absence of clinical disease, suggesting either that antibodies were from imported vaccinated animals or previously infected (i.e., from Tanzania and/or DRC) or false positives (Bedane personal communication, roadmap meeting). The situation in Mozambique is similar (15). The borders between Tanzania, DRC, and Angola and neighboring non-infected countries represent important entry gates for PPR into the rest of southern Africa. Namibia (Northern Communal Area), Malawi, Mozambique, and Zambia are therefore considered at high-risk of PPR infection. Botswana, Eswatini, Mauritius and South Africa and the southern zone of Namibia, are declared by the OIE as PPR free. Lesotho and Zimbabwe are also considered at lower-risk of PPR infection (**Figure 1B**). Madagascar and Seychelles could be considered at risk because of the maritime trade of small ruminants with Comoros (12). However, Madagascar has been declared PPR free by the OIE in 2018, where now efforts for surveillance need to be strengthened to avoid reversal of this status.

Epidemiology of PPR in Southern Africa

PPR appears a good candidate for eradication according to criteria for eradication (16). However, the large populations of sheep and goats and their high population turnover (annual turnover rates of up to 30%) necessitate a higher effort (and costs) for control (14). The epidemiology of PPR is relatively well-defined but gaps in knowledge still exist and variability between regions may occur.

Firstly, following initial exposure of small-ruminant populations to PPR, a high mortality and morbidity is expected, which provides a visible clinical picture detectable by passive surveillance systems. However, in African small-scale farming systems, co-infection by multiple pathogens is frequent and could blur the expected clinical picture (17). PPR is also known to be a seasonal disease in some African endemic regions with peak infections usually occurring during the cool, dry season (18). This season in southern Africa starts in April and extends to August in some areas, providing a long environmental window for PPRV transmission. Under these climatic conditions, little is known about the PPRV persistence in urine and faeces (14).

Secondly, as in other African regions, the SADC region hosts countries with large small-ruminant populations (e.g., South Africa) and many are still free of PPR unlike all other African countries. Long-range cross-border trade of small ruminants involving two or more countries is frequent in the region (19). The patterns of this trade are largely unknown despite their relevance for the introduction and spread of animal diseases. Short-range trade (involving adjacent districts in neighboring countries), considered also to be illegal, represents an important socio-cultural component of local livelihoods. In addition, climate change is expected to increase extreme climatic events including droughts (20). Those events will affect mainly the poorest populations depending mostly on small ruminant production and living in the most arid areas. Droughts and political instability have been shown already to play their role in PPR spread (21).

Finally, some questions still remain on the host range of PPRV and their role in the local PPR epidemiology (22). In particular, little is known regarding virus excretion in infected camels, cattle, and wildlife (23, 24). In West Africa, cattle seem to be a dead-end host for PPR (25) but the role of local southern African breeds could be different (e.g., these breeds experienced different selective pressures by the rinderpest virus). In Africa, the role

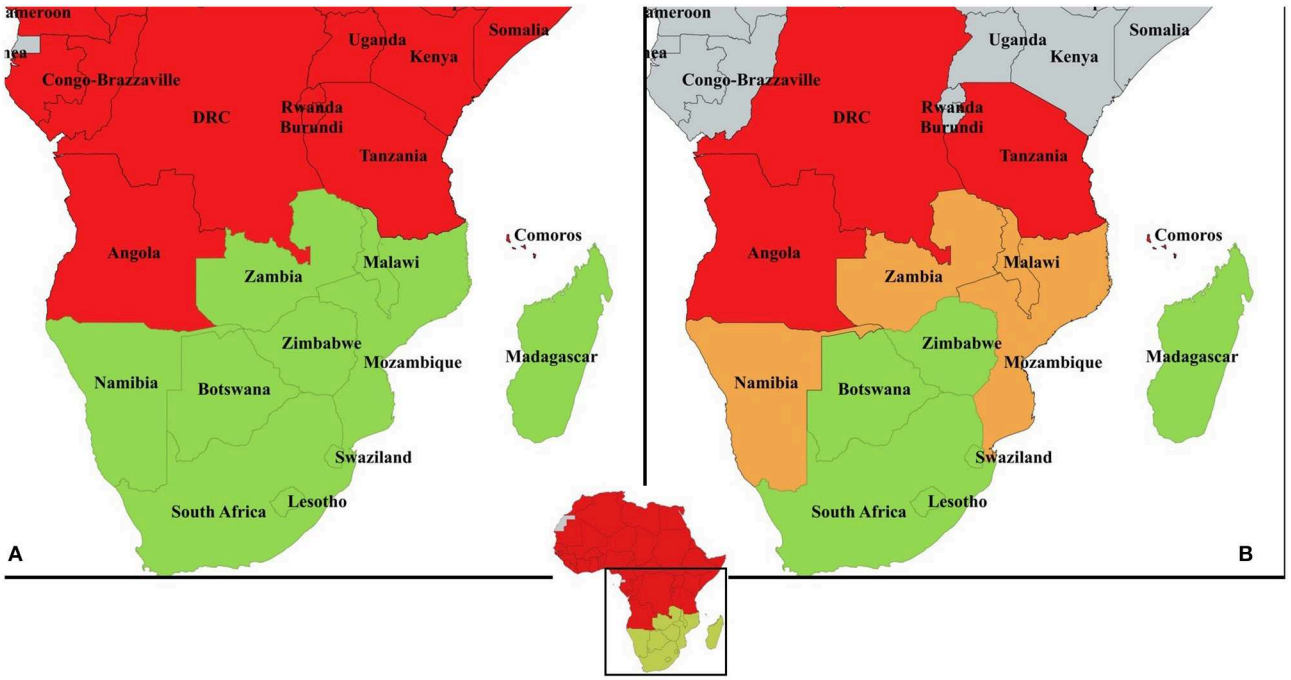

FIGURE 1 | (A) PPR country data compiled from official reports and literature between 2008 and 2018. In red, countries with at least one occurrence of disease reported, in green countries with absence of disease or disease never been reported. Angola is considered infected in at least one zone by multiple references (see text) despite no OIE report of clinical disease. Zambia has reported seropositivity in 2015 to OIE but subsequent surveillance failed to prove occurrence of disease; **(B)** suggested risk-based approach for PPR surveillance and control in the Southern African Development Community: in red, "infected countries" with presence of the disease in at least one zone; in orange, "high-risk countries" sharing a border with an infected country; in green, "lower-risk countries" with no border shared with any infected country. Madagascar and Seychelles could be considered at risk because of the maritime trade of small ruminants with Comoros. However, the scale of this trade in intensity and frequency is not quantified. Mauritius is considered lower-risk country given its assumed low level of maritime trade with Comoros.

of most wild ungulate species in PPR epidemiology is largely unknown, as no clinical disease has ever been reported despite exposure (26). Clinical disease has been observed in African ungulates in zoo environments elsewhere (27) and in other wild ungulate species in central Asia (28, 29). The southern African region has large and healthy wildlife populations with relative freedom of movements across borders thanks to the creation of Transfrontier Conservation Areas (TFCAs) (30, 31). In addition, several species are endemic to the region (e.g., springbok) and some countries such as South Africa and Namibia have developed an important wildlife industry where animals maybe bred in conditions in-between natural and zoo settings where they could become particularly susceptible to PPR.

Regional Capacity for PPR Surveillance and Control

The SADC Secretariat has identified PPR as one of the three major Transboundary Animal Diseases affecting regional and international trade (32). The SADC strategy (8) describes the limited PPR control capacity in SADC region in relation to diagnosis and surveillance, knowledge of virus transmission and susceptible species and differentiation of infected and vaccinated animals. Legislation on the use of PPR vaccines was also noted as an issue in most countries. The Pan African Veterinary Vaccine Center (AU-PANVAC) is mandated to provide quality assurance of all veterinary vaccines produced or imported into Africa and to coordinate the harmonization of veterinary vaccine registration with the support of the Global Alliance for Livestock Veterinary Medicines (GALVmed) and the OIE, which will be important for many SADC countries should they require PPR vaccine quickly due to an incursion.

Effective vaccination campaigns to ensure sustained herd immunity with 80 percent population coverage, will be pivotal to eradicating PPR as it was for eradicating rinderpest (14) though the high reproductive rate of small ruminants may warrant the need for annual vaccination in some flocks. Vaccination of small ruminants is limited in some areas due to the cost of vaccines, delivery and access to animals. Current vaccines against PPR virus are homologous vaccines (33) and require only one dose for life-long protection. The first vaccine was against lineage II (Nigeria 75/1) Africa PPR virus strain and has been used for 30 years. The impossibility to differentiate between vaccinated and infected animals and its thermolability are some of the limitations of this vaccine. Recent research on freeze-drying these types of live-attenuated vaccines have enabled thermostability and resistance to high temperatures in the field (34). The Botswana Veterinary Institutes (BVI) capacity in establishing and maintaining PPR-VAC® was confirmed during a recent FAO supported project. This live-attenuated vaccine has also been assessed recently using an *in-vivo* challenge model in goats (35).

Additionally, a thermo-adapted live-attenuated PPR vaccine has been trialed in goats in India (36). Assessment of the cross-lineage efficacy of different PPR vaccines is important given SADC has several lineages circulating (37). Recently comparative studies have indicated that the Nigeria 75/1 strain vaccines produce stronger antibody responses than the India S96, though the Indian strain vaccine elicits a greater cell-mediated immune response (38).

Given concurrent infection of sheep and goats with PPR and other diseases such as FMD or goat-pox (17, 39) a bivalent vaccine or concurrent vaccination would be of benefit to livestock owners and would be in line with the GSCE targeting other small ruminant diseases during the eradication programme. Development of vaccines based on Differentiating Infected from Vaccinated Animals (DIVA) technology will assist in surveillance and eradication (37). Unfortunately, these recombinant vaccines require booster doses and cost more than conventional vaccines but they have the advantage of temperature stability and their DIVA properties.

The SADC member states have a network of laboratories (provincial and national laboratories) for the surveillance of PPR and PPR diagnostic capacity which varies between countries. As in most national laboratories, the laboratories in Malawi, Mozambique, Namibia, Zambia, and Zimbabwe have been using c-ELISA assays to conduct PPR sero-surveillance in high-risk areas to detect the presence or absence of PPRV (Country reports, 2019). To increase the test sensitivity and affordability, AU-PANVAC has developed a blocking (b)-ELISA test (40). Some SADC countries have participated in the validation trial of this test (e.g., Malawi), others have been supplied kits (e.g., Mozambique) and others have requested them (Bedane personal communication). Most of the national laboratories have molecular PPR diagnostic capacity (e.g., PCR or qPCR). The capacity to conduct virus neutralization tests—OIE gold standard—and virus isolation and sequencing is absent from most national laboratories in SADC. Consequently, PPR confirmatory diagnostics of doubtful results requires countries to send samples to OIE reference laboratories for PPR (e.g., CIRAD or Pirbright Institute) (41) or to AU-PANVAC.

New field surveillance strategies may assist in the early diagnosis of disease and provide increased sensitivity and specificity of tests by targeting PPR virus specific antibodies, antigens, or genetic material (41–43). The direct detection of PPR virus genetic material and antigen in fecal samples could be used in small ruminant and wildlife surveillance (41). A pen-side test using quantum dots with a lateral-flow test strip has been evaluated in the field with similar results to c-ELISA (43). Such, a pen-side test that could confirm several small ruminant pneumo-enteritis diseases would be useful (34).

FAO and OIE Guidance and Support

FAO and OIE have established a Global Secretariat, which coordinates efforts for the PPR Global Eradication Programme (GEP) (44) based on a Progressive Control Pathway (PCP). The Global Secretariat is conducting Regional Roadmap workshops for the PCP implementation. In southern Africa, two Regional Roadmap meetings took place in October 2016 in Harare, Zimbabwe and in March 2019 in Lusaka, Zambia (45). The PPR Roadmap meetings ensure continuous evaluation and monitoring of the PPR situation and help in harmonizing policies and strategies among countries, as well as with other regions, for the implementation of the PPR GSCE. This strategy follows three core components advocating a risk-based approach to disease control to better target "virus hotspots." The progressive stepwise approach—no available data (stage 1) to OIE free status (stage 5)—(**Figure 2**) and the PPR Monitoring and Assessment Tool (PMAT) are used in these meetings and correspond to a combination of decreasing levels of epidemiological risk and increasing levels of prevention and control capabilities.

The support provided by OIE and FAO both directly and indirectly assists SADC countries to progress along their respective PPR roadmap pathways (**Figure 2**). The FAO has been actively building capacity to prevent PPR introduction into Malawi, Mozambique, and Zambia through a Technical Cooperation Project 2013–2015 involving serological surveillance, local stakeholders awareness, and building rapid diagnostic capacity and national contingency and preparedness plans (TCP/SFS/3403) (46). Additional support by FAO provided to Madagascar and Lesotho enabled the former to obtain "Freedom from PPR certification" in 2018 while Lesotho will soon submit the documentation for its OIE freedom following FAO project TCP/LES/3604 (Pers. Com. Bedane). PPR control and eradication became one of the components of a recently launched SADC-based project financed by EU ("Support Toward the Operationalization of the SADC Regional Agricultural Policy"—GCP /SFS/004/EC). Additionally, OIE Performance of Veterinary Services (PVS) tool (47) will greatly support the assessment of the 47 Critical Competencies of Veterinary Services in countries and of areas specific to PPR control and eradication (7). Better control and diagnosis of other small ruminant diseases is also necessary for improving farmer participation. OIE has also been assisting to build PPR diagnostic capacity through focal point training, including fifth cycle workshop "Wildlife Health Information Management" 2018 and laboratory twinning projects between reference laboratories and SADC laboratories (e.g., in Tanzania).

THE WAY FORWARD

Progress toward the control and eradication of PPR in SADC is now well-planned by many southern African countries. However, there is a need to coordinate efforts at the regional level. Three risk-based categories can be identified (infected, high-risk, lower-risk countries, **Figure 1B**). Better coordination between countries within the same category and between categories should improve harmonized surveillance and targeted control.

Following the PCP, a better understanding of the epidemiology of PPR in the region and its contributing factors will be necessary for eradication and this will require funding for field epidemiology research. Urgent active surveillance is required to establish the extent of PPR sero-positive areas in infected (across country) and high-risk (border areas) countries. In parallel, sheep and goat movements need to be

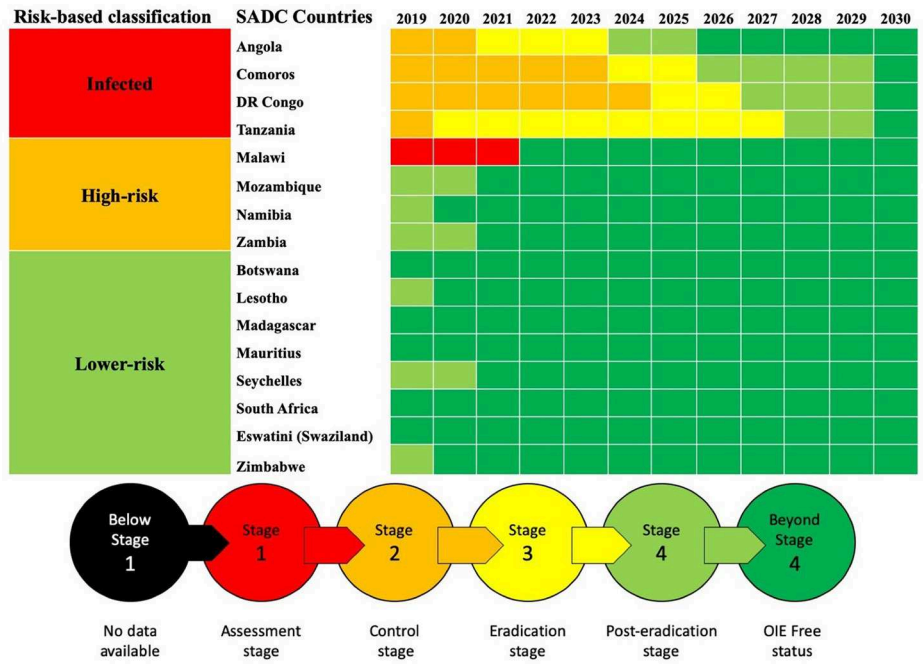

FIGURE 2 | Progressive control pathway for SADC countries as reported during and following the Second Road Map Meeting, March 2019, Lusaka, Zambia.

better understood across the region. Studies on legal animal movement (e.g., by trucks or other vehicles) and other more informal cross-border movements will require participatory methods to enable mapping. A better understanding of cultural and social practices around small ruminant production systems of small-holder farmers in southern Africa is necessary in order to optimize surveillance and control of PPR (and other diseases). Women are known to be managing small ruminant production systems in Africa and, through communication and training tools, they should be empowered with the primary level of passive surveillance systems and control tools as identified in a study on gendered barriers to livestock vaccine uptake and ongoing gender inclusive vaccine study in Kenya (48, 49). Clarifying the role of wildlife and wildlife/livestock interfaces is also of paramount importance for SADC.

Risk-based approaches should be used to better understand the risks of introduction from infected to high-risk countries; the risk of disease spread once introduced into a new country and from there to other lower-risk countries. Spatial epidemiology can include different types of data layers such as the presence of wildlife populations, roads, density of small ruminants, each weighted by expert knowledge (50). These risk assessments are important to inform policy development, contingency planning, and for allocating scarce resources to high-risk areas within countries (13).

Veterinary services' capacity building is necessary in order to survey, control and eradicate PPR from SADC. In infected countries, going through stage 2–4 should be done through good communication with neighboring non-infected countries in order for them to survey for PPR with the most updated information. In high-risk countries, controlling animal movements is difficult with porous borders. Therefore, strategic passive surveillance for early detection (e.g., clinical and laboratory surveillance in markets or cross-border trade hubs) and early-response (e.g., vaccination) is needed to prevent outbreaks in new areas. The specific epidemiological context of SADC countries implies that surveillance systems should be prepared to expect non-conventional disease expression as the incursion of PPR in the Maghreb region showed moderate clinical signs and low rates of mortality. Improving biosecurity and sanitary protection through Public Private Partnerships will also be necessary (51) and FAO and OIE can help by facilitating donor agency-country relationships. Capacity building and experience sharing between infected and non-infected countries are important as demonstrated in FAO/OIE workshops. Countries at lower-risk of PPR introduction should get prepared using risk-based approaches at reacting to PPR outbreaks on their territory given their specific context (in particular given the size of the wildlife industry in some countries). Vaccines that are thermotolerant, produced in large quantities and if possible have DIVA abilities are needed. Further, PPR molecular diagnostic training and laboratory equipment and reagents are also needed in the region.

CONCLUSION

The support of international organizations (i.e., FAO and OIE) and SADC technical committees will be of paramount importance to ensure effective regional collaboration. The experience from meetings and trainings organized by these groups has shown that trust and sustainable relationships between stakeholders and veterinary services is crucial to facilitate information flow within the region. The updated SADC strategy for the control and eradication of PPR will further

guide regional coordination and provide leadership to meet the 2030 goal.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the manuscript/supplementary files.

AUTHOR CONTRIBUTIONS

AB and AC contributed equally to the design and writing of the manuscript. BB contribution to FAO activities, situation analysis of PPR in the region, laboratory capacity, and overall review of the manuscript.

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Peste des Petits Ruminants Virus Surveillance in Domestic Small Ruminants, Mozambique (2015 and 2017)

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Peste des Petits Ruminants (PPR), a transboundary animal disease affecting mainly goats and sheep is caused by a morbillivirus and threatens food security and livelihoods as morbidity and mortality rates can reach 90%. There are no records of PPR in Mozambique, but the disease situation in Tanzania and the ability of PPR virus to rapidly spread across countries constitute a high risk for about 4.7 million goats and sheep in Mozambique. A total of 4,995 goats and sheep were sampled in several provinces during 2015 and 2017 to assess the status of PPR virus (PPRV) in Mozambique and to contribute to surveillance along the border with Tanzania. The sera were screened for anti-PPRV antibodies using a commercial PPR competition ELISA (c-ELISA) and the haemagglutinin based PPR blocking ELISA (HPPR-bELISA). The swabs were tested using one-step RT-PCR for detection of PPRV RNA. The overall percentage of animals with anti-PPRV antibodies by c-ELISA, was 0.46% [0.30–0.70]. However, all the sera positive on c-ELISA were confirmed to be negative by the HPPR-bELISA. Considering that all the swabs were negative for detection of PPRV, no clinical cases were observed during passive surveillance and active sampling, and no symptoms were reported, these results suggest that PPRV is not present in Mozambique.

Keywords: PPR virus, small ruminants, surveillance, Mozambique, antibody, RT-PCR

INTRODUCTION

Peste des Petits Ruminants (PPR), a transboundary animal disease affecting mainly goats and sheep, is a highly contagious small ruminant's disease with significant economic impacts due to the high morbidity and mortality rates ranging from 10–90% and 50–90%, respectively, in naive populations. The disease is caused by a morbillivirus, a single-stranded RNA virus of the family *Paramyxoviridae*, a virus related to the now eradicated Rinderpest virus (1). Once closely associated with the latter in African ruminant populations, triggering cross-immunity and cross-reaction between both viruses, PPR now ranges freely on the African continent and has been spreading since the late 1990s, early 2000s.

The epidemiology of PPR in domestic animals is globally understood (2, 3). In endemic areas, morbidity and mortality can be much lower, blurring the epidemiological picture. The classical clinical expression of the infection includes watery nasal and lachrymal discharges, fever and at later stage diarrhea and coughing. Differential diagnosis can be difficult in African contexts where multiple infections are co-occurring, sometimes simultaneously, in small ruminant populations [e.g., bluetongue, foot and mouth disease (FMD), contagious caprine pleuropneumonia, brucellosis, rift valley fever, or Q fever] (4, 5).

The history of the geographical spread of PPR in Africa is not entirely understood. Endemic for a long time in Western and the Sahelian part of Central Africa, the disease spread to East Africa at the beginning of the twenty-first century, emerging first in Uganda, probably spreading from the then Sudan to subsequently reach Kenya and Tanzania (2). Four lineages (I-IV) are present in Africa with lineage IV being a new invasive strain from the Middle East and Asia, replacing other strains. The recent spread and mixing of lineages, notably in Tanzania could confuse the disease geography and clinical patterns. Tanzania is now endemic for PPR, potentially hosting at least three of the four existing lineages and with a widespread presence of the infection and disease across its territory (6).

In southern Africa, the disease has spread in new areas in recent years. Tanzania represents a significant potential source of PPR viruses for the rest of the region. Tanzania has a large small ruminant population and is engaged in trade with its neighbors, exporting formally or informally large numbers of small ruminants. The disease has already spread from Tanzania to Democratic Republic of Congo (DRC) and Comoros (7), but so far, it has not been reported and confirmed in Malawi, Mozambique, and Zambia. The borders between Tanzania and these last two countries therefore constitute an important entry gate for PPR into the rest of southern Africa, and surveillance and control need to be implemented in order to prevent the disease from spreading further southward, where it could infect not only the countries with a common border (Malawi, Mozambique, and Zambia), but also Botswana, Lesotho, Namibia, South Africa, Swaziland, and Zimbabwe. As demonstrated for other transboundary animal diseases such as FMD, once the virus enters a country such as Mozambique or Zambia, it can easily spread within the region (8). This is due firstly to the extensive informal trade in small ruminants occurring amongst southern African countries and secondly due to the promotion of wildlife population connectivity in the region through the creation of Transfrontier Conservation Areas for the last 20 years. African ungulates, particularly antelopes, are susceptible to the infection but no disease has been reported so far in those species (9), while a recent outbreak in Central Asian ungulate species raises the concern of the impact of PPR on threatened species (10). The role of wildlife in the epidemiology of PPR is not yet fully clarified, and it cannot be excluded that wildlife could spread the disease across borders (11).

In Africa, the disease represents a threat to the livelihoods of some of the most vulnerable and poor communities. Small-scale farmers, notably women largely involved in the small ruminant economy, rely heavily on small ruminants for income, assets, nutrition and health as well as soil management (12). For these reasons, PPR has been identified as a target for control by OIE and FAO with an objective to eradicate the disease worldwide by 2030. However, for the implementation of better PPR control strategies, it will be important to improve our knowledge in epidemiology, genetics, pathogenicity, and virulence characteristics of the virus.

Mozambique shares borders with Tanzania, with endemic PPR, Malawi, South Africa, Zambia, and Zimbabwe with no record of clinical PPR. However, like Mozambique, Zambia, and Malawi are classified as high-risk countries for PPR introduction given their shared borders with Tanzania, DRC, and Angola, all infected countries. Mozambique has a small ruminant population of ∼4.7 million heads, most of them produced in the Central and southern regions. Important wild ungulate populations inhabit large national parks and reserves in all provinces of Mozambique and these populations could play a role in the epidemiology of the disease. The interface between these wildlife populations and livestock has not been characterized and the risk of PPR introduction or spread through the wildlife population is unknown. The country has engaged in the Progressive Step-wise Approach for the prevention and control of PPR (13). To address these needs, an intensive clinical and sero-epidemiological survey of the disease was carried out in Mozambique. In this context, this study reports a clinical, serological, and virological survey in 5 provinces of Mozambique, where the risk of disease transmission could be present, in order to provide information about the PPR status of the country.

MATERIALS AND METHODS

Study Area

The study was conducted in 5 of the 10 Provinces of Mozambique, from the three geographic regions (**Figure 1**). Provinces were selected on the basis of two criteria: sharing a border with Malawi, Tanzania, or Zambia (infected or high-risk country) and hosting national park or reserve with susceptible wildlife populations. In the north, Cabo Delgado and Niassa were selected because they share borders with Tanzania and due to the presence of susceptible wildlife populations in Niassa National Reserve, which covers some districts from both provinces, and Quirimbas National Park in Cabo Delgado. In the Centre, Tete province was part of the study due to PPRV suspected cases in 2015 in Zambia (only positive serology detected, no disease ever reported), while Gorongosa National Park and Marromeu National Reserve were the criteria for Sofala's inclusion. In the South, Gaza was selected due to the existence of Limpopo National Park and Banhine National Park. The study was performed with permission of the National Veterinary Directorate, Ministry of Agriculture and Food Security of Mozambique.

Sampling

A longitudinal study consisting of two cross sectional surveys was carried out across 2015 and 2017. The districts then villages were selected taking into account the density of small ruminants provided by local key informants (mainly district staff from the Department of Veterinary Services) and, then, the accessibility of the site, as some villages are not reachable by car.

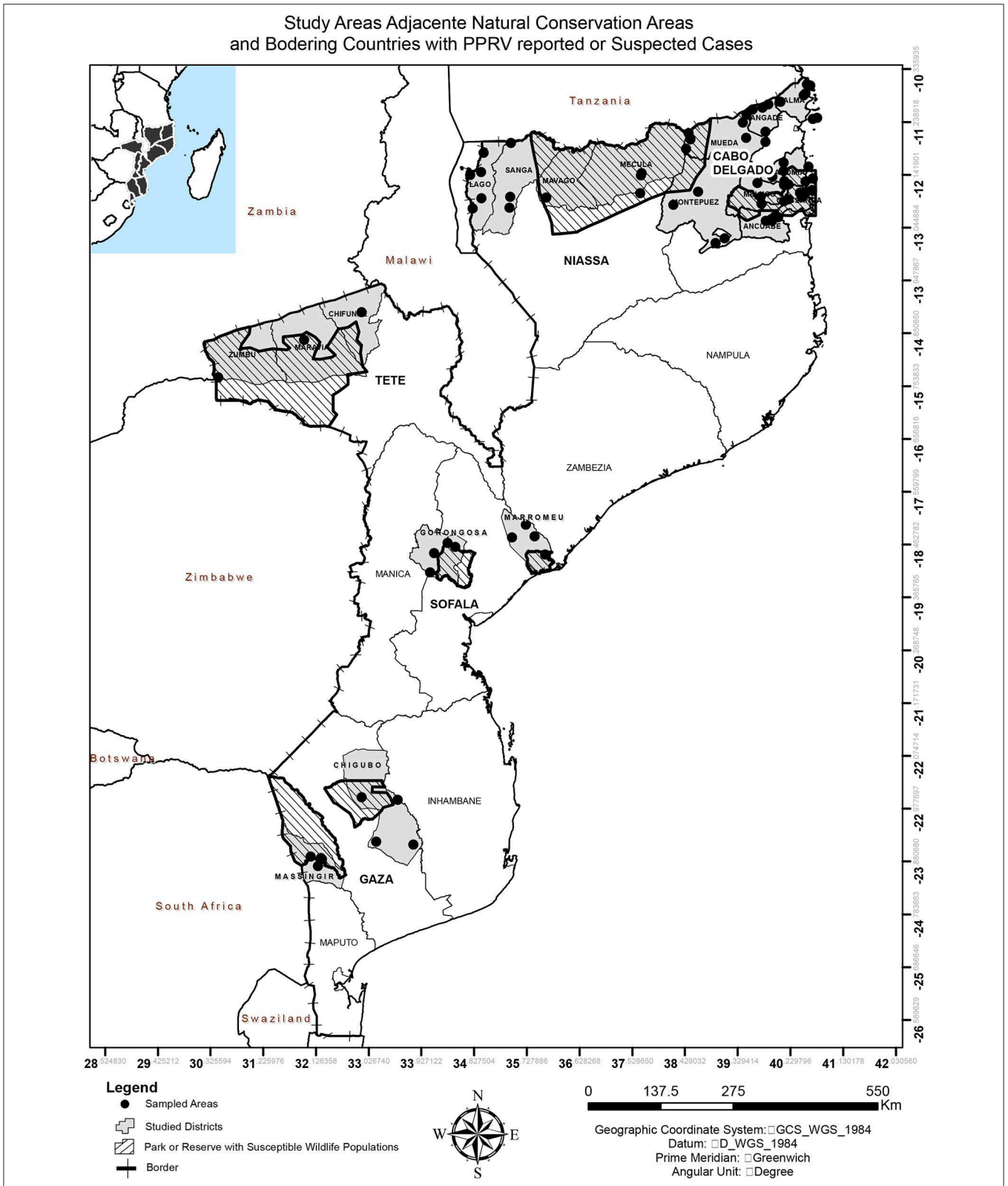

FIGURE 1 | Map of Mozambique indicating the study areas, adjacent natural conservation areas, and bordering countries with PPRV reported or suspected cases.

Finally, inside each village, herds were selected based on the willingness of owners to participate in the study. Therefore, due to these constraints the sampling methodology was a convenient sampling. For herds with <10 animals all were sampled while in case of herds with more than 10 animals, at least 10% of animals were included. Breeds were not considered/identified in this study, just species because the so called small-scale farmers normally keep the indigenous "breeds" that comprise cross- and non-characterized breeds.

The blood samples were collected into plain vacutainer tubes and kept at room temperature for clotting to obtain sera. Ten percent of nasal swabs were intentionally taken from the same population and preserved in Phosphate Buffer Saline (PBS) containing antibiotics (kanamycin, streptomycin, and tetracycline).

Laboratory Testing

Two serological tests were performed to detect PPRV antibodies. First the sera were screened for anti-PPRV antibodies using a commercially available competitive ELISA (c-ELISA) kit (ID-Vet ID Screen® PPR Competition) for the detection of anti-PPRV nucleoprotein antibodies in sheep and goat serum or plasma (14), following the manufacturer's instructions. While analyzing the results we received notification from the kit manufacturer about the specificity shift of the batch that was at that time available on the market (B78) and was being used in this study. Based on the recommendations of the manufacturer and the European Reference Laboratory for PPRV, EURL-PPRV at the CIRAD, and an in-house re-evaluation of the specificity of the batch B78 using sera tested simultaneously with both c-ELISA batch B78 and D52, we interpreted the results with the batch B78 with the following modification; cut-off values: ≤30%: positive; >30% and <35%: doubtful and ≥35%: negative.

All the c-ELISA positive sera were then tested by HPPR-bELISA kit from the Pan African Veterinary Vaccine Centre of the African Union (15) for further confirmation following the manufacturer's instructions.

The swabs from all animals positive on c-ELISA were tested for the presence of PPRV nucleic acid using one-step RT-PCR. The swabs from 2015 were tested using a conventional reverse transcription polymerase chain reaction (RT-PCR) described in the OIE Manual (16), while swabs from 2017 were screened using a real-time reverse transcription polymerase chain reaction, targeting the PPRV N gene (17).

Statiscal Analysis

All data were entered in MS Excel (Microsoft Corporation) spreadsheet and exported to SPSS version 12.1® (Stata IC 12.1 for Windows), software for analysis. Descriptive statistics were based on frequencies and percentages for qualitative variables and means and confidence intervals for quantitative variables. Prevalence data were calculated using either Fisher's exact test or the χ^2-test.

Data generated were entered in Microsoft Excel and analyzed using descriptive statistics. The odds ratio (OR) was calculated to assess the association between being positive for PPR and reusing serological data. The OR assesses the association of being seropositive for PPR where $p < 0.05$ was considered as significant.

RESULTS

A total of 4,995 blood samples were collected from 4,315 goats and 680 sheep (**Table 1**) of different ages and breeds (mainly indigenous), between June and September 2015 and May and November 2017. The sera were analyzed for the presence of anti-PPRV antibodies using c-ELISA, and the overall percentage of positive sera was 0.46% [0.30–0.70]. Positive sera were found across all sampled provinces excluding Tete (**Table 1**). The positive sera on c-ELISA re-tested by HPPR-bELISA were all negative. The PPRV RNA was not detected in swabs submitted to molecular testing. During the sampling, the animals were inspected and no clinical signs resembling PPR infection were seen or reported.

DISCUSSION

PPR is an epizootic disease of small ruminants causing high morbidity and mortality in affected animals, constituting a significant threat to livestock production, and represents a danger to food security in developing countries due to mortality rates that can reach 100% (18). PPR outbreaks have major socioeconomic implications for farmers and agricultural sectors, especially in countries where small ruminants play an integral role in sustainable agriculture and employment, thereby contributing to an increase in poverty in regions with dominant dependence on farming small ruminants.

Traditional livestock trade routes exist between all neighboring countries of Mozambique, although their frequency and intensity have not been measured. Mozambique shares its northern border with the United Republic of Tanzania, a country in which PPR is endemic. The risk of PPR introduction from known infected areas in Tanzania into Mozambique is considered to be high due to this transboundary trade and transport of small ruminants even if its extent is unknown. The Mozambican borders with Zambia and Malawi are considered at lower risk because no clinical disease has ever been reported in these 2 countries. However, the Tete region has a high density and trade of small ruminants and should be specifically targeted for surveillance. Other areas targeted by this study in Sofala and Gaza present a lower risk of PPR circulation because neighboring countries (i.e., South Africa, Swaziland, and Zimbabwe) are far from the nearest outbreaks (in Tanzania and DRC). The presence of large populations of wildlife in some protected areas in these provinces can be a risk factor for PPR circulation because the role of wildlife in PPR epidemiology is largely unknown. Wildlife populations are known to be exposed to the virus in East Africa but no clinical disease has ever been observed in wildlife in Africa.

While serological tests are designed to be sensitive and specific, false positive and false negative results do occur; therefore, it is strongly recommended to confirm any new positive finding by using alternative diagnostic methods.

Positive serum samples were found in four provinces out of five sampled and the global prevalence was 0.46 [0.30–0.70]. The differences between the provinces at high risk (Niassa and Cabo Delgado) and those of medium (Tete) and low risk (Sofala and Gaza) was not significant ($p = 0.543$).

TABLE 1 | c-ELISA results (prevalence).

Province	District	Year	*N*	Nr. of + (%)	[95% CI]
Gaza	Massingir	2017	392	3 (0.77)	[0.20–2.41]
	Chigubo	2017	311	1 (0.32)	[0.02–2.06]
	Total		703	4 (0.57)	[0.18–1.55]
Tete	Chifunde	2015	151	0	–
	Marávia	2015	114	0	–
	Zumbo	2015	82	0	–
	Total		347	0	–
Sofala	Gorongosa	2017	246	1 (0.41)	[0.02–2.60]
	Marromeu	2017	400	3 (0.75)	[0.19–2.36]
	Total		646	4 (0.62)	[0.20–1.69]
Cabo Delgado	Quissanga	2017	278	1 (0.36)	[0.02, 2.30]
	Macomia	2017	338	1 (0.30)	[0.02–1.90]
	Palma	2015	131	0	–
		2017	248	2 (0.81)	[0.14–3.20]
	Mueda	2015	142	1 (0.70)	[0.14–3.20]
		2017	235	5 (2.13)	[0.79–5.17]
	Montepuez	2017	147	2 (1.36)	[0.24–5.33]
	Ancuabe	2017	293	0	–
	Meluco	2017	163	0	–
	Nangade	2015	130	0	–
	Total	2015	403	1 (0.25)	[0.01–1.60]
		2017	1,702	11 (0.65)	[0.34–1.19]
	Total		2105	12 (0.57)	[0.31–1.02]
Niassa	Mecula	2015	101	0	–
		2017	139	1 (0.72)	[0.04–4.54]
	Mavago	2015	132	0	–
		2017	231	1 (0.43)	[0.02–2.76]
	Sanga	2015	39	0	–
		2017	17	0	–
	Lago	2015	103	1 (0.97)	[0.05–6.07]
		2017	432	0	–
	Total	2015	375	1 (0.27)	[0.01–1.71]
		2017	819	2 (0.24)	[0.04–0.98]
	Total		1,194	3 (0.25)	[0.06–0.80]
Total		2015	1,125	2 (0.18)	[0.03–0.71]
		2017	3,870	21 (0.54)	[0.34–0.84]
Total			4,995	23 (0.46)	[0.30–0.70]

The c-ELISA test we used has 99.4% of specificity (14), therefore, the 0.46% we detected in our study is within the expected level for non-infected population. Global seroprevalences of 57.6% in Uganda (19), 48.5% in Pakistan (20), 45.66% in sheep and 38.54% in goats in India (21) and of 45.4, 31.0, and 27.1% in 2009, 2012, and 2015, respectively, in Tanzania (5, 6) have been reported by using c-ELISA test. These studies showed a high seroprevalence because the samples tested were from animals exposed to the virus with or without clinical signs of the disease.

For better interpretation of our results, a confirmation by the HPPR-bELISA with 100% specificity compared to Virus Neutralization Test (15), was performed. All seropositive samples by c-ELISA came out negative with the HPPR-bELISA, invalidating the seroconversion detected by c-ELISA. Our data indicate an overall seronegativity of the sampled populations. In addition to this serosurveillance data, there has never been any reported outbreak of PPR in small ruminants in Mozambique. No official vaccination has been carried out against PPR in Mozambique. As small ruminant populations were expected to be naïve to PPR virus infection, PPRV incursion would result in high morbidity and mortality in the non-vaccinated naïve population of small ruminants in Mozambique.

Low PPR prevalence in non-infected countries can be possible for several reasons. Low level PPRV antibodies in this study detected by the c-ELISA may result from: (i) imported animals from infected countries that have been infected and survived the disease; (ii) imported animals from infected countries that have been vaccinated against PPR; (iii) False positives due to the specificity of the c-ELISA test. In the first two cases, seropositivity would be detected preferentially in areas bordering an infected area (i.e., Tanzania), which is not what has been observed here. However, the likelihood of finding positive animals seemed to be higher for low risk provinces than the high risk ones OR = 1.306 [0.552–3.088]. These findings are somehow contradictory taking into account that the major risk factor of PPRV introduction into Mozambique is the disease situation in Tanzania. Finally, given the size of the sampling, false positives are expected and an absence of seropositivity through c-ELISA screening would be suspicious.

PPRV is highly infectious, often spreading rapidly between groups of susceptible animals, causing disease with distinct clinical signs. Thus, a lack of reports of clinical signs, the absence of RT-PCR positive results and the absence of seroprevalence after double-testing of samples among examined animals indicate that the virus does not actively circulate in the studied populations in Mozambique. These data can enable Mozambique to move forward in its Progressive Control Pathway toward OIE PPR free status. However, this status should not hide the fact that Mozambique is a country at high-risk of contracting PPR due to its border with Tanzania. In addition, the presence of large susceptible wildlife populations sharing space with livestock in the periphery of protected areas is an additional risk factor that should be taken into account (9). In the future, targeted or opportunistic (e.g., for conservation translocation) sampling could be useful to assess the risk of wildlife introducing PPR across border or spreading it between provinces.

Mozambique, together with Malawi, Zambia, and Namibia, should strengthen its surveillance system in border areas. A risk-based approach taking into account small ruminant movements across the Tanzanian-Mozambican border should help in designing a reactive passive surveillance system.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Veterinary National Directorate, Mozambique. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

SA, SZ, and ACa conceived and designed the study, organized protocol developments, contributed to the conception and interpretation of the data, and revised the manuscript. LM developed the sampling design, directed the collection of samples, carried out field sampling and laboratory investigations, interpreted the data, organized the dataset, and wrote the first draft of the manuscript. IM, VN, and DA carried out field sampling and laboratory investigations. ACh performed statistical analysis, contributed to the interpretation of the findings, and revised the manuscript. CQ, JF, and MC contributed to the interpretation of the findings and revised the manuscript.

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Integrated Approach to Facilitate Stakeholder Participation in the Control of Endemic Diseases of Livestock: The Case of Peste Des Petits Ruminants in Mali

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In Mali, small ruminants (SRs) are an important means for enhanced livelihood through income generation, especially for women and youth. Unfortunately, opportunities for livestock farmers to tap into these resources for economic growth are hindered by high burden of endemic diseases such as peste des petits ruminants (PPR). A key component for the control of PPR is vaccination of SRs. However, low participation of farmers to vaccination was identified by stakeholders of the livestock value chains as a key constraint to successful vaccination programs. This study was implemented in the framework of a project which aimed at improving the domestic ruminant livestock value chains in Mali by upscaling proven interventions in animal health, feeds and feeding and livestock marketing. The objectives of the study were to review the context of livestock vaccination in Mali and evaluate the impact of innovation platforms (IP) as a means for engaging stakeholders in the vaccination process. Desk review, key informant interviews (KII) and net-mapping were used to understand the context of livestock vaccination, while vaccination coverage and sero-monitoring together with group interviews were used to measure the impact of the intervention. IPs were created in 24 communes in three regions: 15 IPs in Sikasso, 4 IPs in Mopti and 5 IPs in Timbuktu. They developed work plans and implemented activities focusing on improving interaction among key vaccine chain delivery stakeholders such as farmers, private veterinarians, vaccine manufacturers, local leaders and public veterinary services; involving them in the planning, implementation and evaluation of vaccination programs and fostering knowledge sharing, communication and capacity building. After 2 years of implementation of IPs, vaccination coverage for SRs increased significantly in target communes. During the first year, seroprevalence rate for PPR increased from 57% (CI95: 54–60%) at baseline to 70% (CI95: 67–73%) post-vaccination in Sikasso region,

while in Mopti region, seroprevalence increased from 51% (CI95: 47–55%) at baseline to 57% (CI85: 53–61%) post-vaccination. Stakeholder engagement in the vaccination process through facilitated IPs was successful in fostering participation of farmers to vaccination. However, a sustainable vaccination strategy for Mali would benefit from consolidating the IP model, supported by Government investment to strengthen and adjust the underlying public-private-partnership.

Keywords: small ruminants, PPR, stakeholder, participation, innovation platforms

INTRODUCTION

Mali's economy is primarily based on agriculture and agro-pastoralism (1). Livestock farming is the main source of income for over 30% of the population, contributing 15% of the country gross domestic products (2). Small ruminants (SRs) represent a significant part of the livestock sector with ∼40 million heads in 2016 (3). However, the development of the livestock sector is constrained by high burden of diseases, with peste des petits ruminants (PPR) being a major production constraint (4). PPR is one of the most widespread, infectious and contagious diseases of sheep and goats, with mortality rates exceeding 90% in immunologically naive populations (5). The disease results in high economic impact (6), thus threatening the food security and sustainable livelihood of farmers (7). Although originally characterized and confined in western Africa in the early part of the twentieth century (8), PPR has since been confirmed throughout most of the African continent, as well as the Middle East, central Asia and eastern China (5, 7, 9). The disease is caused by a morbillivirus, PPR virus (PPRV), closely related to the human pathogen measles virus (MV), as well as other animal pathogens such as canine distemper virus (CDV) and rinderpest virus (RPV) (10). Clinical signs of the disease vary and may include ocular and nasal discharges, fever, tissue necrosis, and in most of the cases death of SR livestock occurs within 10–12 days post-infection (11). Once confirmed, the most effective way to control PPR in a given area is mass immunization of SRs (5). There are many vaccines that are commercially available and have shown to be effective for at least 3 years post-vaccination (11, 12), but most of them require a strict cold chain, which represents a key challenge in resources limited countries with high temperatures such as Mali. Since the main route of transmission of PPR is by direct contact, animal movement control is also effective but is difficult to implement in many of the infected countries where extensive and mobile production systems are common (13). In Mali, PPR control strategies have been mainly based on annual national mass vaccination programs (also called "vaccination campaigns") and/or focal vaccination in response to overt outbreaks. However, in practice vaccination of the entire SR population is difficult to achieve and is costly. For several decades, efforts have been made by the Government to support vaccination campaigns against PPR. Despite significant improvements made so far, results have not shown satisfactory vaccination coverage across the country. This is usually explained by the low level of participation of farmers to vaccination (14). The situation is a result of a combination of many factors including low awareness of farmers about the benefits of vaccination, poor planning of vaccination campaings, poor communication among the vaccine chain stakeholders, amongst others (14, 15). To increase vaccination coverage, there is need for an innovation that would encourage participation of stakeholders in the delivery of vaccines. Such innovation would put emphasis on knowledge sharing, communication and interaction among stakeholders.

Our research was conducted through a development project that aimed at improving productivity of ruminant livestock in Sikasso, Mopti, and Timbuktu regions of Mali from 2016 to 2019. The project aimed at improving animal health, feeds and feeding systems and farmer's access to market (16). To address animal health aspects, the project focused on ways to increase livestock vaccination coverage especially for SRs. This specific study addresses the question of whether increased awareness, communication and interaction among stakeholders of the vaccine chain delivery through an innovation platform (IP) (17) can trigger participation of farmers to vaccination.

CONCEPTUAL FRAMEWORK

Livestock vaccination in Mali shares characteristics of complex socio-economical systems given the fact that different stakeholders involved, both private and public, have distinct objectives, capacities and incentives. There is often remarkable lack of interaction among these stakeholders. This situation prevents learning and flow of information between them (14). Decision to adopt a new technology involves critical steps including knowledge (awareness) about the technology, gaining sufficient information on its characteristics, benefits, and costs (18). Thus knowledge and information sharing are important factors that influence technology adoption (19, 20). However, the magnitude of the impact of a technology is determined by the rate of adoption, following the diffusion and learning about the technology or innovation over time (20). An IP approach has huge potential to addressing the organizational constraints of the livestock vaccine chain delivery. The IP framework was developed to provide insights into the complex relationships between the diverse stakeholders including farmers, community leaders, vaccine manufacturers, vaccinators, researchers, livestock traders and other input and service providers. Having been increasingly established within the framework of AR4D initiatives (21), they acknowledge the interdependency of stakeholders to achieve agricultural development outcomes,

and hence address the need for a space where they can learn, negotiate and coordinate to overcome challenges and capture opportunities through a facilitated innovation process (17). In the context of livestock vaccination, IPs are used to enhance learning, communication, interaction, coordination, and innovation capacity among mutually dependent (but disconnected) stakeholders with different backgrounds, expertise and interests. Given that stakeholders are more likely to support the implementation and scaling of innovations when they have been involved in the design and testing process (22, 23), IPs promote participation and contribute to use of knowledge as to generate possible solutions in a more practical and effective way. Bearing in mind that the concept of innovation systems to address complex agricultural problems is not new, this study focused on the practical application of the concept in the context of livestock vaccine delivery in Mali.

MATERIALS AND METHODS

Site Selection

The study was carried out in three major livestock producing regions of Mali, namely, Mopti and Timbuktu (known as pastoral systems) and Sikasso (known as agropastoral system). The choice of the study area was dictated by the development project that supported the IP activities. In the Mopti and Timbuktu regions, reduced rainfall, overgrazing, expansion of grazing areas in crop land, drying of water points, and wind erosion results in major constraints related to feed availability. Therefore, pastoralists are forced to travel during part of the year to feed their animals. For the specific case of Timbuktu, insecurity is a major concern, making access to remote farmers difficult. In contrast, the Sikasso region is among the wettest areas of Mali with a clear dominance of agriculture over livestock farming. It is a system for which pasture rangeland is the basic diet of animals. Access of farmers to veterinary services is easier in this region, compared to other regions [(24); **Figure 1**].

Desk Review

In order to understand the policy and institutional framework in which the livestock vaccination operates in Mali, several key reports related to animal health delivery system were reviewed. They include annual reports of 2016 and 2017 of the National Directorate of the Veterinary Services (DNSV) and the National Directorate of Industry and Animal Production (DNPIA), the

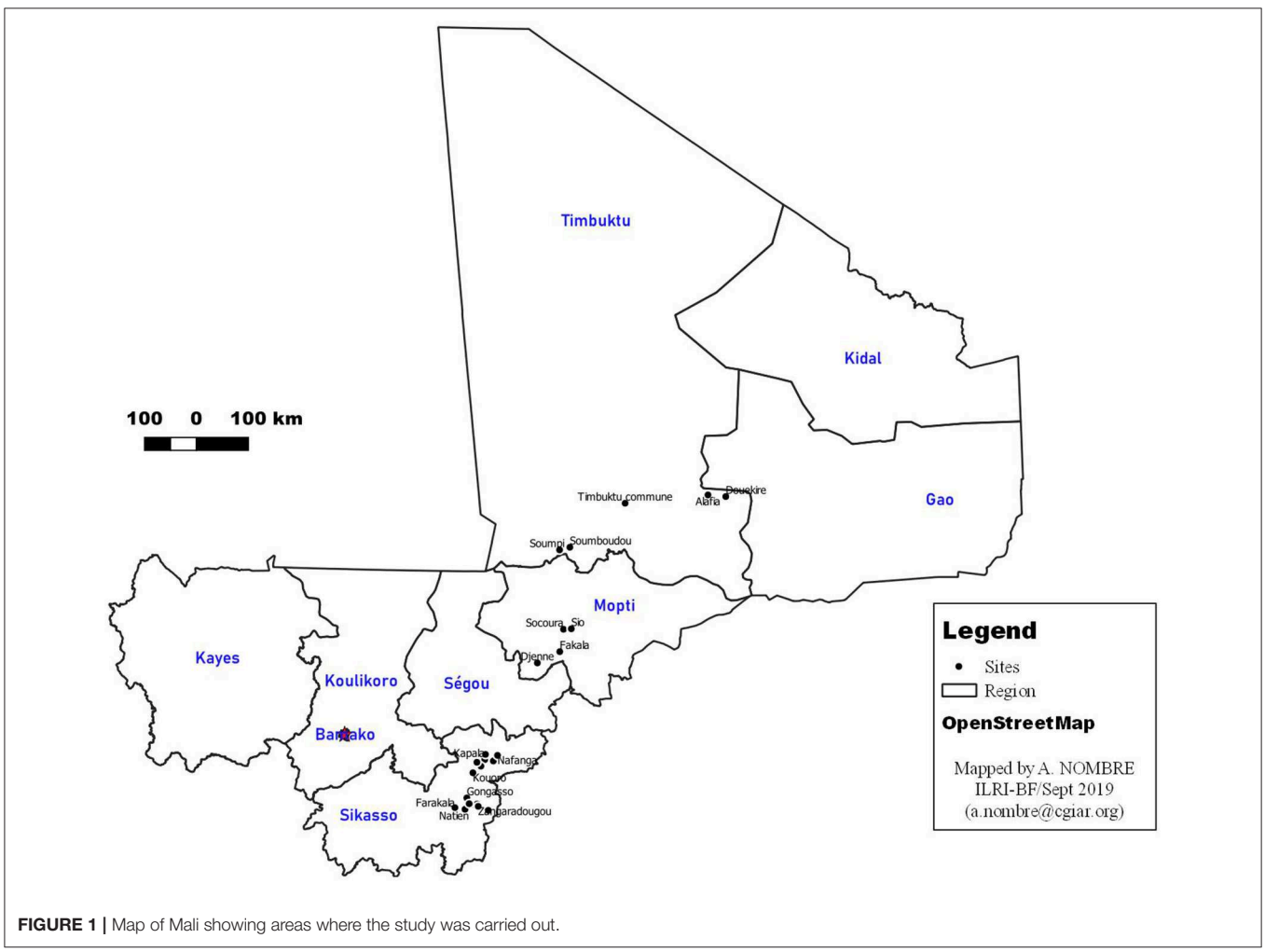

FIGURE 1 | Map of Mali showing areas where the study was carried out.

OIE country Assessment of Performance of Veterinary Services, the National Strategy Plan for Eradication of PPR, the National One Health Plan (2019–2020) and the Strategic Framework for Economic and Sustainable Development Plan (2019–2023).

Stakeholder Engagement

This exercise enabled in-depth assessment of the different stakeholders of the vaccination process, their roles, locations, and perceptions about current vaccination strategies.

Key Informant Interviews (KII)

KII can help determine not only what people do but why they do it. Such interviews are excellent for documenting people's reasons for their behavior and people's understandings or misunderstanding of issues (25). We used KII to get insights from key high-level stakeholders about the vaccination process. Participants were officially contacted either by emails or by phone calls to be interviewed at their work places. A variety of stakeholders including researchers, policy makers, public and private veterinary services and livestock vaccine manufacturers were interviewed (either the Director /President or any other resource person). The following organizations were consulted: DNSV, National Centre for Animal Health (CNASA), DNPIA, National School of Applied Rural Economics (EIR), Agricultural Market Observatory (OMA), Central Veterinary Laboratory (LCV), Ministry of Livestock and Fisheries, Association of Private Veterinarians (COVEM), National Association of Veterinarians (ANAVEM), Livestock for Growth Development Project (L4G), and development NGOs partnering with the project.

Stakeholder Workshop

A workshop was organized at the beginning of the project in 2016, and brought together high-level stakeholders, mostly those that were interviewed during the KII sessions to discuss issues of animal health service delivery in Mali. A special session was held with animal health experts to further discuss keys issues related to vaccination. Recommendations for improvement of vaccination coverage were also provided.

Context Specific Stakeholder Mapping and System Challenges

Net-Mapping (NM) was carried out to gain more in-depth understanding of the vaccination process tailored to the local context. It also enabled further scrutinization of the mains issues of vaccination from the field and local perspectives. NM was a powerful tool to explore the roles and relations between the different stakeholders on the ground. Drawing on social network approaches (26), the tool is particularly suitable since it can help identify stakeholders and their formal and informal interactions, as well as examine the flows of information from researchers to help determine the pathways of research-based information (27) It uses interviews and maps as the main research method. The NM exercise was carried out by the project team composed of an animal health, capacity development and livestock experts and a MSc student, with assistance from staff of the project implementing partners. In first instance, information gathered from the desk review and KIIs were used to identify broader stakeholders involved in the delivery of animal health services, who were then invited for the NM exercises. Participants were chosen purposively to represent a specific stakeholder group of the vaccine delivery chain. Two NM processes focusing on livestock vaccination were carried out in each region. Twenty-six stakeholders attended the NM exercise in Mopti region, and 19 attended the NM in Sikasso region. The participants were invited to attend a half day workshop facilitated by the researchers and the project partners. The NM process for each group comprised of three steps: identification of the main stakeholders involved in vaccination and their relationships (who does what? why? how? and with who?), determination of the perceived level of influence of the vaccination by different stakeholders (which stakeholder is seen as more important in the process and why?) and identification of constraints and recommendations for improving vaccination campaigns. The NM process was not carried out in Timbuktu as researchers were not able to access the area due to high insecurity.

Process Development of the Innovation Platforms

To establish the IPs, we adopted guidelines as described by Schut et al. (28). IPs were set up in 24 communes of the project: 15 in Sikasso (Natien, Pimperna, Diamatènè, Kafouziela, Zangaradougou, Farakala, Kouoro, Gongasso, Fama, Zangasso, Sinkolo, Kapala, Kolonigué, Nafanga, and N'goutjina); 4 in Mopti (Sio, Djenné, Fakala, and Socoura) and 5 in Timbuktu (Soumpi, Somboudou, Douekire, Alafia, and Timbuktu commune). They were established at the level of a "commune" which is an urban or rural territory collectively acting as a legal administrative entity with financial autonomy. A commune comprises of an average of 32 village with a minimum of 6 villages and a maximum of 58 villages (**Table 2**). There is a municipal council of elected officials that regulates the economic, social and cultural development affairs of the commune. The project management team held 2 days workshops in each commune to facilitate the creation of the IPs. They were made of representatives of stakeholders identified during the stakeholder mapping namely direct actors involved in the livestock vaccine chain delivery such as farmers, "mandataires," vaccine producers and public veterinary services; actors directly supporting farmers such as livestock traders, feed stockists and meat processors and institutions supporting the livestock value chain such as financial organizations, community leaders, NGOs, and information systems (**Figure 2**). Each IP had set up a steering committee comprising at least a coordinator, secretary, treasurer, and communication lead. Representation of women was ensured in each steering committee with at least two positions held by women. IP steering committee members were trained on governance and leadership by the project. Their roles were to convey meetings, develop work plans, document activities, follow up implementation of innovations. During the process of creating the IPs, facilitators identified by the project implementing partners were invited to attend the first meetings and received training in facilitation skills. They were then mentored by the project to ran IP meetings. An IP steering committee met whenever possible (on average once in a month)

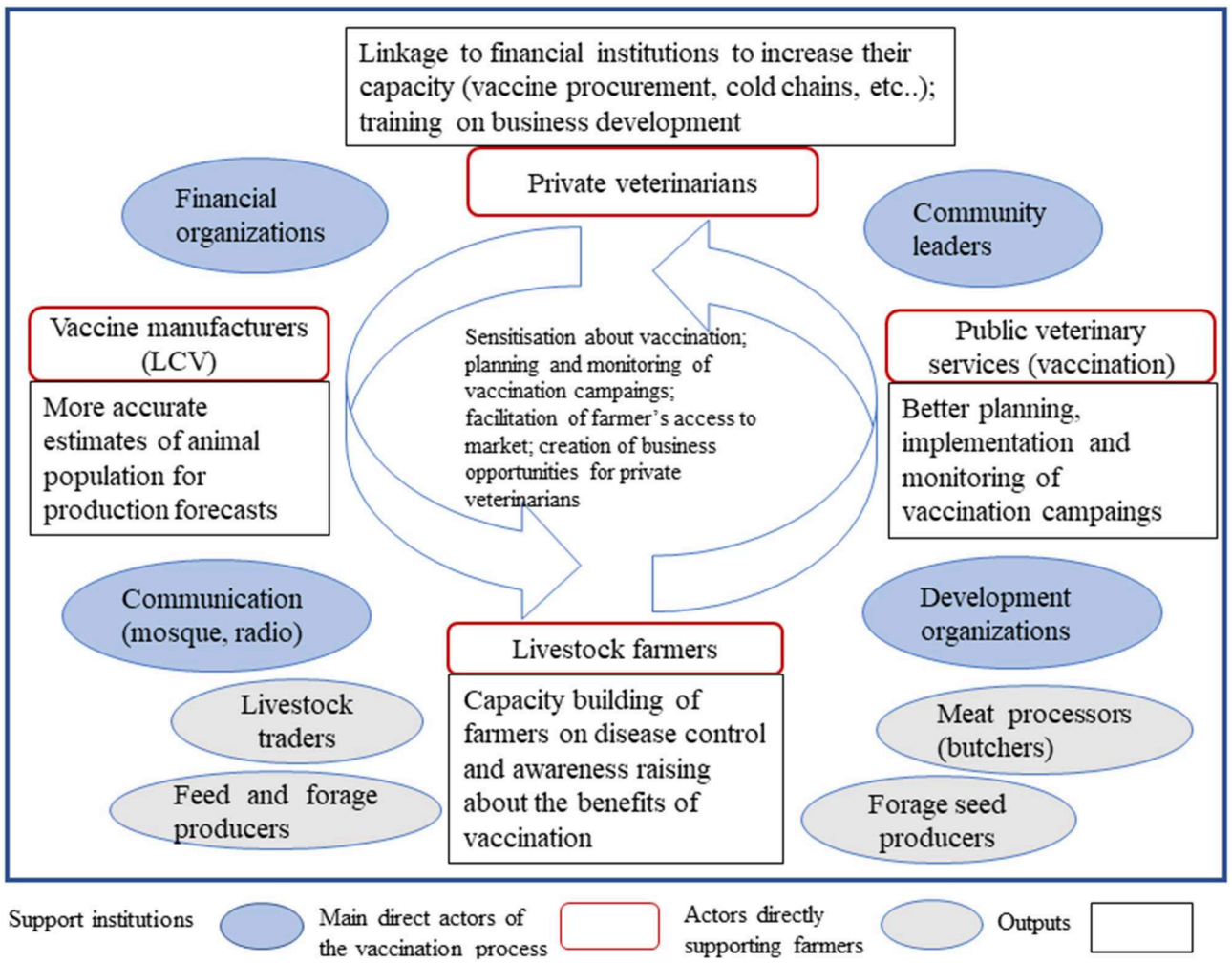

FIGURE 2 | IP structure with types of activities and outcomes.

to review progress of activities, challenges, and opportunities. Capacity development activities were regularly conducted by the project to strengthen technical and organizational capacities of IPs. To ensure adequate documentation of activities and outcomes, monitoring, and evaluation of the IPs followed the project guidelines as advised by the donor. IPs used notebooks to document activities such as meetings and trainings. Project implementing partners draw information and collected data to develop reports sent to the project monitoring and evaluation team at a monthly, quarterly and annual basis. A project planning workshop organized at the beginning of each year during the lifespan of the project allowed interaction between stakeholders, project implementing partners and project core team to discuss successes and issues related to implementation of IPs.

Impacts Assessment of the IPs

Baseline data on numbers of SRs vaccinated was provided by the "mandataires" in their respective communes and backed up with data obtained from the public veterinary services in each target communes prior the start of the intervention in 2016. The same information was collected after two consecutive vaccination campaigns (2016–2017 and 2017–2018). In addition, a post-vaccination sero-monitoring survey was carried out for the 2016–2017 vaccination campaign, 1 year after the implementation of the IPs. The calculation of the sample size for the sero-monitoring study was based on the recommended 80% sero-prevalence to achieve herd immunity. Blood and serum samples were randomly collected from 1,500 animals before vaccination and the same number starting from 4 months after vaccination. Competitive ELISA was used to measure the level of sero-conversion of animals following vaccination. Laboratory tests were carried out at the LCV in Bamako, Mali.

An evaluation of the status of the IPs was carried out by the project team in 2018, with 15 IPs that responded to the survey. The evaluation team was composed of the project expert on capacity development and implementing partner in each region. An evaluation guideline was developed and administered to a group of two to three IP steering committee members who were

selected to be part of the interviews. However, a single response based on group-consensus was recorded. In total, 40 members participated in the interviews. The criteria that were retained for the evaluation were: good understanding of the basic concepts and objectives of the IP by their members; good understanding of the roles of the steering committee; structuration process of the IP in place to see if the process is taking shape; functioning of the IPs and mechanism of self-funding for sustainability.

RESULTS

Understanding the Context of Livestock Vaccination in Mali

Currently, disease control in Mali (esp. vaccination) is run through a public-private-partnership (PPP) with farmers largely covering vaccination costs. In the PPP model, private veterinarians hold the sanitary mandate, so they are called "mandataires." They are supervised by the public veterinary services to implement livestock vaccination in their assigned areas. In areas where private veterinarians are not operating, vaccination campaigns are carried out directly by public veterinary agents. Development organizations support free of charge vaccination in specific areas such as those of high insecurity like Timbuktu region. The objectives of the vaccination campaigns are set by the public veterinary services in consultation with the "mandataires" of each region. The targets (number of animals to be vaccinated during the campaign) depend on the capacities of both public and private veterinary services including availability of funds, equipment and human resources. Several factors that limit performance of vaccination campaigns have been identified in our study. They were groups into three categories: limited participation of farmers to vaccination, limited access of farmers to quality vaccines and socio-economic factors including policy, gender and cultural barriers.

Limited Participation of Farmers in Vaccination Campaigns

The high cost of vaccination was pointed out by various stakeholders as being a limitation to farmer's participation to vaccination. Contrary to what is observed for drugs, where costs for SR are below costs for cattle, the cost of vaccination of SR is the same as that for cattle and camel for any disease. This is perceived as not economically sound and psychologically acceptable to farmers who think that it is unfair given the huge difference in value of these animals. Making farmers better understand the purpose and procedures of vaccination was thus seen as necessary. This situation is exacerbated by the packaging size of the vaccine (100 doses per vial) which is not suited to farmers who hold small flock sizes who would require group vaccination to reduce the cost. However, such arrangements (group vaccination) entail additional costs related to farmer mobilization which requires extra time, especially for women, if not well-coordinated. On the other hand, the lack of transparency in the communication of the conditions and side-effects of vaccination was considered by stakeholders as a major concern to farmers. This is caused by the fact that many farmers think that PPR vaccination may result in serious side effects as observed for CBPP vaccine. This situation causes reluctance and fuels the lack of trust between farmers and veterinarians. Therefore, the acceptance of vaccination by farmers will largely depend on their level of awareness about the vaccines used (efficiency and safety). In addition, there is mis-perception about the objectives of vaccination by some farmers who think that vaccination is for fattening animals or for treating already sick animals. This leads to farmers missing opportunity to vaccinate their animals at the right time. Added to that, the poor planning, coordination and evaluation of vaccination campaigns was regarded as a major constraint, causing a fragmented vaccine chain delivery where stakeholders do not have the same information at the same time.

Limited Access of Farmers to Vaccines (Quantity and Quality)

Frequent vaccine shortages during the vaccination campaigns have been reported. The inaccurate livestock census prior to vaccination is a major cause for this. Often, animal population statistics provided by veterinary services as a basis for forecasting the vaccine demand are far underestimated because most farmers do not declare all their animals to avoid being taxed, yet the census of animals for vaccination is different to the one for tax collectors, and they are even carried out by different government bodies. In addition, the limited capacities of "mandataires" to stock large quantities of vaccines at required temperatures has raised concerns about the quality of vaccines delivered to farmers. This situation creates a fragile business environment for "mandataires" who need to be supported according to stakeholders. Support to the "mandataires" could be achieved through strengthening their business opportunities by facilitating their access to financial institutions to access loans to purchase equipment and grow their business.

Gender and Socio-Cultural Factors

In traditional livestock systems, sheep, goats, and poultry are the main livestock owned and managed by women, who then play an important role in disease prevention and control. The fact that SRs belong to women or are primarily managed by them, especially in sedentary areas, means that men do not feel bothered by their vaccination, so women do not get enough support to participate in vaccination programs. Furthermore, women face time constraints and limited access to information about vaccination schedules. In addition, in most rural communities, women cannot declare ownership of their animals or register themselves for vaccination because they are not recognized as head of the household. For example, during the livestock census, women who own livestock register them under the name of their husband or son. This situation often leads to wrong perception of communities (especially women) that SRs do not need to get vaccinated.

Often factors affecting performance of vaccination programs are present at all levels of the vaccine delivery chain, and they are interlinked and often involve a range of stakeholders at a time. Thus, an integrated participatory process through IP to tackle the main issues seemed a promising approach.

Stakeholders Involved in the Vaccination Process

The results of the net- mapping revealed a diversity of stakeholders involved in the livestock vaccination process. In both pastoral (Mopti) and agro-pastoral (Sikasso) regions, farmers, vaccine producers, and "mandataires" were perceived as having the greatest level of influence by stakeholders. However, in pastoral area, the decentralized public veterinary services such as Veterinary Sector (SV), Veterinary Post (PV), and the CAHWs held medium level power of influence because they provide vaccination in areas without "mandataires." In agro-pastoral areas, the central decision-making units such as MEP and DNSV were attributed medium level of power because they are more present. CAHWs scored more in pastoral areas, as compared to agro-pastoral areas. This is probably because in pastoral areas, qualified veterinarians are not readily available. In both areas, the administrative officers, police, and the community leaders scored low. This shows their limited involvement in the vaccination process (**Table 1**).

Activities Carried Out During the Implementation of the Innovation Platforms

Initially, multiple functions were assigned to IPs besides livestock disease control. However, challenges related to the implementation of vaccination campaigns were considered as a priority to be immediately addressed. Main issues were the poor communication among vaccine chain delivery stakeholders, the poor knowledge of farmers about benefits of vaccination, their low awareness about vaccination schedules, the inappropriate estimation of livestock population for vaccination, the limited implication of women in vaccination and the low capacity of "mandataires." Each IP developed a yearly work-plan in a participatory manner and carried out the following key activities during each vaccination campaign:

Community Census Livestock Population

In each commune, a committee made up of the area "mandataire," a representative of the IP and a local leader (mayor delegate or village chief) was created to carry out census of SRs prior vaccination to better inform the vaccine demand. Information collected in each village was relayed to the veterinary services and used by the association of "mandataires" to forecast their vaccine stocks with the vaccine manufacturer.

Involvement of IPs in the Official Launch of the Vaccination Campaign

Every year an official launching ceremony of the vaccination campaign is organized by the government in one of the

TABLE 1 | Stakeholders and their level of involvement in the delivery of vaccination.

Pastoral systems (Mopti)		Agro-pastoral systems (Sikasso)	
Stakeholder	**Score**	**Stakeholder**	**Score**
Farmer	9	LCV	11
LCV	7	"Mandataires"	9
"Mandataires"	6.5	Farmer	7
PV	5.5	DNSV	4
Formal drug shop	5	PV	3
SV	4	MEP	2.5
CAHWs	3.5	NGO	2.5
DRSV	3	Administrative officer	2.5
NGO	2.5	SV	2
DNSV	2	CAHWs	2
MEP	1	Community leader	1.5
Ministerial council	0.5	DRSV	1
Police	0.5	DNPIA	1
DNPIA	0	Legal drug shop	1
Community leader	0	Ministerial council	0
Administrative officer	0	Police	0

During the net-mapping process, participants were asked about their perception of the level of influence of each actor in the livestock vaccination delivery process by stacking small disks according to the level of influence so that the most influential actor has the most stacked disks unlike the least influential actor who has less or none. The allocation of influence scores was set in relation to the delivery of vaccination and not between the actors themselves. To do this, fifty disks were available to all participants, according to their experiences and knowledge, they distributed these discs between different actors. The distribution of influence disks already made was then readjusted if necessary, until the participants were completely satisfied with the degrees of influence attributed. The allocated rank represent an average of two net-mapping exercises per region.

TABLE 2 | Monitoring and evaluation activities of the IPs.

Region	Commune	Number of villages	*Number of IP events	**Number of meeting between IPs and project implementing partners
Sikasso	Natien	9	39	11
	Pimperna	17	26	9
	Diamatènè	8	18	14
	Kafouziela	7	12	10
	Zangaradougou	7	11	21
	Farakala	12	72	38
	Kouoro	16	68	43
	Gongasso	12	61	37
	Fama	7	27	31
	Zangasso	11	48	31
	Kapala	15	46	20
	Nafaga	6	28	13
	Sinkolo	9	27	22
	Kolonigué	13	42	41
	N'goutjina	8	30	19
Mopti	Sio	35	19	26
	Djenné	16	60	20
	Fakala	46	77	54
	Socoura	58	72	35
Timbuktu	Soumpi	25	27	0
	Somboudou	51	34	0
	Douekire	41	18	0
	Alafia	17	20	0
	Timbuktu commune	8	29	0

**This include IP and community meetings and **this include facilitation of IPs and evaluation visits.*

communes. During this meeting, the national vaccination calendar and the objectives of the vaccination campaign are communicated. IP members sent a representative to the meeting to get information about these plans. The information is then used to plan sensitization campaigns in their respective communes.

Organization of Sensitization/Awareness Campaigns

IPs supported the public veterinary services in organizing awareness campaign about vaccination and dissemination of vaccination calendar through community radio broadcasting in several local languages.

Creation of Community Level Committees for the Implementation of Vaccination

IP facilitated the creation of village vaccination teams. The teams were made up of the area "mandataire," a public authority, a representative of the IP and a local leader. The main roles of the vaccination team were to facilitate the linkage between the community and the vaccinators by setting up the vaccination dates in each village in consultation with the communities and mobilizing farmers for vaccination. Overall, the vaccination team supported the local planning execution, supervision and evaluation of vaccination campaigns together with the veterinary services. Because of insecurity, vaccination teams in Timbuktu region were exclusively composed of CAHWs who are usually supported by GNOs.

Capacity Development

IPs facilitated the implementation of capacity development activities for value chain actors on animal health, food safety and livestock production through the promotion of an integrated technological package composed of health, feeding and SR housing training modules.

Advocacy for Business Support to "Mandataires"

IPs facilitated linkage between "mandataires" and financial institutions. They supported development of bankable business models through facilitation of trainings of mandataires on business development and management through the project.

Besides vaccination, IPs also discussed and carried out interventions on other topics relevant to them to improve productivity of their livestock such as feeds and feeding, fattening and access markets. Non-specific activities to animal health carried out by IPs to support the livestock value chains include:

Support for the Development of Business Models for Livestock Fattening

The main roles of the IPs were to facilitate sheep and cattle fattening activities with an emphasis on promoting group marketing and facilitating linkage between farmers and local and regional markets.

Support of the Development of Business Models for Women

IPs foster a conducive environment for women farmer cooperatives to diversify their sources of income through the development and rolling out of viable business models, such as the production and sale of mineral blocks for livestock feeding.

Development of a Community-Based Bracharia Seed System to Address Feeding Constraints

IPs, supported model farmers to produce Brachia seed for business. They also mentored farmers to upscale the innovation.

In total, 911 IP events and 495 meetings between IPs and project implementing partners were reported (**Table 2**). Because of insecurity in the region of Timbuktu, project implementing partners could not join IP meetings.

Outcomes of the Innovation Platforms

Increased Vaccination Coverage of SRs

Increased participation of farmers to vaccination was shown by the increase in vaccination coverage. Vaccination coverage of SRs has more than doubled over 2 years in target communes compared to previous campaigns (**Figure 3**). High vaccination rates have been reported in communes of Mopti (Sio, Djenné, and Fakala), Sikasso (Natien), and Timbuktu (Douekire) where vaccination of SRs has never been reported before. In Timbuktu, vaccination is mostly carried out by development NGOs and is free of charge because of insecurity issues. This might explain the lack of noticeable change in vaccination coverage compared to previous years. Also, the monitoring of the IPs was difficult to achieve given that project implementing partners could not directly intervene in this area.

Increased Herd Immunity of SRs

Post-vaccination sero-monitoring after 1 year implementation of the IPs revealed an increased sero-prevalence rate for PPR in Mopti and Sikasso regions from 57% (CI95: 54–60%) at baseline to 70% (CI95: 67–73%) post-vaccination, and from 51% (CI95: 47–55%) at baseline to 58% (CI85: 53–61%) post-vaccination, respectively (**Figure 4**).

Performance Assessment of the IPs

Assessment of the IPs showed a good understanding of the objectives of the IPs by their members, clear activities, and road map were defined and a good documentation of activities was in place for most IPs. There was however a medium to low level

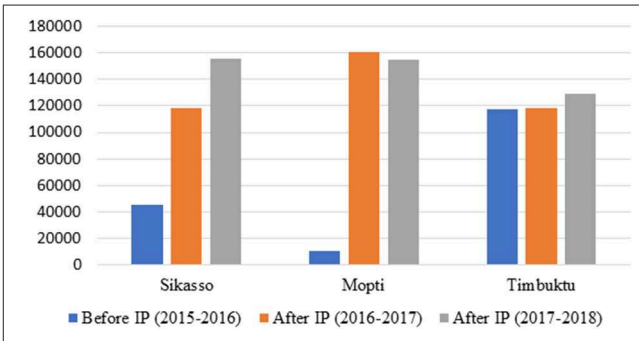

FIGURE 3 | Number of SRs vaccinated in each region before and after establishment of IPs.

of understanding of the IP concepts by IP members, as well as a medium to low frequency of meetings among the steering committee members. Most IPs did not yet have a sustainable self-funding mechanism in place, so they still rely of project support to run their activities (**Figure 5**). Major recommendations that emanated from this evaluation include the need for strengthening the endogenous dynamics of IPs and increasing senses of ownership by members; clarifed the terms of references of the steering committees of respective IPs to avoid conflict of interest; reinforce leadership and most importantly intensify the search for self-funding mechanism to ensure sustainability.

DISCUSSION

Importance of Stakeholder Engagement in the Vaccination Process

Vaccines are one of the most cost-effective and sometimes the only means to prevent disease in livestock. Commercial vaccines are available for prevention and control of many livestock diseases, however, these vaccines frequently do not reach, and thus are not often used by, smallholder farmers (29). A key challenge to adoption of livestock vaccines in Mali has been the lack of active involvement and limited interaction among stakeholders of the vaccination process (15). In rural sub-saharan Africa, most agricultural development policies have failed to involve stakeholders actively (30). Many studies put the emphasis the importance of stakeholder engagement in livestock disease control (31, 32) but there are few documented case studies. According to Donadeu et al. (29) strategies that could be implemented to increase vaccine adoption should not only consider the use by farmers (access and demand) but also vaccine manufacturing strategies that will ensure adequate vaccine production (availability), because these are the main areas of weakness in the existing vaccine supply chains. The limited involvement of grassroots stakeholders such as livestock farmers and community leaders in the vaccination process was obvious in our project areas, yet these stakeholders were perceived as critical in the vaccine delivery if one wants to reach many farmers with vaccination. This is the reason why an emphasis was put on the participation of local level stakeholder support which is likely to determine disease management success according to Cowie et al. (33). The global strategy for the control and eradication of PPR argues that the true progress in control of PPR and eventually eradication cannot be achieved without serious involvement of relevant stakeholders in all sectors (private and public veterinarians, para-professionals, livestock keepers and their community-based animal health workers, traders, NGOs, and other development partners) (34). Rathod et al. (35) added that global eradication of rinderpest was only possible due to the roles played by all stakeholders, including livestock owners. So, the fact that PPR eradication has been estimated to have the same chances of success as rinderpest, justifies the promotion of approaches that aim at increasing involvement of stakeholders in the control of PPR, hence IP.

The IPs focused on three pillars: knowledge sharing, capacity building and communication. A study in Bolivia and India highlighted the importance of knowledge sharing. The authors concluded that uptake of livestock vaccination was unlikely to

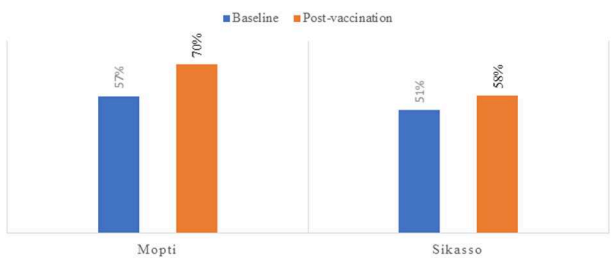

FIGURE 4 | Results of the post-vaccination sero-monitoring of the 2016–2017 vaccination campaign.

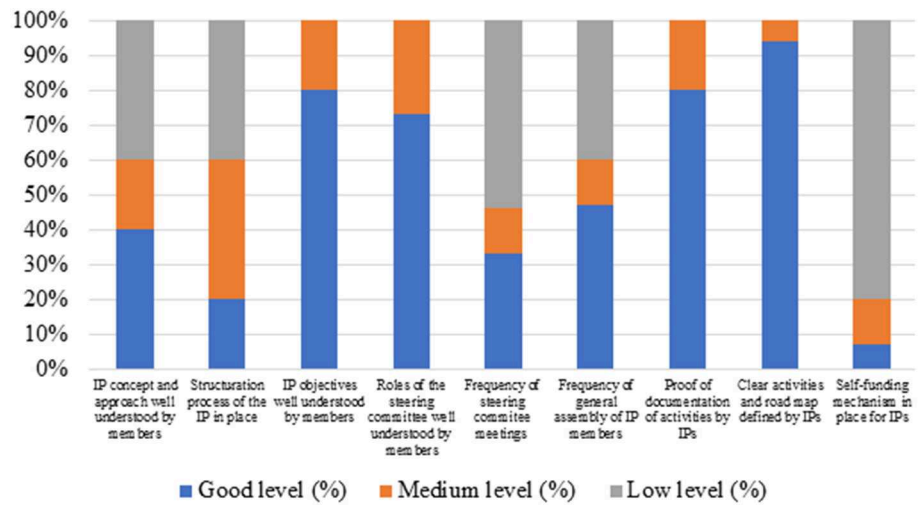

FIGURE 5 | Evaluation of the performance of IPs ($n = 15$) after 2 years of operation.

improve without knowledge transfer that acknowledges local epistemologies for livestock disease (36, 37). According to Donadeu et al. (29), a good strategy to increase vaccine demand is to increase awareness of the benefits of vaccines and disease control programs. Regular training to livestock owners on vaccination was also suggested in India to boost adoption (38).

The involvement of key stakeholders in all steps of the vaccination process might have contributed to the consolidation of trust among stakeholders, especially between "mandataires" and farmers, resulting in better appreciation of the roles and relations among stakeholders of the vaccine chain delivery. The sensitization campaings that have raised awareness of farmers about the roles and benefits of vaccination might have also motivated farmers to participate in vaccination, hence improvement in vaccination coverage achieved after implementation in the target communes. Although IPs used participatory community approaches for knowledge sharing and dissemination of information, to reach more farmers digital communication channels tools such as interactive voice recording, and text messaging service should be promoted alongside IPs. These are valuable technologies and likely to succeed given the increasing number of farmers who uses mobile phones for business.

Toward Stronger Public-Private-Partnerships

The PPP in the form of the sanitary mandate is considered by as a suitable approach to control PPR. However, its implementation in Mali has faced many challenges. First, the public good nature of vaccination against diseases such as PPR, that should entail limited vaccine cost to farmers, is contradicted by the current policy of full vaccine cost recovery underway. Resource poor farmers may not see vaccination of their livestock assets as their priority investments, especially if they do not understand the possible long-term benefits. Hence vaccination coverage is below target, which hampers effective disease control. Second, there is an increasing demand from stakeholders to review the legal roles of para-veterinarians and CAHWs who seems to be the only animal health service resource for farmers in areas where qualified veterinarians are absent. In those areas, community initiatives would be a solution to support disease control; and third given the lack of financial incentive in private veterinary practice, many veterinarians have redirected their efforts to other activities in the livestock sector such as production, or even other professions, because current business models are not profitable. Which seems a paradox given the importance of livestock for the country. Therefore, there is imminent need for strengthening PPP and ensure that they are fair.

In the short term the focus should be on finding ways of improving the situation for the already established private veterinarians by strengthening their capacity. This could be achieved through diversification of their activities beyond the sanitary mandate to generate more business opportunities, which could serve as an incentive for them to remain in the job. This could for example be the extension of their mandate to the control of food of animal origin and contribution to epidemiological surveillance or include more activities such as provision of extension services. There is also an urgent need to fill up the current critically low human capacity in the public and private veterinary sector through increasing the number of trained qualified veterinarians and support them in establishing private businesses. This could be achieved by creating a Government support fund for the newly graduated veterinarians. Furthermore, business models that uses private partners such as socio-professional organizations of farmers, economic operators or financial institution for financing vaccination campaigns against major endemic livestock diseases could be tested. In any case, the level of the financial cost contribution of the farmers to vaccination of important endemic diseases such as PPR should be reviewed to ensure these are affordable and fair given that PPR vaccination is considered a public good.

Sustainability of the Innovation Platform

Agricultural innovation has an important institutional dimension that takes time (39). Ayantunde et al. (40) argue that the performance of IPs seems to improve with the lifespan which underscores the necessity of a long-term perspective for IPs. However, sustainability of IPs will depend on their capacity to generate own funding to run activities. Options for self-financing through private sector actors, such as "mandataires," are already being promoted by the project, with some IPs pilot testing them. This involves allocation of a percentage of their ("mandataires") vaccination income to the IPs for their functioning. Other options include diversification of activities of IPs besides animal health. In addition, IPs should be supported with a legal framework that will enable them to be formally recognized by the government irrespective of the form they adopt, either association or cooperative providing it is in line with government regulations. This could help them be well-placed to attract funding from various sources including financial institutions.

In our case, 3 years of implementation was considered short to fully assess sustainably of IPs. However, present achievements provide a basis to capitalize on. Long term monitoring the IPs is necessary to lay solid foundation that will lead to sustainability. Follow up studies will focus on better understanding the social dimensions and dynamics of IPs, to better reveal key drivers for behavioral change of stakeholders.

CONCLUSION

Stakeholder involvement in the vaccination process through IP approach has led to an increase of participation of farmers to vaccination, resulting in an increase in vaccination coverage against PPR in target communes. While we promote the upscaling of IPs in other parts of the country, we also call for addressing critical challenges they face in their sustainability pathway. A private business model supported by a solid policy framework is required to sustain such innovation. Although significant progress has been made in increasing vaccination coverage in Mali, the national vaccination coverage is still not enough to guarantee control

of PPR anytime soon. A sustainable vaccination strategy will require concerted efforts among stakeholders of the livestock value chains and those of the vaccine delivery, supported by Government investment to strengthen and adjust the PPP models.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because the activity was implemented with the National Directorate of Veterinary Services (DNSV) in the framework of their national legal mandate under authorization number: N0057/MEP-DNSV. The human subjects were the program beneficiaries. They provided their written informed consent to participate in this study. Ethical review and approval were not required for the animal study because the sero-monitoring activity was carried out by the Central Veterinary Laboratory (LCV) with the approval of the DNSV (reference: N0057/MEP-DNSV) in accordance with their national mandate. Written informed consent for participation was not obtained from the owners of the animals because the sero-monitoring is a routine activity carried under the same approval.

AUTHOR CONTRIBUTIONS

AF and MMD conceived the study. MMD compiled the whole information and wrote the manuscript. MMD, IT, HK, ANS, CT, CS, AS, AY, MD, OD, MN, CF, MT, and AF participated in the data collection for key informants and workshops. MMD and AY designed the net mapping tools and collected the data. MMD, IT, and AF designed the questionnaire for the assessment of the innovation platforms. MMD, BW, CS, and AS designed the sero-monitoring study and tools. CS, MD, and AS collected the data for the sero-monitoring and carried out the laboratory analysis. BW, AF, OD, and MMD participated in the structuring and orientation of the write-up. All authors contributed to the literature review performed to build this review, critical review of the manuscript, and approved the final version.

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Spatial Multicriteria Evaluation for Mapping the Risk of Occurrence of Peste des Petits Ruminants in Eastern Africa and the Union of the Comoros

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Peste des petits ruminants virus (PPRV), responsible for peste des petits ruminants (PPR), is widely circulating in Africa and Asia. The disease is a huge burden for the economy and development of the affected countries. In Eastern Africa, the disease is considered endemic. Because of the geographic proximity and existing trade between eastern African countries and the Comoros archipelago, the latter is at risk of introduction and spread, and the first PPR outbreaks occurred in the Union of the Comoros in 2012. The objective of this study was to map the areas suitable for PPR occurrence and spread in the Union of the Comoros and four eastern African countries, namely Ethiopia, Uganda, Kenya, and Tanzania. A Geographic Information System (GIS)-based Multicriteria Evaluation (MCE) was developed. Risk factors for PPR occurrence and spread, and their relative importance, were identified using literature review and expert-based knowledge. Corresponding geographic data were collected, standardized, and combined based on a weighted linear combination to obtain PPR suitability maps. The accuracy of the maps was assessed using outbreak data from the EMPRES database and a ROC curve analysis. Our model showed an excellent ability to distinguish between absence and presence of outbreaks in Eastern Africa (AUC = 0.907; 95% CI [0.820–0.994]), and a very good performance in the Union of the Comoros (AUC = 0.889, 95% CI: [0.694–1]). These results highlight the efficiency of the GIS-MCE method, which can be applied at different geographic scales: continental, national and local. The resulting maps provide decision support tools for implementation of disease surveillance and control measures, thus contributing to the PPR eradication goal of OIE and FAO by 2030.

Keywords: geographic information system, multi-criteria evaluation, peste des petits ruminants, Eastern Africa, Union of the Comoros, risk mapping

INTRODUCTION

Peste des petits ruminants (PPR) is a highly contagious viral animal disease, mainly affecting domestic ruminants such as sheep and goats but also cattle and camels (1, 2). Captive or free wild ruminants can also be infected, including representatives of the Caprinae (wild goats, ibex, blue sheep), Antilopinae (gazelles, springbuck, saiga), Bovinae (buffalos, bushbuck, nilgai), Reduncinae (kobs, waterbucks), Hippotraginae (Oryx), Cephalophinae (duikers), Alcelaphinae (hartebeests), and Aepycerotinae (impalas) subfamilies (2–6). PPR is caused by a non-segmented negative strand RNA virus belonging to the *Morbillivirus* genus, family *Paramyxoviridae*, and as such closely related to rinderpest virus. The clinical phase is characterized by high fever, ocular and nasal discharge, pneumonia, dyspnea, and severe diarrhea (1), with mortality and morbidity rates as high as 90 and 100%. However, depending on the susceptibility of the population, as well as the virulence of the pathogen itself, severity of clinical signs may be highly variable (7).

PPR virus (PPRV) is transmitted by direct contact with infected animals through excretions (oral, nasal, feces) (8). The virus cannot survive for long outside the host. The infectious period is short, and animals either die or recover with a lifelong immunity (9). Within herds, PPRV disseminates between animals in close contact. Between herds, disease transmission occurs when sharing pastures and/or water points, and at live animal markets. Infected livestock movements are responsible for virus spread over medium or large distances (10). PPRV is also suspected to circulate silently, occasionally causing sporadic epidemics when the host population's immunity levels are low (2). In areas of Africa where the disease is endemic, PPR exhibits a seasonal pattern with an increased number of outbreaks at the beginning of the cooler wet season (11). This seasonality may be related to an increased survival and spread of the virus facilitated during the coldest months. Furthermore, as the dry season is a period of nutritional stress for ruminants due to the strong reduction in the quality and the availability of forage resources, physiological conditions and health status of animals are altered and their resistance to infections thus reduced by the end of the dry season/beginning of the wet season (12). Wildlife is often considered to play a negligible epidemiological role in PPRV persistence and spread (4, 9, 13). However, recent outbreaks of PPR in wild sheep and goat species indicate that PPRV is likely to be transmitted between domestic small ruminants and wild ungulates that share the same pasture. The potential and the direction of these spill-overs are still poorly understood (14).

PPRV was first described in West Africa in 1940 (15), and later recognized as endemic in West and Central Africa (16). The disease subsequently spread into Eastern Africa. The presence of PPR in Ethiopia has been clinically suspected since 1977 but was confirmed for the first time in 1991 from an outbreak near Addis Ababa (17) and is now endemic (18). The circulation of the disease across Eastern Africa was subsequently shown through the detection of the virus and/or of antibodies to PPRV in Kenya (1999), Uganda (2005 and 2007) and more recently in Tanzania (2010) (19–22). PPR is nowadays widely spread in the whole of Africa and is endemic in most eastern African countries (2, 23). In the Comoros archipelago, located in the Northern Mozambique Channel about 300 km of the southern coast of Tanzania (**Figure 1**), the first PPR outbreak occurred in 2012 (24). According to the results of phylogenetic analyses, this outbreak could be due to the introduction of goats infected by PPRV lineage III from the African continent (24). Although the outbreak was rapidly under control, the risk of re-emergence of PPRV remains high since the Union of the Comoros has strong livestock trading relationships with the African continent, importing large and small ruminants all year round (25).

In the Union of the Comoros islands and in Eastern Africa, livestock production is one of the main sources of income for the rural population. PPR is thus an important concern for poverty alleviation. Indeed, PPR has a huge economic impact, because of its high mortality rate for small ruminants, and high production losses caused by weight loss and abortions when animals are infected (26). The significant impacts on household-level livelihood, well-being and food security, as well as on rural communities and national economies have made PPR a priority for eradication (9). Due to the effective live attenuated vaccine producing lifelong immunity against the four PPRV lineages after a single administration (27), mass vaccination is recognized as one of the most important pillars of the future eradication of PPR. However, these mass vaccination campaigns are costly and difficult to implement due to several factors including lack of information and awareness regarding the disease, a sparse knowledge of the small ruminant population demography, a quick turnover of small ruminant population, and high mobility (9). Moreover, small ruminant population sizes may be huge in affected countries. Thus, the vaccination effort needs to be intense to maintain the population immunity high enough to eradicate the disease. Lastly, sheep and goats have a lower *per capita* value than cattle, and owners may be sometimes reluctant to invest money for vaccination for these animals. As stated in Mariner et al. (9), reaching an efficient vaccination coverage at a national level is hardly possible. Yet, targeted vaccination in endemic areas and in well-defined populations could be an efficient tool to eradicate the disease at the source. A recent modeling survey in Ethiopia suggested that viral spread could be prevented if the proportion of immune small ruminants is kept permanently above 37% in at least 71% of pastoral village populations (28). However, further spatiotemporal information in PPRV distribution identifying areas suitable for PPRV transmission and spread and on a larger scale is necessary.

Given the high risk of re-introduction of PPRV in the Union of the Comoros and its high level of endemicity in large territories of Eastern Africa, there is a need for tools which could help in prioritizing vaccination areas and optimizing allocation of limited resources. In this study we used expert knowledge and available geographic data to conduct a Geographic Information System (GIS)-based Multi Criteria Evaluation (MCE) to identify areas at risk of PPR occurrence and spread in the Union of the Comoros and in four countries of Eastern Africa: Tanzania because of its proximity to the Union of the Comoros, and Kenya, Uganda

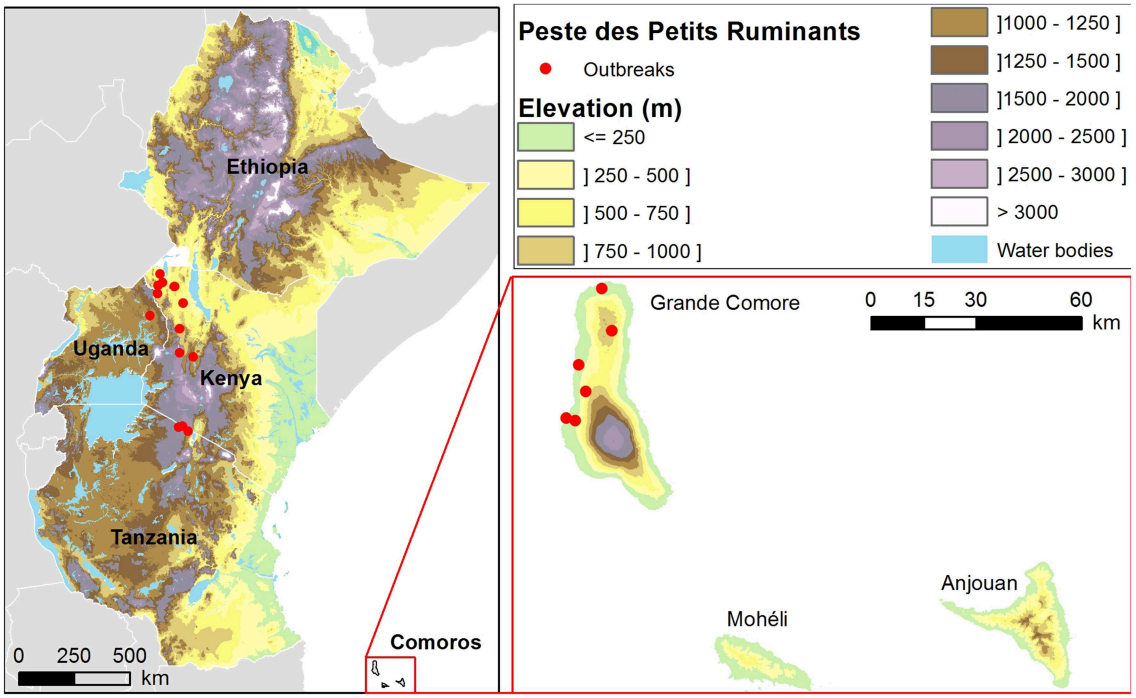

FIGURE 1 | Location of the study area and peste des petits ruminants outbreaks (Source: EMPRES-i database) reported between 2007 and 2018 in Ethiopia, Uganda, Kenya, Tanzania and the Union of the Comoros.

and Ethiopia because of their links with Tanzania through intensive intra-national and cross-border livestock trade. The objective was to provide a ready to use tool to implement PPR control strategies, in a context of PPR eradication by 2030 (29).

MATERIALS AND METHODS

Spatial MCE Approach

GIS-based MCE is a process that transforms and combines geographical data and value judgments to obtain appropriate and useful information for decision making (30). The general approach of spatial MCE method and its applications in epidemiology have been detailed elsewhere (31–36). GIS-based MCE is particularly relevant in the absence of available or reliable field-based disease surveillance data, as it can be used to create preliminary maps that, while imperfect, may be used for risk-based surveillance (33).

The key stages of this method include (i) the identification of the factors, or criteria, that play a role in the risk to be mapped (e.g., risk of introduction, amplification, spread, maintenance, etc.), (ii) the weighting of these factors based on expert opinions or bibliographic knowledge, (iii) the collection of geographical data corresponding to the factors identified, and the creation of spatial, standardized suitability indices, (iv) the combination of the spatial suitability indices to produce a risk map.

Identification of Environmental and Socio-Economic Factors for PPR Spread

Searches were performed in two journal databases (PubMed/Medline and ISI Web of Knowledge) with the keyword "peste des petits ruminants." Papers were screened and articles dealing with the identification of risk factors were taken into account (**Supplementary Table 1**). From this bibliographic review, the following factors were identified as potentially associated with the transmission and spread of PPR in livestock in the Union of the Comoros and Eastern Africa:

- The density of small ruminants (goats, sheep): since PPRV is transmitted through direct contact between infected and susceptible animals, its spread is affected by host density;
- The proximity to water bodies: water bodies such as rivers can be a gathering point for livestock, and thus increase the risk of contact between animals of different herds;
- The movement of animals for trade and/or transhumance: animal movements are a major cause for long-distance spread of PPR;
- The density of roads: this factor is used as a proxy for short-distance animal movements for trade purpose;

Additional risk factors were identified for Eastern Africa only:

- The density of camels;
- The density of railways: this factor is used as a proxy for animal movements for trade purpose. Although railway is not the primary mode of livestock transportation—a lot of movements

are on foot rather than by rail or road, it is used here as a proxy of the main axes linking cities which can be used by breeders and their animals to reach important livestock markets (37);
- The proximity to dry areas. Increasing risk is expected in dry and semi-dry areas where nomadic pastoralism is mostly practiced and more prone to livestock theft. Moreover, pastoralists often have larger herds than sedentary people - who can also rely on agriculture, and are less accessible to veterinarians;
- The proximity to protected areas as a proxy of the main areas where wild ungulates, a potential reservoir of PPRV, are present in large concentrations and where the wild/domestic ungulate interface occurs.

Weighting of the Factors Associated With PPR Occurrence and Spread

The results of questionnaires addressed to 14 PPR experts (authors having published more than two scientific publications on PPR epidemiology and/or risk factors) (38) were used to generate the weights of the risk factors of PPR occurrence and spread in Africa through an Analytical Hierarchy Process (AHP) (39). With this method, experts compare two criteria at a time: (1) experts firstly specify whether risk factor A is more or less important than risk factor B and (2) they specify the degree of importance of factor A regarding factor B on a nine-point scale (factor A can be extremely more important, very strongly more important, strongly more important, moderately more important, equally important, moderately less important, strongly less important, very strongly less important or extremely less important than factor B), resulting in a pair-wise comparison matrix. A numerical weight is derived for each risk factor from the pair-wise comparison matrix, and a consistency ratio (CR) is determined (40–42). Details on the calculation of the CR are provided in **Supplementary File 1**. The final weight value of each risk factor is the median value of the *n* weight values determined by the *n* experts.

For the Union of the Comoros, the weights of the following risk factors were set to zero: camel density, railways density, proximity to dry areas, proximity to protected areas, as these risk factors are not relevant for this country. The weights of the other risk factors were proportionally increased such that the sum of the weights equaled 1.

Collection of Geographical Data and Creation of Spatial, Standardized Suitability Indices

Geographical data were collected for each country (**Figure 1**) from different sources (**Table 1**), imported into a Geographic Information System (GIS), and processed to produce standardized spatial suitability indices with values ranging from 0 (completely unsuitable for occurrence and spread) to 1 (completely suitable) (GIS software: ESRI ArcGIS^{TM}, Spatial Analyst). The standardized spatial suitability indices for all countries were: sheep density, goat density, animal mobility index, road density, and proximity to water bodies. The animal mobility index was derived from the proximity to markets for eastern African countries, and from results from a mobility study for the Union of the Comoros (43). Additional standardized spatial suitability indices for eastern African countries were: camel density, railways density, proximity to wildlife national parks and proximity to dry areas. The calculation methods of the standardized geographical layers are provided in **Table 2**. At the end of the process, standardized spatial suitability indices were raster layers with pixel dimensions of 300 × 300 m, a good compromise between computational limitations due to the size of the study area (2,874,667 km^2) and the spatial resolutions of the different datasets. The correlation between the different suitability indices was assessed (**Supplementary Table 2**). The resulting maps for the standardized spatial suitability indices are presented in **Supplementary Figures 1, 2**.

Combination of the Spatial Suitability Indices

The standardized spatial suitability indices for PPR occurrence and spread (sheep density, goat density, animal mobility index, road density, proximity to water bodies, camel density, railways density, proximity to wildlife national parks, and proximity to dry areas) were combined using a weighted linear combination (WLC) with their corresponding weights (41). The resulting map is a suitability map for PPR occurrence and spread, with pixel values ranging from 0 (completely unsuitable) to 1 (completely suitable).

Assessment of the PPR Suitability Map

PPR outbreaks reported and geo-located between 2007 and 2018 were used to assess the consistency of PPR risk maps (Source: EMPRES-i database). In total, 23 PPR outbreaks, so called "presence," were recorded, including 13 outbreaks in Kenya, 3 in United Republic of Tanzania, 1 in Uganda, and 6 in Union of the Comoros (**Figure 1**, **Supplementary Table 3**). As no outbreaks were reported in Ethiopia, the assessment of the PPR suitability map could not be performed for this country.

One hundred locations of disease "pseudo absence" were randomly generated in the countries where PPR outbreaks occurred in continental Africa (Uganda, Kenya, and Tanzania), under the condition of being 25 km distant from other "absence" or "presence" locations (**Supplementary Figure 3**). In the Union of the Comoros, 6 locations of PPR "pseudo absence" were randomly generated in the Grande Comore Island, under the condition of being 5 km distant from other "absence" or "presence" locations, taking into account the size of the Comoros islands (**Figure 1**).

Then, the value of the quantitative suitability estimates for PPR occurrence and spread was extracted for each "presence" or "pseudo absence" location. The AUC (area under curve) of the ROC curve (44) was calculated to evaluate the capacity of the model to distinguish "presence" from "absence" locations with good predictive accuracy. The suitability maps were evaluated separately for (i) continental countries where outbreaks were reported (i.e., Kenya, Tanzania and Uganda) and (ii) the Union of the Comoros (pROC package, R software, https://cran.r-project.org/web/packages/pROC/index.html).

TABLE 1 | Factors associated with the transmission of peste des petits ruminants in livestock populations for which spatial data were available, the hypothesized relationship between each factor and risk of transmission of PPR, and the source of geographic data.

Criteria	Hypothesis	Data source
Sheep and goat densities	Increasing small ruminant density is expected to be associated with a higher contact rate between susceptible and infected small ruminants and therefore greater risk of PPR spread	Geographic data: GADM database of Global Administrative Areas (http://www.gadm.org) Livestock data: national reports (Ethiopian central statistical agency 2013; Ministry of Agriculture United Republic of Tanzania 2012; Uganda Bureau of Statistics 2002; Ministry of Agriculture Kenya—Animal production division 2009; Comoros national census 2004)
Water bodies	Decreasing distance from water bodies is expected to be associated with increasing risk of spread of disease through increase contact among animals	Eastern Africa: FAO Africover—Rivers and wetlands (http://www.fao.org/geonetwork/) Comoros: data from EU project Global Climate Change Alliance "AMCC-Comores" (https://amcc-comores.info/)
Small ruminants' markets	Increasing density of animal movements or trading areas providing live or freshly slaughtered small ruminants is expected to be associated with increasing risk of spread of PPR	Uganda Bureau of statistics Kenya and Ethiopia: FAO data (http://kids.fao.org/glipha/)
Cities as proxy of small ruminants' markets		Tanzania: AFRIPOP data (https://www.worldpop.org)
Animal mobility		Comoros: 2012–2013 mobility data (43) and 2014–2015 mobility data (data collected in the framework of ANIMALRISK project)
Roads and railways	Increasing density of roads and railways is expected to be associated with increasing movements of small ruminants for trade, and thus a higher risk of spread of disease although there is no published evidence for the direct role of roads or railways in the spread of PPR.	Eastern Africa: Digital Chart of the World (http://divagis.org) Comoros: data from EU project Global Climate Change Alliance "AMCC-Comores" (https://amcc-comores.info/)
Camel density	Increasing density of camels may be associated with a greater risk of spread	Map of predicted camels distribution in Africa and Middle East countries 2006 (Source: FAO)
Dry and semi-dry areas, as proxy of pastoralism	Increasing risk would be expected in dry and semi-dry areas where nomadic pastoralism is mostly practiced	Global Land Cover Map: Globcover 2009 (http://due.esrin.esa.int/page_globcover.php)
Wildlife national parks, as proxy for wild ruminants densities	Proximity to wildlife national parks may be associated with increased risk of spread of PPR	World database on protected areas (https://www.protectedplanet.net/)

RESULTS

The resulting weights of the factors associated with PPR occurrence and spread in the four countries of Eastern Africa and in the Union of the Comoros are presented in **Table 3**.

According to results of questionnaires, small ruminant densities were identified as the most important factors for PPR circulation and spread for all countries. In Eastern Africa, the proximity to dry areas was identified as the next important factor, followed by (in decreasing order) road density, camel density, proximity to water bodies, animal mobility index, proximity to wildlife parks, and railways density. In the Union of the Comoros, the animal mobility index and the road density were identified as important factors, followed by the proximity to water bodies.

Figure 2 presents the suitability map of PPR occurrence in Ethiopia, Kenya, Tanzania, Uganda, and the Union of the Comoros produced from the MCE process. In the text, we refer to green areas on the map (**Figure 2**) as very low (below 0.05) and low (between 0.05 and 0.1) risk for PPR occurrence and spread, and to yellow, orange, and red areas as medium, high and very high risk, respectively.

According to our model, in Ethiopia areas at high risk of occurrence and spread are mainly located in the highlands. The rest of the country is at medium risk, except for the horn of Ethiopia, and lowlands located in the south as well as in areas neighboring Sudan.

In Kenya, almost the whole country appears to be at risk, except the fertile plateau of the southeastern part. Areas identified at high risk by the model are mainly located on the northwestern part, including the Turkana region, an area constituting a mixed landscape with high altitudes plateau and lowland in the extreme north. A second area at risk is identified in a lowland region at the northeast side of the country. A third pocket at risk is highlighted in the center of the country, this region including both highlands and lowlands. The last area at risk, the Narok region, is neighboring Tanzania.

In Uganda, few areas are identified at high risk by the model, except a small region in the north east, overlapping with Karamodja region. North of Lake Victoria and areas surrounding Lake Kyoga are identified at medium risk, with some additional pockets in the southern extremity of the country, near Rwanda.

The majority of Tanzania is identified as medium or low risk by the model, except in the northeastern part of the country neighboring the boundary with Kenya.

In contrast to Eastern Africa, in the Union of the Comoros high risk areas are located mostly along the coast at low elevations. In Moheli, only very restricted areas are at high risk: the high risk areas correspond to the regions around the

TABLE 2 | Details of the geographic information systems manipulations required to convert the collected data into risk factor layers.

Suitability index raster	Collected data associated to PPRV transmission suitability	GIS manipulation	Scaling function
Sheep density	Districts (polygons) Table with number of sheep per district	Join geographic layer and table Calculate animal densities (nb animal/km²)	Positive linear relationship
Goat density	Districts (polygons) Table with number of goats per district	Join geographic layer and table Calculate animal densities (nb animal/km²)	Positive linear relationship
Animal mobility	Small ruminants' markets of Uganda, Ethiopia, and Kenya (points)	Calculate and map distance (km) to markets	Sigmoidal, monotonically decreasing relationship between 0 and 50 km, with negligible risk after 50 km
	Tanzania: population map (spatial resolution 0.000833333° ~900 m at the latitude of the study area)	Calculate and map distance (km) to areas with population densities >1000 inhab./km², with elevation map[a] as cost map	Sigmoidal, monotonically decreasing relationship between 0 and 50 km, with negligible risk after 50 km.
	Comoros: Districts (polygons) Table with number of imported animals per district	Join geographic layer and table	Positive linear relationship
Proximity to water bodies	Rivers and wetlands (polylines and polygons)	Calculate and map distance (km) to rivers and wetlands, with elevation map as cost map	Sigmoidal, monotonically decreasing relationship between 0 and 50 km, with negligible risk after 50 km.
Road density	Roads (polylines)	Calculate and map density of roads per 100 km²	Positive linear relationship
Railways density	Railways (polylines)	Calculate and map density of railways per 100 km²	Positive linear relationship
Camel density	Camel density map (resolution 0.000833333° ~900 m)	No manipulation required	Positive linear relationship
Proximity to dry areas	Land cover map (resolution 300 × 300 m)	Extract dry areas, calculate and map distance (km) to dry areas, with elevation map as cost map	Sigmoidal, monotonically decreasing relationship between 0 and 50 km, with negligible risk after 50 km
Proximity to wildlife national parks	Wildlife national parks (polygons)	Calculate and map distance (km) to: Conservation Area, Controlled Hunting Area, Game Controlled Area, Game Reserve, Game sanctuary, Hunting reserve, National Park, National Reserve, Nature Reserve, Sanctuary, Wildlife Reserve. Use elevation map as cost map	Sigmoidal, monotonically decreasing relationship between 0 and 100 km, with negligible risk after 100 km.

[a] *Source of elevation data: Shuttle Radar Topographic Mission (SRTM) downloaded from http://srtm.csi.cgiar.org/srtmdata/.*

two largest cities of the island, Fomboni and Nioumachoua. According to the model, the rest of the island is at middle to low risk for PPR occurrence and spread. In Anjouan the main area at risk for PPR suitability ranges from the North coast around the city of Ouani to the third largest city of the island, Tsembehou, located in a natural circus, a circular steep-sided hollow, in the middle of the island. The risk of PPR occurrence is more variable in Grande Comore. The main high risk areas are located around Moroni, the capital city, and in the southern extremity of the island. The northern part of the island is at low to very low risk for PPR transmission and spread, except the East coast.

The ROC AUC associated with the suitability map for PPR occurrence and spread in Eastern Africa (Kenya, Tanzania and Uganda) demonstrated the capacity of the model to distinguish "presence" from "absence" locations with very good predictive accuracy (AUC = 0.891; 95% CI [0.821–0.960]) (**Figure 3**).

According to the ROC analysis, the suitability map for PPR spread in Grande Comore, Union of the Comoros showed a very good fitting (AUC = 0.889, 95% CI: [0.694–1]).

DISCUSSION

The identification of areas at-risk for PPR is essential for implementing risk-based surveillance and control measures. To our knowledge, this is the first study aiming to produce regional suitability maps for PPR using GIS-MCE method combined with outbreak dataset validation.

TABLE 3 | Weights of the factors associated with risk of PPR outbreaks in Eastern Africa and the Union of the Comoros [in brackets: minimum and maximum weight values obtained from the questionnaires].

	Ethiopia, Kenya, Tanzania, Uganda	Union of the Comoros
Goat density	0.255 [0.180–0.345]	0.357 [0.224–0.490]
Sheep density	0.225 [0.135–0.276]	0.315 [0.192–0.387]
Road density	0.100 [0.020–0.301]	0.140 [0.062–0.456]
Proximity to water bodies	0.069 [0.015–0.077]	0.096 [0.028–0.172]
Animal mobility index	0.066 [0.044–0.161]	0.092 [0.058–0.093]
Proximity to dry areas	0.108 [0.030–0.127]	0
Camel density	0.094 [0.043–0.164]	0
Proximity to wildlife national parks	0.042 [0.021–0.171]	0
Railways density	0.041 [0.015–0.081]	0

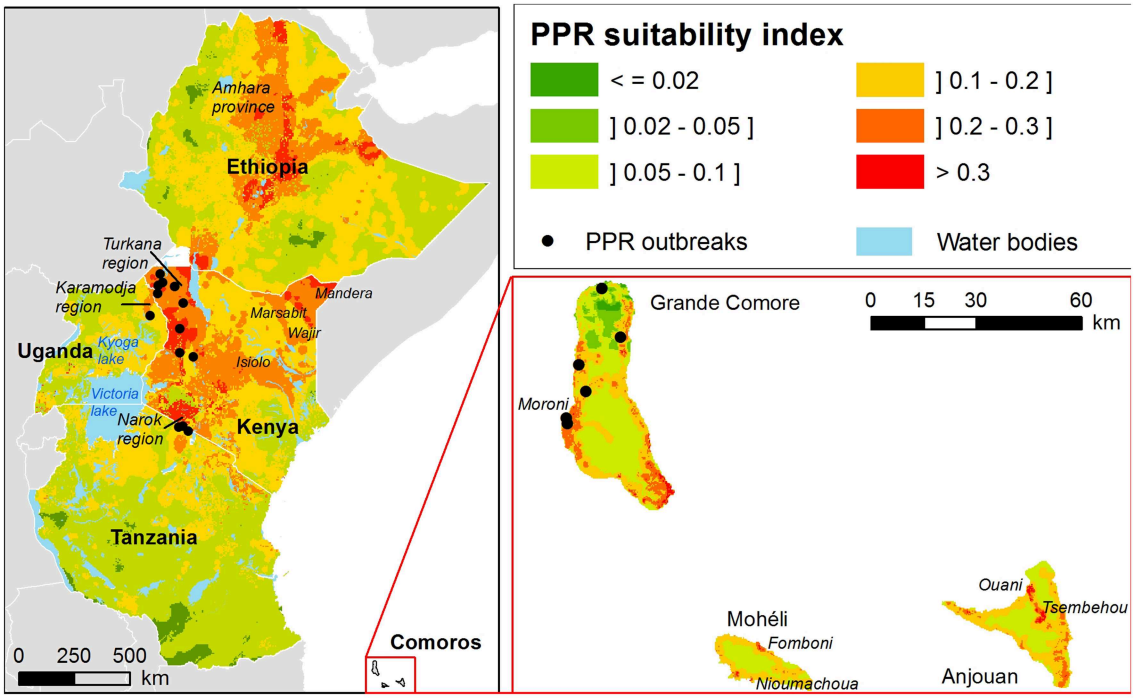

FIGURE 2 | Suitability maps for PPR outbreaks in Eastern Africa and the Union of the Comoros.

As a whole, there is a good consistency between areas identified at risk by the model and what is known about PPR circulation in the five countries of interest. In the next paragraphs, we discuss in detail the comparison of the obtained suitability maps and results of previous epidemiological studies, for each studied country. Regarding the eastern African countries, one should keep in mind that the number of outbreaks used for validation is very low compared to the surface of the territories studied. In addition, PPR outbreaks may be underreported in the four eastern African countries, where the disease is endemic and thus declaration non-mandatory. The validation results should therefore be taken with caution, and regularly re-assessed, as more cases are reported.

In Kenya, the Turkana region located in the north-western part of the country is identified as high risk: in 2011 in this area, PPRV Lineage III was detected from tissue samples collected from goats suspected of having died of PPR (45). The results of a seroprevalence study showed that 40% of the sheep (n = 431) and 32% of the goats (n = 538) sampled were seropositive (46). In 2016, PPR occurrence was confirmed in both camels and goats in the second main area identified at risk by our model, i.e., the north-eastern part of the country including Mandera, Wajir, Isiolo, and Marsabit districts (22).

In Tanzania, seropositive cases were found in the north-eastern part of the country during a nationwide surveillance in 2008–2013: this region is identified as a high to medium risky area by the model. As emphasized by Spiegel and Havas (47),

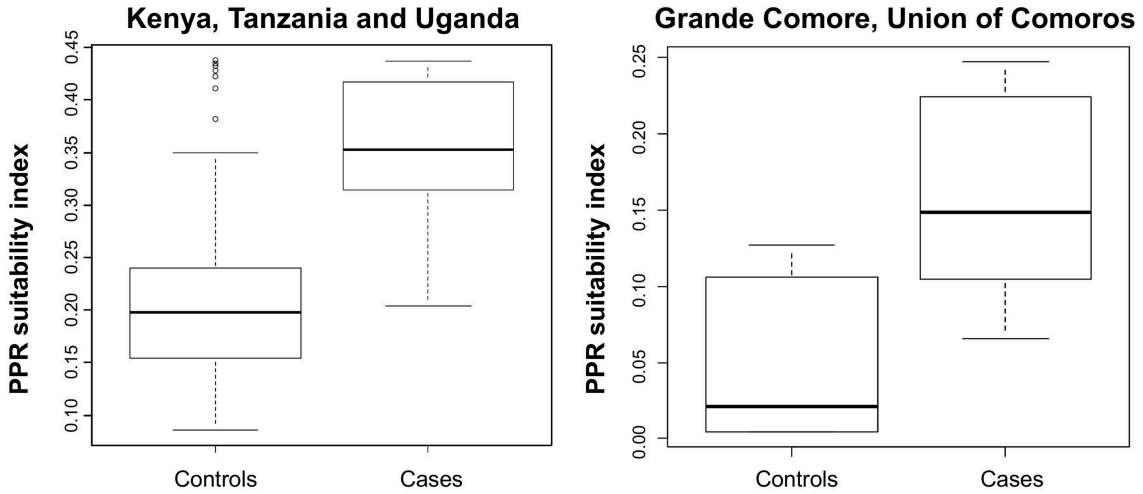

FIGURE 3 | Assessment of the suitability index for PPR occurrence in livestock in continental Eastern Africa countries where PPR outbreaks occurred (Kenya, Uganda, Tanzania) and in the Union of the Comoros. Box-plots showing PPR occurrence suitability index values for cases (PPR outbreak locations) and controls (random "pseudoabsence" locations) in continental Africa (left panel) and in the Union of the Comoros (right panel). Box-plots show median values (solid horizontal line), 50th percentile values (box-plot outline), 90th percentile values (whiskers), and outlier values (open circles).

the Tanzanian outbreak overlapped with trade routes that travel through Nakuru, in south-west Kenya, and go all the way to Nairobi and down into Tanzania. However, some cases were detected in the south of the Lake Victoria, identified as low risk by our model (23).

Little is known about PPR circulation in Uganda. Nevertheless, in 2007–2008 an outbreak occurred in sheep and goats in Karamodja region identified as at risk by our model. A survey was performed to characterize this outbreak: of the 338 small ruminants sampled, 38.1% (26/67) and 13.0% (41/316) of samples were found positive by PCR in 2007 and 2008, respectively (48).

PPR is known to be endemic in Ethiopia. However, few studies have been undertaken to document areas where the virus is currently circulating. The largest serosurvey, performed in 1999, demonstrated high seroprevalence rates in the Afar, Amhara, Oromia, Southern Nations, Nationalities, and Peoples' Region (SNNPR), Somali Tigray and Benishangul Gumuz regions (11). According to this work, areas of low altitudes, where pastoralists prevail, were more affected than highlands that are home to sedentary mixed livestock–crop farms (11). In 2010, lineage IV PPRV was isolated in Amhara region and a further study performed in eastern Amhara provides evidence of the continued spread of the same lineage in this area (49, 50). Our model, in accordance with these findings, identified the eastern Amhara as at high risk of PPR occurrence (**Figure 2**). Moreover, high seroprevalence of PPRV in small ruminants was reported in neighboring lowland pastoral areas (11, 18, 51, 52), identified at medium risk by our model. According to our model, highlands are at higher risk for PPR outbreaks than adjacent areas (**Figure 2**), which seems in apparent contradiction with the cited serosurveys. Yet, it should be noted that a large part of highlands could not be included in the sampling frame of the national serosurvey (11): high risk areas may have been missed. On the other hand, our results are consistent with a recent modeling study suggesting that the pastoral production system, mainly located in the lowlands act as a PPRV reservoir, and that the virus frequently spreads to the highlands through herd movements (28). Finally, it should be noted that (i) updated livestock census data would certainly improve the predictive accuracy of the model and (ii) the construction of GIS-MCE maps at regional scale may introduce a bias in suitability predictions at national level (with weights discussed with national experts). In particular, the weight of pastoral areas may be underestimated, which will strongly impact the suitability maps in Ethiopia, where pastoralism covers large areas.

In the Union of the Comoros, our model shows a good performance, although only few data from the 2012 outbreak were available. The 2012 outbreak was rapidly controlled, thanks to farmer practices, who slaughtered animals as soon as the first clinical signs were described by the animal health local authorities (24). These control measures limited the spread of PPR, and no outbreaks were reported in some areas identified at risk by our model (**Figure 2**). The majority of the Union of the Comoros is predicted to be at low risk by our model, which is in agreement with what one would expect. Indeed, farmers are sedentary and usually own few animals; the small ruminant population of the three islands is around 110,000 according to the 2004 census. The volcanic topography and the paucity of water bodies are likely to limit direct contact among animals. These factors play in favor of a lower risk for PPR spread in Union of the Comoros. However, because of the proximity with Eastern Africa and the historical trade link between the two areas, the Union of the Comoros remains at risk of introduction. Around 3,000 small ruminants are introduced every year in Moroni (**Figure 2**), capital city of Comoros and main entry port for livestock from

continental Africa. Most of the time, these animals are bought and slaughtered for "Grand Mariages" ceremonies, part of the Comorian culture. In some cases, animals are kept for improving the genetic level of herds. There is no quarantine on arrival and the animals are first kept in small size facilities belonging to the importers for few days before being moved either to local slaughtering places or introduced into a herd (53). In this context, combining the identification of areas at risk of PPR transmission with an assessment of the risk of introduction in the one main entry port, would allow the targeting of surveillance measures and a better allocation of available funds to limit pathogens introduction due to animal importations.

Studies have shown that PPR outbreaks are related to factors that promote hosts contacts such as livestock trade, husbandry practices, nomadism, as well as socio-economic and ecological factors (47, 54). In this work, we aimed to integrate all known risk factors and available associated geographic data. The main limitations of the produced maps are firstly related to the quality of the data used as risk factors. Small ruminant density is the most important risk factor in our study. In resource limited settings, animal censuses are often partial, occurring too rarely, leading to poor and not up-to-date data. More precise census data accounting, for example, for the number of animals per holding and its geographical location, would increase the precision of the resulting risk map. Secondly, as animal movements play a crucial role in the long distance spread of livestock disease (55), instead of using proxies (i.e., the proximity to markets), an exhaustive knowledge of the movement networks would improve the spatial risk factor for animal mobility. Third, the occurrence of outbreaks is strongly linked in endemic areas to interventions and control measures in place, as well as the immunity of the population: survival after infection resulting in lifelong immunity, herd population dynamics and renewal rates, as well as individual and herd level immunity are key factors that largely modulate the circulation of the virus in a given area. These factors were not incorporated in our model and this can result in discrepancies between the predicted suitability maps and results of epidemiological studies. Fourth, it must be stressed that our results include uncertainties inherent in the expert-based approach, regarding the relative importance of the different risk factors (**Table 3**). In the future, the weights of the different factors have to be re-evaluated according to scientific knowledge development (**Supplementary Table 1**), in particular regarding the role of camels or wildlife in PPR transmission, for which there is so far little evidence. Finally, it is worth noting that we used random generated "disease absence locations" for computing ROC AUC, assuming that absence of reported outbreaks is likely to result from an absence of the pathogen, which may not be true. The use of more extensive serological data from future studies, national surveillance datasets, or information extracted from published reports (56) could be easily integrated in the framework of the model validation and would make our results stronger.

In our study, the GIS-MCE method was applied to territories with different sizes, including small islands and continental countries. Our results demonstrated the effectiveness of the GIS-MCE method, which has been successfully applied at different geographic scales and settings. Indeed, the validation of the suitability maps using reported PPR outbreaks produced good results according to the ROC AUC method. These results suggest that the output regional-scale suitability maps have a reasonable predictive accuracy and could be used for risk-based surveillance and control purposes. As shown by rinderpest eradication, regional and international approaches should be combined for transboundary animal diseases (57, 58). The GIS-MCE method developed in this study intended to respond to this need. Applied to PPR at regional and international scales, it enables discussion among stakeholders and experts from the different countries concerned, and a comprehensive overview of the disease suitability areas.

In conclusion, the knowledge-driven approach proposed in this work to map the areas suitable for PPR occurrence and spread in Eastern Africa and Union of the Comoros provide valuable tools for several purposes: (i) to integrate the available knowledge about the disease; (ii) to provide suitability maps at regional scale using free geographic data. Applied in different geographical and epidemiological contexts (33, 34, 36, 59, 60), such an approach allows straightforward and easy updating of maps for users by including more precise geographic data, newly described risk factors, by modifying the weights of each factor, or by comparing scenarios of transmission. Another perspective of this work deals with the combination of the produced PPR suitability maps with modeling approaches accounting for temporal variability and transmission processes (28), in order to provide recommendations for vaccination strategies.

DATA AVAILABILITY STATEMENT

The datasets and PPR suitability maps of this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AT, VC, EC, and CC-S: conceptualization. AT, A-SR, and AW-S: data curation. AT, VC, A-SR, and AW-S: formal analysis. AT, VC, and AW-S: methodology. VC, EC, and CC-S: project administration. AT, VC, A-SR, AW-S, YM, and OC: resources. AT and A-SR: software and visualization. VC and CC-S: supervision. AT, VC, and A-SR: validation and writing—original draft preparation. All co-authors: writing—review and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00455/full#supplementary-material

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Willingness to Vaccinate (WTV) and Willingness to Pay (WTP) for Vaccination Against Peste des Petits Ruminants (PPR) in Mali

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PPR remains a major challenge to smallholder farmers in Mali. To understand the drivers of low adoption of vaccination by farmers, we analyzed the socio-economic factors influencing farmer WTV during and in the absence of vaccination campaigns. Given that the costs associated with vaccination are largely borne by farmers, we assessed factors that associated with farmer willingness to pay (WTP) more than the current price (150 XOF per dose) by considering two attributes of improvement of the vaccines empirically highlighted as potential leverage points for intervention: access of farmers to vaccines (reducing the distance to the vaccine) and availability of information about the quality of the vaccine (introducing a vaccine viability detector). Data were collected in Mopti and Sikasso regions from 304 producers. Overall ($n = 304$), 89 percent of respondents vaccinated their herds during official vaccination campaigns. They are associated with receiving information on the campaign calendar more quickly if information is relayed at places of worship and if they have an awareness of the benefits of vaccination, including the protection of third parties. Only 39 percent of respondents vaccinate outside vaccination campaigns. They are positively linked to the credibility of private veterinarians and a recognition of the vital importance of vaccines but are negatively associated with ignorance of vaccination needs and concern about vaccine side-effects. Both distance-effects and quality-tracker effects are associated with farmer willingness to pay more than the current vaccine prices. Farmers practicing semi-intensive production systems are willing to pay 20 percent more than the current vaccine prices, as are users who believe in the beneficial effects of vaccination, users who consider the prices of vaccines as fair, and those who believe that some vaccines are more important than others. Factors that discourage producers from vaccinating or from paying more for vaccination would be more effectively managed with better communication on vaccine benefits through targeted information dissemination campaigns by Malian authorities. Greater price transparency throughout the vaccine production and deployment chain is critical, while timely availability of vaccine tested for viability would increase the willingness to vaccinate while improving access.

Keywords: PPR, Mali, small ruminants, willingness to vaccinate (WTV), willingness to pay (WTP)

INTRODUCTION AND BACKGROUND

Livestock plays a critical role in Mali's economy. It represents 25% of the GDP of the primary sector and 11% of the national GDP. Livestock farming is the main source of income for over 30% of the population (1). At least 85% of rural households own domestic ruminants, with small ruminants (SR) representing a significant part of the livestock sector having ∼40 million heads in 2016 (2). SR keeping provides readily available cash in the face of family needs, a source of livelihoods, medium-term assets, protein for daily meals, and socio-cultural functions. However, the multifunctional role of SR is threatened by the high burden of diseases, such as Peste des Petits Ruminants (PPR).

The principal method of control for PPR is vaccination which is reflected in the Global Control and Eradication Strategy for PPR[1]. There are many vaccines that are commercially available and have shown to be effective for at least 3 years post-vaccination (3, 4). However, most of them require the application of a strict cold chain during their deployment in the field. It is important that all SR are vaccinated because introduction of unvaccinated animals into a naïve population presents a high risk. Thus, the PPR Global Control and Eradication Strategy recommends at least 80% of vaccination coverage for SR above 3 months old (5).

Despite heavy investment of the public veterinary services of Mali in vaccination campaigns against PPR, countrywide vaccination coverage for SR is very low at just 7% (6). Nonetheless, demand exists for PPR vaccines, especially where innovative delivery mechanisms can be deployed. For instance, reports from ongoing development projects showed that up to 55% vaccination coverage in specific communes of the regions of Sikasso and Mopti (7) is possible using participatory approaches through Innovation Platforms to increase stakeholder participation in vaccination. However, there are many challenges encountered by stakeholders in the process of vaccination in Mali. First, private veterinarians still complain of unfair competition from State veterinarians in properly carrying out vaccination. Furthermore, vaccine delivery systems are often not very effective in reaching all SR livestock producers, particularly women, due to logistical problems caused by poor infrastructure, such as roads to reach remote villages and the absence of vaccination parks for SR. In addition, the cost of vaccination in Mali is largely borne by livestock farmers, constituting a barrier to participation given that not all livestock producers can afford it and some livestock producers do not feel there is enough benefit from investing in vaccination. Some stakeholders argue that the limited participation of livestock farmers in vaccination is not caused by the perceived high cost of vaccination, but rather poor access to good quality vaccines, together with a lack of awareness about timing of vaccination campaigns (6, 8). The maintenance of the cold chain throughout the vaccine delivery might also be a constraint.

The objective of this study was to assess farmer perceptions about vaccination of SR livestock, with particular emphasis on their willingness to vaccinate (WTV) and willingness to pay for vaccination (WTP). For the WTP, as already highlighted by Dione et al. (9) and Sadio (8), we considered the delivery of the vaccines at the closest area of residency (termed "distance-effect") to facilitate accessibility and improved information on the quality of the vaccine (termed "quality tracker-effect" by introducing a vaccine viability detector[2]).

MATERIALS AND METHODS

Literature Review and Theoretical Framework

Decisions for vaccination, whether human or livestock, can often be more associated with religious and spiritual reasons, personal opinions, safety worries and additional information, beyond any knowledge of risks, costs, and benefits (10, 11).

Through a qualitative study, Abakar et al. (11) identified a number of demand-side barriers to vaccination, including mistrust of vaccination programmes/services and health system issues, among mobile pastoralists in Chad. Given the singular relationships of Sub-Saharan pastoralists to their herds (12), it seems reasonable that vaccination hesitancy and refusal might be an issue for immunization operations against animal diseases. Once the decision to vaccinate is taken, and given vaccination is not free in Mali, it would be important to better understand the root causes or drivers of individual decisions to pay for vaccination services.

One approach to gaining such understanding is through the concept of *willingness to pay,* which is defined as the maximum price a consumer accepts to pay for a product or a service (13–16).

There are two main ways to measure the willingness to pay. The first approach, based on revealed preference and pioneered by Samuelson (17), holds that consumer preferences can be expressed through what they purchase under different incomes and prices. This perspective represents evidence-based choices from market data and various types of experiments (laboratory and field experiments or auctions). The second approach is based on stated preference which tries to determine the total economic value by incorporating both non-use value and option value through contingent valuation, conjoint analysis or contingent choice methods. Derived from direct and indirect surveys, the stated preference approach has been popularized by studies of the willingness to vaccinate or to pay for vaccines against human diseases (18–24) and recently against animal diseases (25).

With regard to animal diseases, there is limited evidence describing the decision-making behind the vaccination of livestock. Elbers et al. (26) highlighted economic and social-psychological factors behind farmers' motivations to participate in a voluntary vaccination programme as well as their perceived need to actively be a part of the eradication campaign. Sok et al. (27–29) and Gethmann et al. (30) discussed the motivations, barriers, and willingness to vaccinate

[1]http://www.fao.org/emergencies/resources/documents/resources-detail/en/c/282777/

[2]Producers sometimes have a little trouble judging the quality of a vaccine. Some still use observations (such as the texture of the product) to get an idea of the quality and decide whether or not to vaccinate. Having a detector that can immediately show whether the vaccine is good or not could greatly help.

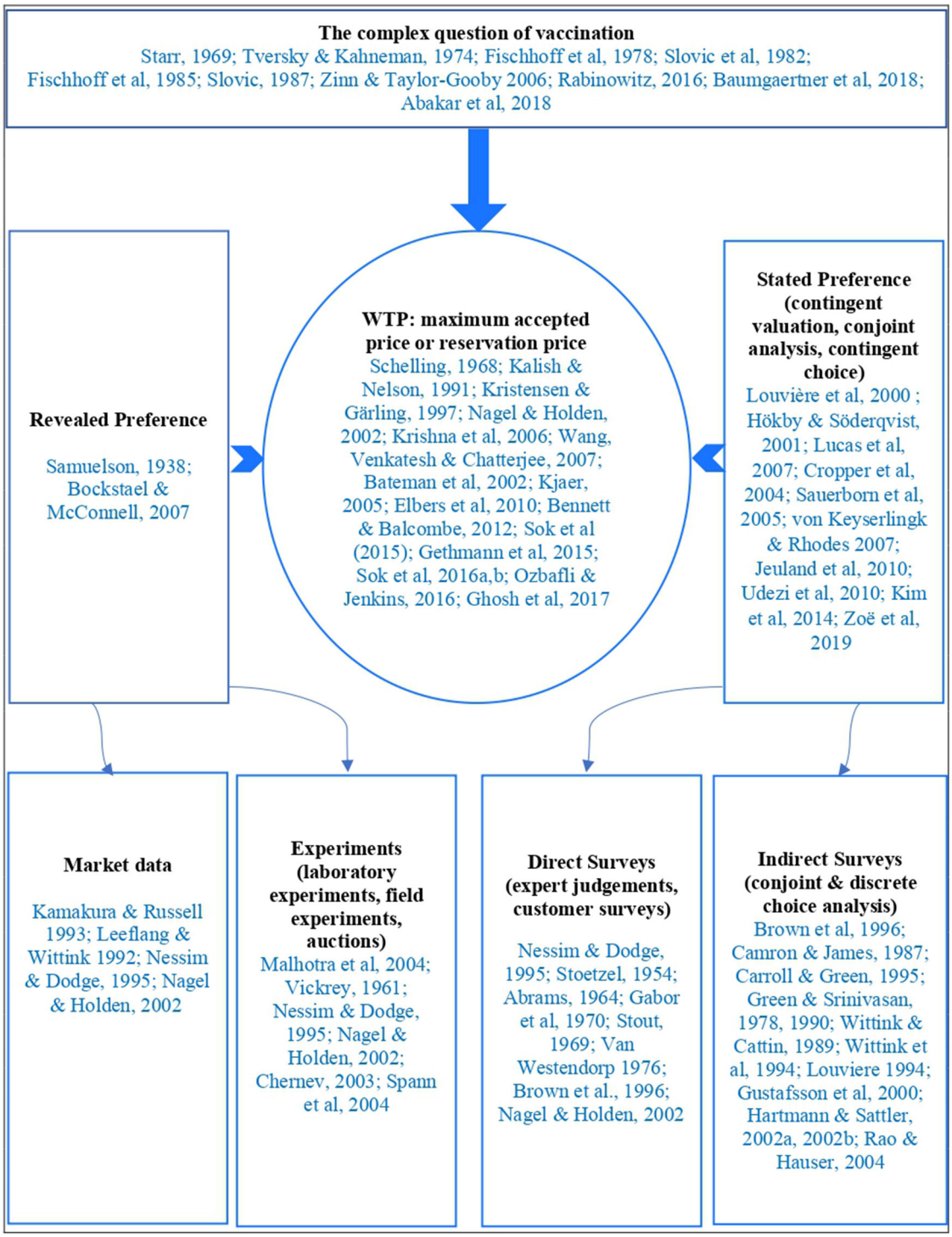
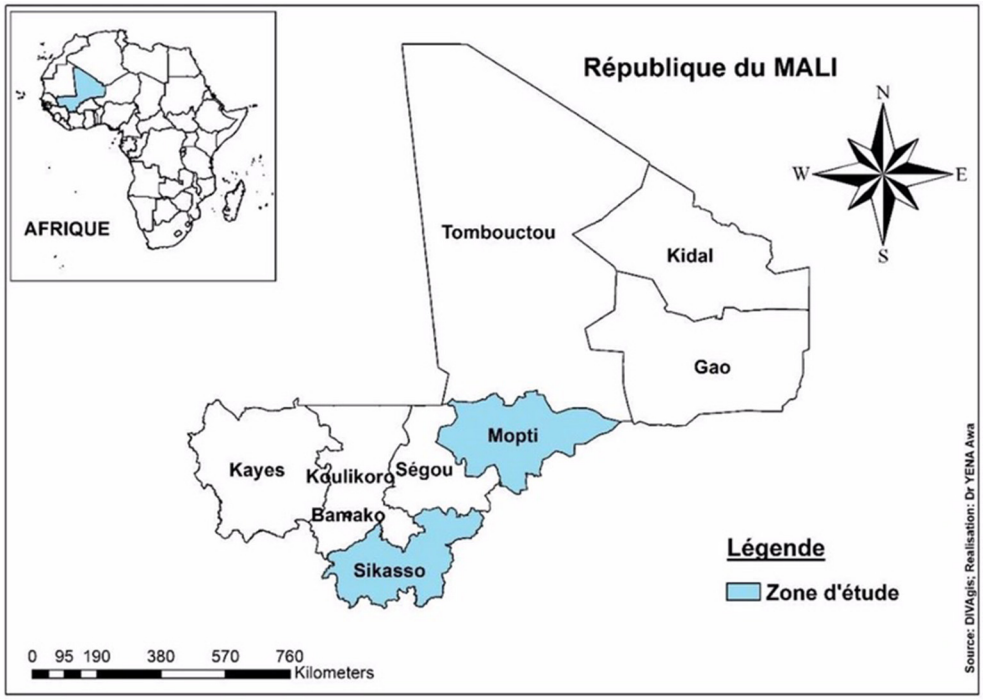


FIGURE 1 | Vaccination behaviors and measurement methods of consumer's willingness to pay.

against bluetongue disease, while Bennett and Balcombe (31) investigated farmers' willingness to pay for a bovine tuberculosis (bTB) vaccine. These studies, however, focused on animal diseases in Europe. Their findings may be different to the situation of West African countries where vaccine coverage is low, health delivery systems insufficiently meet current needs, and effective communication approaches and tools are lacking (**Figure 1**).



Map 1 | Localization of the study areas in Mali (in blue).

Methodology and Data

Objectives

Our overall objective is to assess the willingness of Malian livestock farmers to vaccinate (WTV) and their willingness to pay (WTP) for improved attributes of vaccines against PPR for SR. Two contingent concepts were analyzed separately, as some factors may affect WTV but not WTP for various reasons, such as farmer belief about the unfairness of vaccine pricing mechanisms. Therefore, we address two main questions:

i. ***For the WTV model****: What are the socio-economic determinants of the attitude of livestock farmers regarding vaccination against PPR, i.e., in terms of choosing to vaccinate or not?*
ii. ***For the WTP model****: What are the socio-economic determinants associated with the farmer willingness to pay more than the current price for improved accessibility to the PPR vaccine (distance-effect) and quality of the vaccine (quality-tracker effect)?*[3]

Survey Tool

A questionnaire (see Appendix) was designed to collect data on household demographic characteristics, Production systems, vaccination knowledge and practices, constraints of livestock producers to vaccination and farmer WTV and WTP for vaccination, considering vaccine accessibility and quality.

Sample Size

For our study, a sample was drawn from 4,254 producers who were identified as Feed the Future—Mali Livestock Technology Scaling (FTF-MLTS) program beneficiaries. We initially agreed to work with a margin of error of 3–5%, a confidence interval of 95% and a proportion of 50%. This involved selecting a sample size between 352 and 1,265 producers. Finally, due to access issues mainly related to insecurity[4] and limited budget, 304 livestock farmers keeping either SR only or SR and cattle were reached. Among these livestock producers, 50% were from Mopti and 50% from Sikasso region (**Map 1**).

Data Collection and Processing

The survey tool was designed on ODK (Open Data Kit) and transferred to Samsung tablets for electronic capture. In each region, trained field veterinarians and veterinary technicians were recruited to administer the questionnaire to livestock producers. The team leader of the field activities oversaw data cleaning and quality assurance every day after the enumerators returned from the field. Data was then uploaded to the server and downloaded in Excel and statistical files for further cleaning and analysis.

[3]Intuitively, it is worth bearing in mind that attributes that are to be focused on in the WTP work would come from the WTV analysis that precedes it. In this study, even though WTV is a sine qua non condition of WTP, we opted to test two key criteria related to access to vaccines and the true or false perception of the quality of vaccines.

[4]Mali is facing increased security threats and a protracted political crisis. This raises the security-risk level across the country and constraints interview-based fieldwork.

TABLE 1 | Description of variables used in the regression analyses.

Dependent variables	Independent variables (in order of appearance in the paper)	Modalities of independent variables (in order of appearance in the paper)
Willingness to vaccinate Yes = 1 No = 2	Information availability/access of/to vaccination campaign	Yes = 1 No = 2
	Information channel (multiple choices possible)	Radio = 1 Places of worship = 2 Town crier = 3 Word-of-mouth = 4
	Benefit of vaccination	Yes = 1 No = 2
Willingness to pay for vaccination No willingness to pay more = 0 Willingness to pay 5% more = 1 Willingness to pay 10% more = 2 Willingness to pay 20% more = 3	Cattle vaccination frequency	Every vaccination campaign = 1 Every year = 2 Many years = 3 Never = 4
	Vaccination protects others	Disagree = 1 Moderately agree = 2 Agree = 3
	Knowledge of vaccination needs	Yes = 1 No = 2
	Vaccination is vital for my animals	Disagree = 1 Moderately agree = 2 Agree = 3
	Private veterinarians (mandataries) are credible	Disagree = 1 Moderately agree = 2 Agree = 3
	Concerns about side-effects	Disagree = 1 Moderately agree = 2 Agree = 3
	Production system	Intensive production = 1 Semi-intensive production = 2 Extensive production = 3
	Animal species vaccinated	Cattle = 1 Sheep = 2 Goat = 3
	Fairness of PPR vaccine prices	Yes = 1 No = 2
	Some vaccines better than others	Yes = 1 No = 2
	Participation to vaccination campaign	Yes = 1 No = 2

The data were processed in several ways:

- *For willingness to vaccinate (WTV)*: Two binary variables were identified and used: (1) participation in vaccination campaigns and (2) use of vaccination outside of vaccination campaigns. To avoid overloading the analysis with a large number of variables, a correlation analysis was carried out to discriminate variables that have strong correlation with the identified binary variables.
- *For willingness to pay (WTP)*: Questions about WTP generated multiple responses which we considered as polychotomous dependent variables, requiring the use of a multinomial logistic regression.

Correlation and multicollinearity analysis allowed the identification of about fifteen independent variables for the estimation of WTV and WTP. Detailed explanations of the variables used in the regression analyses (described next) are presented in **Table 1**.

Regression Analyses

We used a generic binary logistic regression analysis to better capture the socioeconomic factors that are associated with WTV and a multinomial logistic regression (Gologit model) to analyze WTP.

Binary logistic regression reflects situations in which the observed outcome for a dependent variable can have only two possible categories. Our study on WTV deals with "To vaccinate" vs. "Not to vaccinate." For the multinomial logistic regression approach, its use represents situations in which the outcome can have three or more possible ordered or ranked responses. Our study on WTP involves multiple responses, such as "Not willing to pay a supplement," or "Willing to pay a supplement of 5%," "Willing to pay a supplement of 10%," or "Willing to pay a supplement of 20%" for potential improvements in access to a vaccine and information on the quality of the vaccine.

We can generalize the Gologit model used in this paper by generalizing the bivariate logit model and considering an ordered dependent variable taking j modalities, written as:

$$y_i^* = \theta_0 + \theta_1 x_{1i} + \ldots + \theta_k x_{ki} + e_i = e_i{}'\theta + e_i \quad (1)$$

where $x_1 \ldots x_k$ are the regressors that influence y^*, y_i^* is latent, and e_i is the error term. As in the binomial case, the y^* modalities would depend directly on the position of y^* with respect to different threshold parameters or cutoffs that demarcate the boundaries of the various categories:

$$y = \begin{cases} 1 \text{ if } y_i^* < c_1 \\ 2 \text{ if } c_1 \le y_i^* < c_2 \\ \quad . \\ \quad . \\ \quad . \\ J \text{ if } y_i^* > c_{J-1} \end{cases}$$

By defining F as the function for distributing error terms that follows a logistic law, we have:

$$Prob\left(y_i = 1\right) = Prob\left(x_i{}'\theta + e_i < c_1\right) = F\left(c_1 - x_i{}'\theta\right) \quad (2)$$

$$Prob\left(y_i = j\right) = Prob\left(c_{j-1} \le x_i{}'\theta + e_i < c_j\right) = F\left(c_j - x_i{}'\theta\right) - F\left(c_{j-1} - x_i{}'\theta\right),\ 2 \le J \le J - 1 \quad (3)$$

$$Prob\left(y_i = J\right) = Prob\left(x_i{}'\theta + e_i > c_j\right) = 1 - F\left(c_{j-1} - x_i{}'\theta\right) \quad (4)$$

The model coefficients θ are estimated by maximum likelihood. In addition, it is essential to understand and test an implicit hypothesis of this model, known as the parallel regression hypothesis, for the ordered logit model, and the odds proportion hypothesis (32–34).

Equations (2–4) can be used to derive the cumulative probabilities that are written in the simplified form by: $Prob\left(y_i \leq j\right) = F\left(c_j - x_i'\theta\right),\ 1 \leq j \leq J-1$.

These last equations show that the ordered regression model is equivalent to $J-1$ binary regressions under the fundamental assumption that estimated coefficients with respect to the explanatory variables are identical in each of the equations.

In contrast to binary models, interpreting the coefficients of an ordered model is complicated, especially for intermediate modalities. To do so, we calculate the marginal effects of variables on the probabilities (as in Equations 5–7) and resort to the transformation of coefficients into odds ratios or conditional probabilities.

$$\frac{\partial Prob\left(y_i = 1|\ x_i\right)}{\partial x_{ik}} \quad (5)$$

$$\frac{\partial Prob\left(y_i = j|\ x_i\right)}{\partial x_{ik}} \quad (6)$$

$$\frac{\partial Prob\left(y_i = J|\ x_i\right)}{\partial x_{ik}} \quad (7)$$

There are two ways to determine the overall marginal effects on the sample: evaluate at mean data value or evaluate for each observation and calculate the average of the individual marginal effects in the sample. For large samples, both methods give similar results. For our paper, we chose to calculate the marginal effects in relation to the median individual.

When outcome variables are ordinal, the ordinal logit model has been popularly used. However, some researchers, such as Williams (33, 34) prefer to use the Generalized ordered logit/partial proportional odds models (Gologit/ppo) as they provide more robust results even if the interpretation of model outcomes becomes more difficult. Therefore, Williams (33, 34) writes the Gologit model as:

$$P\left(Y_i > j\right) = \frac{\exp(\theta_i + X_i\beta_j)}{1 + \left[\exp\left(\theta_i + X_i\beta_j\right)\right]},\ with\ j = 1, 2, \ldots, M \quad (8)$$

where M is the number of categories of the ordinal dependent variable.

Finally, the probabilities that Y will take on each of the values $1, 2, \ldots, M$ can be determinated by:

$$P\left(Y_i = 1\right) = 1 - g\left(X_i\beta_1\right) \quad (9)$$

$$P\left(Y_i = j\right) = g\left(X_i\beta_{j-1}\right) - g\left(X_i\beta_j\right)\ with\ j = 2, \ldots, M-1 \quad (10)$$

$$P\left(Y_i = M\right) = g\left(X_i\beta_{M-1}\right) \quad (11)$$

Depending on the values of M, it would be possible to have an equivalent of a logistic regression model ($M = 2$), or a series of binary logistic regressions ($M > 2$).

Context and Study Area

Livestock vaccination is run through public-private partnership. It is mainly carried out by established private veterinarians called "*mandataires*" (or mandataries) under the supervision of the public veterinary services except in areas where these public veterinary services are not established. In high insecurity regions, vaccination is provided free of charge by the government or some development organizations. In contrast, private veterinarians fully recover the cost of vaccination from farmers. Every year, official vaccination campaigns for livestock are launched by the Government in early October and will last to March. However, given random sources of funding and mobility of livestock keepers, farmers who miss this vaccination campaigns can get their animals vaccinated by available veterinarians in their communities at any time of the year; this is referred to as "outside vaccination campaigns."

The FTF-MLTS program seeks to contribute to the inclusive growth of the ruminant livestock value chains for increased income, food and nutrition security for 266,000 cattle, sheep, and goat keepers and other value chains actors in three regions in the country (Mopti, Timbuktu and Sikasso), as a means of lifting them out of poverty. Supported by the United States Agency for International Development (USAID) as part of the US government's Feed the Future initiative, the program sets out to bridge ruminant livestock productivity gaps and to enhance the volume and value of ruminant livestock marketed through a wide-scale dissemination of proven livestock technologies and best practices. The FTF-MLTS program has made priority investments in designing and rolling out innovative approaches to increase vaccination coverage of SR and cattle against PPR and Contagious Bovine Pleuro-Pneumonia (CBPP), respectively and bovine/ovine pasteurellosis (7).

RESULTS

Contingent valuation methods for eliciting preferences for non-marketed goods are useful in addressing actor WTP. In this survey, we first asked farmers if they are willing to pay 20% more than the current PPR vaccine price, then 10% more and finally 5% more if the health services were delivered at the closest area of residency (distance-effect) to facilitate accessibility. The same questions were asked for improved information about the quality of the vaccine (quality-tracker effect).

Almost all livestock producers (96%) perceive tangible benefits of vaccines for herd size, as they expect fewer animal losses. However, while 44% of them are not aware that vaccinating their herds can also protect those of others, 29% thought that vaccination is required only during outbreaks, and 24% believed that vaccination serves to fatten animals.

Regression Analysis Results for the Willingness to Vaccinate (WTV)

Almost 89% of the 304 respondents vaccinate their herds during the vaccination campaigns formally organized by public authorities while 11% of them did not vaccinate. Outside formal vaccination campaigns, only 39% of respondents vaccinate their herds while 61% stated that they did not vaccinate outside the period of organized campaigns (**Table 2**).

Factors Associated With the WTV During Vaccination Campaigns

WTV during vaccination campaigns was found to be significantly associated with the availability, access and attributes of information provided about the vaccination campaigns (**Table 3**).

Given the prominent place of religions in Mali, places of worship play an important role for information sharing. Through them, information on vaccination campaigns is more effective in incentivizing actors to vaccinate their animals. Previous experiences with cattle vaccination could, however, constraint the care of small ruminants as this factor is negatively associated with the WTV. For an equivalent price per dose of vaccine, there seems to be a trade-off between the different species to protect. The respective odds ratio of each of these attributes, however, is relatively small, implying a limited effect on the probability of participating in vaccination campaigns.

In Malian rural areas, scrutiny and judgment of community members are important social values that reinforce peer effects. Recognition that vaccinating can help to protect herds other than those owned by themselves constitutes an important incentive for vaccination. With regard to the potential impacts on third parties, the farmers who agree that vaccination protects their herds have a WTV that is 129.4 times more often than the farmers who disagree.

Factors Associated With the WTV Outside Vaccination Campaigns

Even though only 39% of respondents claim to vaccinate their flocks outside of official vaccination campaigns, we observe that lack of knowledge about vaccination needs (different from vaccination benefits) and concerns about side-effects discourage actors from vaccinating (**Table 4**). This may be due to the presence of less experienced or non-trained technicians handling vaccination outside of official campaigns, leading to a greater incidence of side effects due to poor vaccination techniques. On the other hand, the credibility of private veterinarians (referred to as the variable "Mandataries are credible") and the recognition of the vital importance of the vaccines were all shown to have a positive effect on their WTV. The strong odds ratios indicate that farmers who moderately and fully agree that vaccination is vital have a WTV that is 243 to 262 time higher compared to farmers who disagree (**Table 4**).

TABLE 2 | Distribution of farmers' responses on vaccination participation.

Variable	Modalities	Numbers	%
Vaccination campaign	Yes: 1	272	89.474
	No: 2	32	10.526
Outside the vaccination campaign	Yes: 1	119	39.145
	No: 2	185	60.855

Regression Analysis Results for Willingness to Pay (WTP) for Vaccination

We recoded the variables and created new ones to allow their use in an ordered logit regression: ***Distv*** and **Qv** were the

TABLE 3 | Factors associated with the WTV during vaccination campaigns.

Logistic regression **LR chi^2(10) = 155.38**
Number of observations = 304 **Log likelihood = −24.606224**
LR chi2(10) = 155.38 **Pseudo R^2 = 0.7595**

Variables		Coefficient	Odds Ratio	95% confidence interval		*P*-value
Information availability/access	Yes*					
	No	−4.8	0.008	0.0008	0.0874	<0.001
Information channel	Radio*					
	Places of worship	2.7	0.070	0.0043	1.1342	0.061
	Town crier	1.0	0.364	0.0277	4.7699	0.441
	Word-of-mouth	0.7	0.506	0.0513	4.9889	0.560
Benefit of vaccination	Yes*					
	No	−2.3	0.102	0.0147	0.7134	0.021
Cattle vaccination frequency	Every vaccination campaign*					
	Every year	−4.1	0.016	0.0012	0.2357	0.002
	Many years	−5.7	0.003	0.00005	0.2184	0.007
	Never	−4.3	0.014	0.0006	0.3557	0.010
Vaccination protects others	Disagree*					
	Moderately agree	0.8	2.279	0.1125	46.1685	0.591
	Agree	4.9	129.431	1.1750	14257.18**	0.043

A common practice would consist to fuse the reference category with the other levels of the variable that are not significantly different from the reference category. We proceed to these supplemental analyses but this process did not give conclusive results. For the "Information channel" variable, the new reference category resulted from the regrouping provided p-values of 0.868 and 0.771 for the odds ratios.

**Reference category.*

***Abnormally wide confidence interval can raise with small sample size or when some variables have several categories with small frequencies.*

TABLE 4 | Factors influencing the WTV outside the vaccination campaigns.

Logistic regression						
Number of observations = 304			**Prob > chi^2 = 0.000**			
LR chi^2-11 = 78.37			**Pseudo R^2 = 0.1926**			
Variables		**Coefficient**	**Odds ratio**	**95% confidence interval**		***P*-value**
Information channel	Radio*					
	Places of worship	0.1	0.9	0.2	3.9	0.936
	Town crier	1.1	0.3	0.1	0.9	0.038
	Word-of-mouth	0.9	0.4	0.1	1.2	0.106
Knowledge of vaccination needs	Yes*					
	No	−1.0	0.4	0.2	0.8	0.006
Vaccination is vital for my animals	Disagree*					
	Moderately agree	5.5	243.3	10.8	5,477.8**	0.001
	Agree	5.6	261.8	14.6	4,689.0**	<0.001
Private veterinarians (mandataries) are credible	Disagree*					
	Moderately agree	1.3	0.3	0.1	1.2	0.080
	Agree	2.2	0.1	0.0	0.4	0.002
Concerns about side-effects	Disagree*					
	Moderately agree	−2.3	0.1	0.0	0.3	<0.001
	Agree	−1.2	0.3	0.1	0.7	0.004

**Reference category.*

***Abnormally wide confidence interval can raise with small sample size or when some variables have several categories with small frequencies.*

TABLE 5 | Distribution of dependent variables on the WTP for distance and quality parameters.

Distv	**Freq.**	**Percent**	**Cum.**	**Qv**	**Freq.**	**Percent**	**Cum.**
0	43	14.14	14.14	0	39	12.83	12.83
1	11	3.62	17.76	1	9	2.96	15.79
2	40	13.16	30.92	2	38	12.50	28.29
3	210	69.08	100.00	3	218	71.71	100.00
Total	304	100.00		Total	304	100.00	

variables measuring the willingness to pay a premium for vaccine delivery to be significantly shortened and for a quality-tracker to be implemented on the vaccine packages, respectively. Their modalities are: "1" if the farmer is willing to pay 5% more on the current price of the vaccine; "2" if he/she is willing to pay 10% more; "3" if he/she is willing to pay 20% more and "0" if he/she refuses all three options and therefore does not want to pay anything more on the price of the vaccine. From field investigations, a large majority of farmers (69% and 71%) say they are willing to pay 20% more than the current price of the dose of PPR vaccine if, respectively, the delivery distance and quality-tracking of the vaccines are improved (**Table 5**). It should be noted that between 13 and 14% of farmers say they are not prepared to pay more regardless of the improvement made in the delivery and quality-tracking of vaccines, respectively.

A generalized ordered logit (Gologit) model was used to address shortcomings of the ordered logit model and parallel-lines model as stated by the Brant's test (33, 34), which rejected the parallel regression assumption (**Table 6**).

TABLE 6 | Test of parallel regression assumption.

	Chi^2	***df***	***p* > Chi^2**
Brant	44.21	14	0.000

Based on the existing literature, our knowledge of the Malian context, and the use of a stepwise approach, the following predictive variables were included:

- *For the distance-effect-**Distv***: "Production system," "Animal species vaccinated," "Mandataries are credible," "Fairness of PPR vaccine prices," "Benefit awareness," "Some vaccines better than others," "Cattle vaccination frequency."
- *For the quality-tracker effect-**Qv***: "Production system," "Animal species vaccinated," "Mandataries are credible," "Fairness of PPR vaccine prices," "Benefit awareness," "Some vaccines better than others," "Cattle vaccination frequency," "Vaccination campaign participation."

Finally, the regression was done successively on the distance-effect (**Distv**) and the quality-effect (**Qv**).

For the Distance-Effect: Distv

Table 7 shows that, all other things being equal, farmers in semi-intensive production systems, those who perceive that PPR vaccine prices are fair, that vaccination is beneficial, including the comparative advantage of PPR vaccines, are willing to pay a premium if the physical access of vaccines is improved.

The regression analysis further reveals that the coefficients for "Production system" and "Benefit awareness" do not vary

TABLE 7 | Regression analysis results for the distance-effect.

Dependent variable: Distance-Effect (WTP 0%, 5%, 10%, 20)		Generalized ordered logit model					
		Distv = 0		Distv = 1		Distv = 2	
Independent variables		Coefficient	t-statistic	Coefficient	t-statistic	Coefficient	t-statistic
Livestock production system	Extensive*						
	Semi-intensive	−0.868	0.010	−0.868	0.010	−0.868	0.010
	Intensive	0.074	0.952	0.073	0.952	0.074	0.952
Benefit of vaccination	Yes*						
	No	−1.925	0.007	−1.925	0.007	−1.925	0.007
Fairness of PPR vaccine prices	Yes*						
	No	−2.733	0.000	−2.151	0.000	−1.367	0.000
Some vaccines better than others	Yes*						
	No	−0.465	0.263	−1.059	0.003	−1.178	0.000
Constant		3.576	0.000	3.474	0.000	2.514	0.000

**Reference category.*

across the categories of the response variable, i.e., the distance-effect. This means "Production system" and "Benefit awareness" have positive impacts on the distance-effect. Therefore, the more the farmers in semi-intensive production system are aware of the benefits of vaccination, the greater their willingness to pay a premium for a shorter vaccine delivery distance.

These trends are visible only through sign and significance at this stage. To improve the quality of interpretation of the regression results (**Table 8**), we tabulate the marginal effects and coefficients into odds ratios or conditional probabilities.

Farmers declare that they are willing to pay a higher price than the current vaccine price if physical access to it is improved by a significant reduction in the distance of supply and also if other conditions are met. When farmers consider the price of PPR vaccines to be fair, their probability of paying 20% more than the current price of a vaccine dose increases by 73%. When they are well aware of the beneficial effects of vaccination against PPR, the probability increases by 71%. When farmers are in semi-intensive production system, the probability of paying 20% more increases by 65%. When they believe that some vaccines are better than others, the probability increases by 61%.

For the Quality-Tracker Effect: Qv

WTP for improved quality tracking of PPR vaccines is associated with the same significant variables: "Production system," "Benefit awareness of PPR vaccination," "Fairness of the PPR vaccine prices," and "Comparative advantages of some vaccines" (**Table 9**). When respondents indicate "No" to one or more of these variables, this has a negative impact on WTP for a vaccine-quality tracker. Thus, when a farmer is frustrated about these variables (e.g., feels prices are not fair), it reduces their willingness to pay a premium above the current vaccine prices (**Table 9**).

If they are convinced that vaccine prices are fair, their probability of paying 20% more on the current price of vaccines increases by 77% (**Table 10**). In the same way, if they are aware of the benefit of PPR vaccination, the probability for paying the vaccines 20% more is 73% (**Table 10**). The practice of semi-intensive production activities also leads them to an increase in the probability of paying 20% more to 68% if the quality of vaccines is improved. And finally, the awareness of farmers about the relative comparative advantage of some vaccines increases their probability of paying 20% more for vaccines than their current prices by 82% (**Table 10**).

TABLE 8 | Marginal effects of the variables used in the model on distance parameter.

	Marginal effects	t-statistics	95% confidence interval	
Fairness of PPR vaccine prices				
Pr(Distv = 0); independent variable = 1	0.076	0.000	0.043	0.109
Pr(Distv = 1); independent variable = 1	0.045	0.001	0.019	0.071
Pr(Distv = 2); independent variable = 1	0.144	0.000	0.102	0.186
Pr(Distv = 3); independent variable = 1	0.735	0.000	0.683	0.786
Benefit awareness				
Pr(Distv = 0); independent variable = 1	0.127	0.000	0.093	0.162
Pr(Distv = 1); independent variable = 1	0.034	0.001	0.014	0.053
Pr(Distv = 2); independent variable = 1	0.131	0.000	0.093	0.168
Pr(Distv = 3); independent variable = 1	0.708	0.000	0.658	0.758
Production system				
Pr(Distv = 0); independent variable = 2	0.167	0.000	0.126	0.208
Pr(Distv = 1); independent variable = 2	0.039	0.000	0.017	0.061
Pr(Distv = 2); independent variable = 2	0.143	0.000	0.102	0.184
Pr(Distv = 3); independent variable = 2	0.650	0.000	0.592	0.709
Some vaccines better than others				
Pr(Distv = 0); independent variable = 2	0.155	0.000	0.109	0.202
Pr(Distv = 1); independent variable = 2	0.064	0.001	0.028	0.101
Pr(Distv = 2); independent variable = 2	0.172	0.000	0.117	0.226
Pr(Distv = 3); independent variable = 2	0.608	0.000	0.540	0.677

DISCUSSION

PPR is a concern for the Malian livestock sector where the vaccination coverage is still very low. Although effective vaccines are available, the disease remains endemic for various reasons. Many of these reasons relate to the willingness of livestock producers to vaccinate or to pay for vaccination. Our study focused on socioeconomic factors influencing the WTV and

TABLE 9 | Regression analysis results for the quality-effect.

Dependent variable: Quality-Effect (WTP 0%, 5%, 10%, 20)		Generalized ordered logit model					
Independent variables		**Qv = 0**		**Qv = 1**		**Qv = 2**	
		Coeff.	**t-statistic**	**Coeff.**	**t-statistic**	**Coeff.**	**t-statistic**
Fairness of PPR vaccine prices	Yes*						
	No	−2.911	0.000	−2.592	0.000	−1.565	0.000
Benefit of vaccination	Yes*						
	No	−1.722	0.019	−1.722	0.019	−1.722	0.019
Some vaccines better than others	Yes*						
	No	−0.956	0.001	−0.956	0.001	−0.956	0.001
Participation to vaccination campaign	Yes*						
	No	0.528	0.336	0.528	0.336	0.528	0.336
Livestock production system	Extensive*						
	Semi-intensive	−0.838	0.026	−0.838	0.026	−0.838	0.026
	Intensive	−0.214	0.858	−0.214	0.858	−0.214	0.858
Constant		4.018	0.000	3.592	0.000	2.458	0.000

**Reference category.*

TABLE 10 | Marginal effects of the variables used in the model on quality parameter.

	Marginal effects	**t-statistics**	**95% Confidence Interval**	
Fairness of the PPR vaccine prices				
Pr(qv = 0), Independent variable = 1	0.065	0.000	0.036	0.095
Pr(qv = 1), Independent variable = 1	0.030	0.004	0.010	0.050
Pr(qv = 2), Independent variable = 1	0.139	0.000	0.010	0.181
Pr(qv = 3), Independent variable = 1	0.765	0.000	0.715	0.815
Benefit awareness				
Pr(qv = 0), Independent variable = 1	0.117	0.000	0.084	0.150
Pr(qv = 1), Independent variable = 1	0.029	0.002	0.010	0.047
Pr(qv = 2), Independent variable = 1	0.122	0.000	0.086	0.158
Pr(qv = 3), Independent variable = 1	0.733	0.000	0.684	0.781
Production system				
Pr(qv = 0), Independent variable = 2	0.151	0.000	0.110	0.192
Pr(qv = 1), Independent variable = 2	0.033	0.002	0.012	0.054
Pr(qv = 2), Independent variable = 2	0.137	0.000	0.096	0.178
Pr(qv = 3), Independent variable = 2	0.679	0.000	0.619	0.739
Some vaccines more important than others				
Pr(qv = 0), Independent variable = 1	0.081	0.000	0.046	0.116
Pr(qv = 1), Independent variable = 1	0.018	0.008	0.005	0.031
Pr(qv = 2), Independent variable = 1	0.083	0.000	0.047	0.119
Pr(qv = 3), Independent variable = 1	0.818	0.000	0.751	0.885

WTP for vaccines against PPR in Sikasso and Mopti regions in Mali. The study led to interesting findings which highlight a number of important policy implications.

First, the place and function of beliefs in the decision-making process are often neglected, even though they can validly be the result of rational behavior. Vaccination programmes against animal diseases are mostly evaluated by using availability and access to vaccines. Although these two elements are very important, it appears that farmer beliefs associated with their participation in vaccination programmes are crucial to understand their decision-making process to vaccinate or pay for vaccination (26–30). The challenge of considering farmer beliefs and perceptions about vaccination is to better understand their behavior, but also to develop appropriate policy instruments to increase their participation in vaccination campaigns and improve the effectiveness and efficiency of voluntary vaccination strategies (26). Our study places greater emphasis on the behavior of farmers and shows that their decisions are based on their perceptions of the characteristics and effects of vaccination against PPR.

Second, market orientation (semi-intensive production) plays an important role in the willingness to pay for vaccination. The use of fattening operations, while still maintaining some flexibility for animal mobility, suggests a stronger market orientation compared to the extensive system. Vaccination, even when paid for, appears to be a part of this strategy, more than in other production systems.

Third, our results show that making information on vaccination campaigns more accessible and livestock producers more aware of the benefits of vaccines, may change their WTV and WTP. This requires working both on the content and form of information dissemination. The information must go beyond simply informing livestock producers about the dates and periods of vaccination campaigns. Rather, such information needs to effectively communicate the positive role of vaccines in the control of animal diseases; on their protective effects on the herd and those of neighbors; and their potential side effects, whether positive or negative.

Dissemination of information through different media, such as places of worship, communal radio stations, mouth-to-mouth, etc. have proven to be somewhat effective, though future research must accurately assess these platforms in greater depth. All these media require physical access while there are great opportunities to expand information access through innovative ways with the growing accessibility of internet-based web applications and mobile phones in this country.

Fourth, the results highlight the negative impact of livestock farmers' perceptions about inequity of vaccine prices. Our study does not directly show this; however, discussions we had after the study indicate that farmers seem to perceive differentiated (and unfair) vaccine pricing between cattle and SR that does not consider the differences in size and value of each species. This involves trade-off behaviors between vaccinating cattle and small ruminants. They do not seem to be aware of the costs of producing and deploying the vaccines to be considered. Therefore, the Malian authorities might benefit from including greater price transparency throughout the vaccine production and deployment chain by facilitating an equal access to and greater clarity about price information. For instance, enhanced communication about the subsidies supported by Malian authorities could help in this transparency.

Fifth, regarding farmers' trust of private veterinarians, the FTF-MLTS program took an important step to address this lack of trust through better planning of vaccination campaigns using participatory approaches vaccination delivery through Innovation Platforms (IPs). Preliminary results show that IPs have been able to strengthen trust between farmers and private veterinarians, consequently improving performance of vaccination campaigns (9).

Finally, results of our model clearly suggest that distance and quality perceptions are critical issues underpinning farmer willingness to pay for improved vaccines. Developing logistical support and efficient supply chains that improve access to vaccines in a timely manner is critical. Porphyre et al. (35) showed that the initial availability of vaccine stock at the start of an outbreak significantly contributes to optimal control strategies for disease outbreaks. Therefore, development of basic infrastructure and control of the cold chain are critical in the implementation of optimal health delivery systems. This can explain the respondents' desire and WTP for a test that shows them whether a vaccine is viable.

The main limitation of this study is intrinsically linked to the inaccessibility of some areas due to the security problems that have characterized the country for more than a decade. This security situation is even more tense in the livestock areas in particular from Mopti region to the extreme Northern part of the country. Thus, the sampling of households to be surveyed was carried out only in accessible areas, particularly those targeted by the FTF-MLTS program. Based on our survey results, this area's PPR vaccination participation rates (89% during and 39% outside of campaigns), seem relatively high compared to estimates of the country's overall PPR vaccination coverage of 7%. Therefore, our survey sample and results might not reflect all relevant drivers of WTV or WTP for livestock farmers throughout the country.

Another limitation is that dichotomous and polychotomous categorial variables were used with two or more categories or levels. Responses from livestock producers can be too narrow in relation to the question, such that they create or magnify bias that is not factored into the survey. For instance, on the question about satisfaction with vaccines, people might be satisfied with the intrinsic quality of vaccines but upset about the behavior of vaccinators. Combining our approach with a more quantitative approach on the household economics allowing to collect data related to household income, expenditures and budgets might help to refine further the analysis. In addition, a qualitative approach (e.g., open-ended interviews) could also help to clarify some of the producers' responses.

CONCLUSION

This study focused on livestock farmers' attitudes and behaviors around vaccination, identifying socioeconomic factors that are associated with WTV animals and WTP for vaccination. These factors could be effectively managed by improving information on the benefits of vaccination, confidence in the viability of vaccines upon arrival at producers' herds, the qualifications of private veterinarians in charge of vaccination, vaccine pricing transparency, and improved information sharing about vaccination campaigns.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was implemented in the framework of a larger programme that aimed at improving access of livestock producers to veterinary inputs in Mali. All participants to this specific study were already enrolled by the programme to receive interventions for increasing vaccination coverage against PPR in their areas. For the individual interviews, informed oral consents were obtained from all participants. In addition, an official approval was obtained from the National Directorate of Veterinary Services in accordance with their national mandate to carry out post-vaccination sero-monitoring for PPR and evaluate vaccination campaigns in the target regions (approval reference number N0057/MEP-DNSV).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial contribution to the work and approved for publication. MD, AW, AF, and BW conceived the study. AW, MD, and AY supervised the data collection and performed the preliminary data analysis. MD, BW, and AF developed and implemented the PPR control in Mali. AW and KR supervised and performed the economic analysis on WTV and WTP.

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REVIEW
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Expanding Diversity of Susceptible Hosts in Peste Des Petits Ruminants Virus Infection and Its Potential Mechanism Beyond

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Peste des petits ruminants (PPR) is a severe respiratory and digestive tract disease of domestic small ruminants caused by PPR virus (PPRV) of the genus *Morbillivirus*. Although the primary hosts of PPRV are goats and sheep, the host range of PPRV has been continuously expanding and reported to infect various animal hosts over the last decades, which could bring a potential challenge to effectively control and eradicate PPR globally. In this review, we focused on current knowledge about host expansion and interspecies infection of PPRV and discussed the potential mechanisms involved.

Keywords: *Morbillivirus*, peste des petits ruminants, peste des petits ruminants virus, susceptible hosts, expanding, potential mechanism

INTRODUCTION

Peste des petits ruminants (PPR) is a highly contagious fatal viral disease of small ruminants characterized by fever, pneumonia, diarrhea, and inflammation of the respiratory and digestive tracts. The morbidity and mortality rates of PPR can reach up to 100%. Therefore, it has a severe socio-economic impact in the livestock industry in countries whose economy relies on small ruminants, particularly in endemic poor countries. After the successful global eradication of Rinderpest (RP) in 2011, the Food and Agriculture Organization (FAO) and World Organization for Animal Health (OIE) have targeted PPR as the next aim for its global eradication. The etiological agent PPR virus (PPRV) is a member of the genus *Morbillivirus,* family *Paramyxoviridae* and order *Mononegavirales.* PPRV primarily infects goats and sheep, but over the last decades the host range of PPRV has been continuously expanding to many other non-natural hosts by unknown mechanisms.This indicates that PPRV has a potential capability of adapting to various new hosts, which might impact on the successful implementation of the PPR global eradication plan. In this review, recent epidemiological findings of PPRV are summarized based on transmission and evolution in relation to PPRV host expansion and interspecies infection, and the potential mechanism beyond was then discussed.

GLOBAL DISTRIBUTION OF PESTE DES PETITS RUMINANTS VIRUS

Peste Des Petits Ruminants Virus Spreads Alarmingly Over Last Decades

Since its first report in 1942 in Cote-d'Ivoire, PPR has spread far beyond its origin in Western Africa (**Figure 1**). In 1999, the prevalence of PPRV antibodies was reported to be 29.2 and 20% in sheep and goats in Turkey/Europe, respectively (18). PPRV reemerged in many African countries including Tanzania (2008 & 2013) (7, 39), Kenya (2014) (40), Democratic Republic of Congo and Angola (2012) (41), and in North Africa such as in Tunisia (2012–2013), Morocco (2015), Algeria (2014) (42–44), and Burundi (2017) (45). In Asia, the virus spread to China in 2007 and again in 2013, spreading rapidly throughout 22 provinces (46–48), and from 2013 to 2014, PPR was also reported from countries surrounding China such as India, Vietnam, and Pakistan where high level of antibody to PPRV was observed in small domestic ruminants and wildlife (49). A risk assessment of PPRV infection in developing countries indicated that ∼63% of small ruminants were at risk of infection (50). Therefore, over the last two decades, PPR dissemination has increased exponentially. According to OIE data, PPR was reported in 39 countries in 2007, 43 countries in 2013, and is present in over 70 countries across Asia, Africa, and Europe (**Figure 1**). As a result, PPR affects 30 million small ruminants yearly, resulting in the economic loss of approximately US$1.2–1.7 billion (42, 43, 51–53). Therefore, following the global eradication of Rinderpest (RP) in 2011, which is the first animal disease and the second disease to have been eradicated in the world, the World Organization for Animal Health (OIE) and Food and Agriculture Organization (FAO) have identified PPR as the next target for eradication by 2030.

Peste Des Petits Ruminants Virus Origin and Evolutionary Relationship Among *Morbilliviruses*

As a member of *Morbilliviruses*, PPRV is a negative-sense, single-stranded RNA virus of ∼16,000 nucleotides (nt), which consists of six open reading frames encoding for six structural proteins: Nucleocapsid (N), Phosphoprotein (P), Matrix (M), Fusion (F), Hemagglutinin-neuraminidase (HN), Large RNA-dependent polymerase (L), and two non-structural protein (C and V) (27). The HN and F proteins are embedded in the viral envelope, which constitute the fibers of the virion surface. Only one serotype of PPRV is so far known. However, phylogenetic analysis based on the small region of the N/F gene classifies PPRV into four distinct lineages (I–IV) (41, 54). In comparison to the phylogenetic analysis based on the N, F, M, and HN genes, HN gene seems to be more important to evaluate the epidemiology and the circulating PPRV in endemic areas (55), which may be due to the fact that HN protein is a major determinant for the host tropism. For many years PPR was considered as a variant of RP, specifically adapted for goats and sheep and have lost its virulence

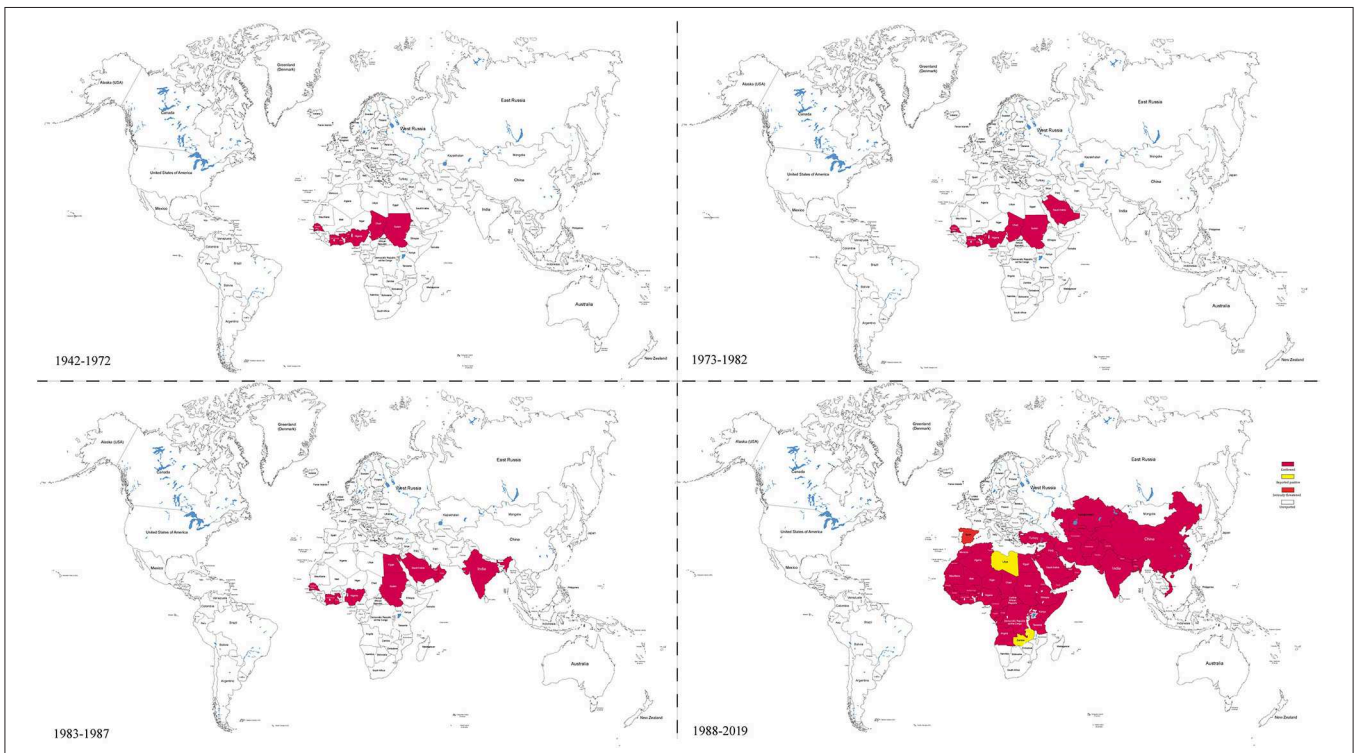

FIGURE 1 | Global distribution of PPRV at different time periods. This figure is drawn according to the relevant reports of PPR and the **Table 1** references by Illustrator CS6 software. It shows that the PPRV spread from west to east and the infection is rapidly expanding.

for cattle. However, it is now revealed that the PPRV and RP virus (PRV) are biologically and epidemiologically distinct although they are closely related antigenically.

Until 1988, the genus *Morbillivirus* was thought to comprise only four viruses, namely, Measles virus (MV), PPRV, RPV, and Canine distemper virus (CDV) (56). Later on, three new morbilliviruses have been identified, namely, cetacean morbillivirus (CeMV), phocine distemper virus (PDV) (57–60), and feline morbillivirus (FmoPV or FMV) (61). Previously, clinical description and analysis of the genetic relationship suggested that MV may have originated from an ancestral morbillivirus, and RPV was believed to be the most ancient of morbilliviruses (62–65). Phylogenetic tree of morbilliviruses based on H gene indicated that the genetic relationship of MV and PPRV was the closest of morbilliviruses, and phocine distemper virus (PDV) and CDV were located on the same evolutionary branch (**Figure 2**). However, the genetic relationship of FmoPV and the other morbilliviruses was highly distant. Molecular evolution analysis of the viruses suggested that the time to the most recent common ancestors (TMRCA) of PPRV/MV/RPV first appeared during 1616 [95% HPD (highest posterior density) 1072–1859] (66). A TMRCA of PPRV was estimated to be in 1904 (95% HPD 1730–1966). Considering the prediction of TMRCA as reasonable and referring to the evolutionary origin theory of measle viruses, it is also possible to estimate that PPRV may have evolved from the ancient virus (RPV). Although, the first description of PPRV was documented in 1942, it was revealed as a new member of the genus *Morbillivirus* based on the biological and biochemical characteristics in 1979 (67). A study on the phylogenetic analysis of PPRV HN gene (68) exhibited that PPRV strain which caused an outbreak in China in 2007 was not the ancestor virus which caused an outbreak in China in 2013–2014. Around the twenty-first century, genetic diversity of PPRV dramatically increased and caused many outbreaks of PPR as described above. The reasons for this phenomenon are not fully understood, but this could be due to the impact of the RPV eradication program which may promote PPRV to spread rapidly.

CROSS-SPECIES INFECTION OF PESTE DES PETITS RUMINANTS VIRUS

Expanding Diversity of Susceptible Hosts

PPRV primarily infects domestic goats and sheep, in which mortality can reach up to 100%. However, there are increasing reports of PPRV infection in other domestic and wild animals with or without showing clinical symptoms (**Table 1**).

PPR Infection in Cattle and Buffaloes

PPRV infection was also reported from cattle and buffaloes. A serological survey of 2,159 bovine samples from Southern Peninsular India between 2009 and 2010 showed the prevalence of PPRV antibody to be 5.21 and 4.82% in cattle and buffaloes, respectively (5). Further analysis of 1,498 samples collected in 2011 indicated the overall seroprevalence of 21.83% with 16.20% in buffaloes and 11.07% in cattle (6), while a high seroprevalence of 41.86% in cattle and 67.42% in buffaloes was reported from Pakistan (2). Recent serological survey detected PPRV antibodies at the rate of 17.5 and 22.5% in cattle and buffaloes, respectively (3). Additionally PPRV infection in Buffaloes (*Syncerus caffer)* was also reported in Tamil Nadu state, India (4). Experimental study showed that calves infected with PPRV developed subclinical signs of PPRV infection along with specific anti-PPRV antibodies (69). PPRV can be isolated from Peripheral blood mononuclear cell (PBMC), but the virus was not detected from oral, nasal, and rectal swabs by ELISA/RT-PCR assays (69), indicating that cattle is unlikely to pose a risk in transmitting PPRV to other animals. Nevertheless, the persistence of PPRV in infected calves for long periods is still unknown (69). Also, this study emphasizes on the importance of an investigation as to whether goat or sheep maintain PPRV for long periods subclinically. A recent study (70) also reported that the cattle infected with wild-type PPRV from each lineage (Lineage 1 strain CIV89, lineage strain 2 Nigeria 75/3; lineage 3 strain Ethiopia, and lineage 4 strain India-Calcutta) neither showed any sign of PPRV replication in the epithelial cells nor the transmission of PPR virus to in-contact animals such as goats. Similarly, a higher seroprevalence of 42% (420/1000) among cattle populations in the Sudan was reported when tested by competitive ELISA (71). Even though the infected cattle did produce specific anti-PPRV antibodies as in the previous studies mentioned above (69), cattle are unlikely to act as a PPRV reservoir and to play a role in the maintenance and transmission of PPRV because these findings indicated that cattle are a dead-end host for PPRV.

PPRV Infection in Camelids

There have been several reports of PPRV infection in camels. Serological survey undertaken earlier in 1995 after the occurrence of a rinder-pest-like disease syndrome in the camel population in Ethiopia showed a global seroprevalence of 7.8% for PPRV antibodies in camels (72), indicating the occurrence of PPRV infection in camels. Subsequent serological survey on naïve camels and other ruminants in Ethiopia in 2001 showed that the prevalence of the PPRV antibody to be 3% in camels, which was less compared to cattle (9%), goats (9%), and sheep (13%) (8). In addition, PPRV-positive serology in camels has been documented in other countries, with prevalence of PPRV antibody varying from 14/100 (12), 38/49 (10), 214/474 (11), and 51/1517 in Nigeria (9). A recent serological survey detected PPRV antibodies at the rate of 41/1988 (14). In addition to detection of antibodies in camels, an outbreak of PPR in camels with 7.4% mortality was reported in Sudan in mid-August 2004 (13), indicating camels may be susceptible to PPRV under field conditions. While investigating the prevalence of PPR in camels in different areas of Sudan, PPRV antigen was detected in 45.1% (214/474) of the tested pneumonic lung specimens of clinically healthy camels using immunocapture ELISA (11). Further investigation on PPR in domestic ruminants of Sudan from 2008 to 2012 showed that PPR antigen was detected in 33.6% of the lung tissue samples of camels ($n = 1,276$), which was higher than that in goats (21.1%), sheep (15.4%), and cattle (12.3%) (14). A number of studies have also been

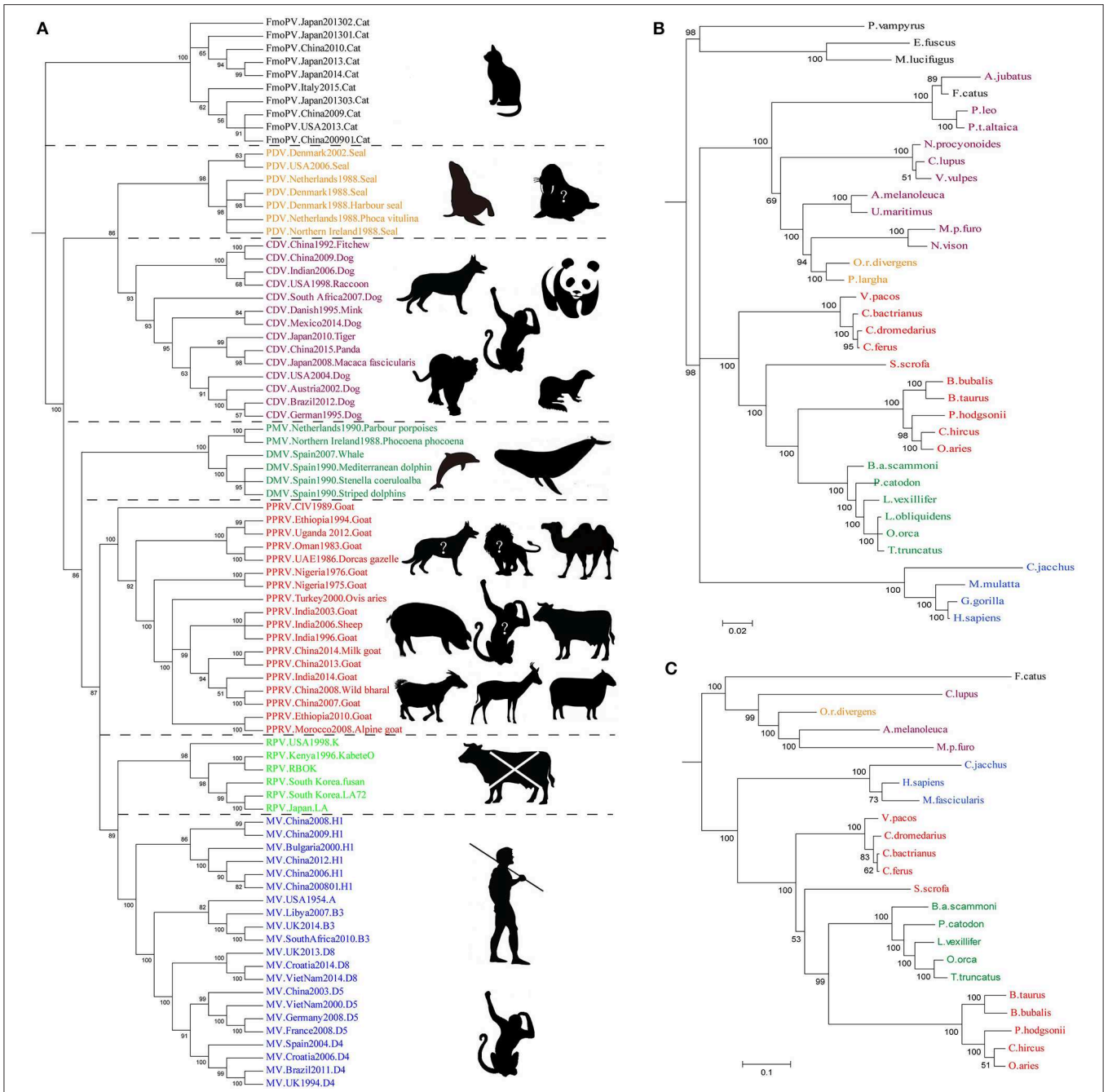

FIGURE 2 | The Bayesian Phylogenetic tree was constructed based on *Morbillivirus* Hemagglutinin and its receptors SLAM and Nectin-4 gene. **(A)** The genetic relationship of MV and PPRV was the closest of morbilliviruses, and PDV and CDV were located on the same evolutionary branch. The genetic relationship of FmoPV and the other morbilliviruses was highly distant. In the right side of the tree, the host or suspicious host exhibits a broad host range of the viruses. The animals tagged with "?" represent potentially infected hosts. **(B,C)** Phylogenetic tree of SLAM and Nectin-4. The evolutionary tree shows that the evolution of the H seems to be strongly associated with the evolution of the SLAM and Nectin-4 receptor, especially in the Nectin-4. The sequences which are used to construct the Bayesian Phylogenetic tree GenBank accession numbers are listed in **Table 2**.

performed in Ethiopia (2001) and Nigeria (2011–2013) giving evidence to the presence of PPRV antigen in camels (8, 9) and supporting that camels could be infected by PPRV. Even though there was an outbreak of PPR in camels in mid-July 2013 in Iran with devastating clinical signs caused by lineage IV PPRV (15), experimental infection showed that camels infected with a virulent PPRV strain (lineage IV) did not develop any clinical symptoms of the disease, and no virus was detected in secretions although seroconversion was observed after 14 days of post-infection (73).

TABLE 1 | PPR infection cases in diverse animals except domestic small ruminants.

Name	Latin name	Country	Time sampling	Positivity	References
Buffaloes	*Bubalus bubalis*	Cote d'Ivoire	2005	-	(1)
		Pakistan	2006	60/89	(2)
			2009	34/240	(3)
		India	1995	50/385	(4)
			2009–2010	48/1001	(5)
			2011	67/432	(6)
		Tanzania	2014	5/10	(7)
Camelids	*Camelus dromedarius*	Ethiopia	2001	10/628	(8)
		Nigeria	2011–2013	51/1516	(9)
		Sudan	2000–2009	38/49	(10)
			2000–2012	214/474	(11)
			2002	14/100	(12)
			2004	-	(13)
			2008-2012	41/1988	(14)
		Iran	2013	-	(15)
		Kenya	2016	1/25	(16)
Cattle	*Bos primigenius taurus*	Ethiopia	2001	46/910	(8)
		Pakistan	2006	18/43	(2)
			2009	24/240	(3)
		India	2009–2010	60/1158	(5)
			2011	67/605	(6)
		Tanzania	2011	46/266	(17)
		Turkey	1999–2000	3/321	(18)
			2009	22/122	(19)
		Sudan	2002	4/35	(12)
			2008–2012	387/1501	(14)
Argali	*Ovis ammon*	China	2013–2016	-	(20)
Afghan Markhor goat	*Capra falconeri*	UAE	2008–2009	-	(21)
Arabian gazelles	*Gazella gazella*	UAE	2008–2009	-	(21)
Arabian mountain gazelles	*Gazella gazella cora*	UAE	2008–2009	-	(21)
Bharals	*Pseudois nayaur*	China	2007–2008	3/4	(22)
Barbary sheep	*Ammotragus lervia*	UAE	2008–2009	-	(21)
Bushbucks	*Tragelaphus scriptus*	UAE	2008–2009	-	(21)
Capra ibex	*Capra ibex sibirica*	China	2013–2016	-	(20)
Dorcas gazelles	*Gazella dorcas*	Saudi Arabia	2002	138/230	(23)
		Sudan	2016–2017	8/11	(24)
Goitered gazelle	*Gazella subgutturosa*	China	2013–2016	-	(20)
		Tanzania	2014	20/30	(7)
		Turkey	-	10/82	(25)
		Sudan	2008–2012	5/23	(14)
Ibex	*Capra ibex*	China	2015	-	(26, 27)
Impala	*Aepyceros melampus*	Tanzania	2014	3/3	(7)
		UAE	2008–2009	-	(21)
Nubian ibex	*Capra nubiana*	UAE	2008–2009	-	(21)
Rheem gazelles	*Gazella subgutturosa marica*	UAE	2008–2009	-	(21)
Sindh Ibex	*Capra aegagrus blythi*	Pakistan	2009	13/20	(28)
Springbuck	*Antidorcas marsupialis*	UAE	2008–2009	-	(21)
Thomson's gazelles	*Gazella thomsoni*	Saudi Arabia	2002	5/5	(23)
Wildebeest	*Connochaetes gnou*	Tanzania	2014	1/2	(7)
White-tailed deer	*Docoileus virginianus*	USA	1979	Ex	(29)
Wild goat	*Capra aegagrus*	Iraq	2010–2011	3/4	(30)
		Iran	2014	-	(31)
			2015	-	
			2016	-	
			2001	-	
Wild sheep	*Ovis orientalis*	Iran	2011	-	(31)
			2015	-	
Water deer	*Hydropotes inermis*	China	2016	-	(32)
Lion	*Panthera leo persica*	India	-	-	(33)
Dog	*Canis familiaris*	India	2015	3/12	(34)
Pig	*Sus scrofa*	UK		Ex	(35)
					(36)
Mice	*Mus musculus*	UK	2000	Ex	(37)
Midges	*Culicoides imicola*	Turkey	2016	7/12	(38)

"-" represents not mentioned and Ex represents experimentally infected.

TABLE 2 | Morbillivirus Hemagglutinin and its receptors gene sequences used for comparison study.

Name of *Morbillivirus* HN gene sequence	GenBank accession numbers
Feline morbillivirus(FmoPV)	
FmoPV.Japan2013 (01,02,03).Cat	AB924122, (AB910311, AB924120, AB924121)
FmoPV.Japan2014.Cat	AB910310
FmoPV.China2009 (01).Cat	JQ411014, (JQ411015)
FmoPV.China2010.Cat	JQ411016
FmoPV.USA2013.Cat	KR014147
FmoPV.Italy2015.Cat	KT825132
Phocine distemper virus (PDV)	
PDV. Denmark2002. Seal	AF479274
PDV.USA2006.Seal	HQ007902
PDV.Netherlands1988.Seal	KC802221
PDV.Denmark1988. Seal	Z36979
PDV.Denmark1988. Harbor seal	FJ648456
PDV.Netherlands1988. Phoca vitulina	AJ224707
PDV.Northern Ireland1988.Seal	D10371
Canine distemper virus (CDV)	
CDV.Austria2002.Dog	GQ214378
CDV.Brazil2012.Dog	KT429765
CDV.China1992.Fitchew	KM926612
CDV.China2009.Dog	HQ403645
CDV.China2015.Panda	KP677502
CDV.Danish1995.Mink	Z47759
CDV.German1995.Dog	X85000
CDV.Indian2006.Dog	AM903376
CDV.Japan2008.Macaca fascicularis	AB687721
CDV.Japan2010.Tiger	AB619774
CDV.Mexico2014.Dog	KT266736
CDV.South Africa2007.Dog	FJ461717
CDV.USA1998.Raccoon	AY548111
CDV.USA2004.Dog	EU716337
Cetacean morbillivirus	
DMV.Spain1990.Mediterranean dolphin	AJ224705
DMV.Spain1990.Striped dolphin	AY586536
DMV.Spain1990.Stenella coeruleoalba	HQ829973
DMV.Spain2007.Whale	HQ829972
PMV.Netherlands1990.Parbour porpoises	AY586537
PMV.Northern Ireland1988. Phocoena phocoena	FJ648457
Peste des petits ruminants virus (PPRV)	
PPRV.China2008.Wild bharal	JX217850
PPRV.China2007.Goat	JF939201
PPRV.Ethiopia2010.Goat	KJ867541
PPRV.Ethiopia1994.Goat	KJ867540
PPRV.Oman1983.Goat	KJ867544
PPRV.CIV1989.Goat	EU267273
PPRV.Nigeria1976.Goat	EU267274
PPRV.Nigeria1975.Goat	X74443
PPRV.Uganda2012.Goat	KJ867543
PPRV.UAE1986.Dorcas gazelle	KJ867545
PPRV.Turkey2000.Ovis aries	NC006383
PPRV.Morocco2008. Alpine goat	KC594074
PPRV.China2014.Milk goat	KP260624
PPRV.China2013. Goat	KM091959
PPRV.India2003.Goat	FJ750563
PPRV.India2006.Sheep	EU344744
PPRV.India2014.Goat	KR261605
PPRV.India1996.Goat	GQ452016
Rinderpest virus (RPV)	
RPV.South Korea.fusan	AB547189
RPV.Kenya1996.KabeteO	X98291
RPV.USA1998.K	Y18816
RPV.South Korea.LA72	JN234008
RPV.RBOK	Z30697
RPV.Japan.LA	M17434
Measles virus (MV)	
MV.Bulgaria2000.H1	FJ808736
MV.Brazil2011.D4	KC291546
MV.China2003.D5	EU914221
MV.China2006.H1	JN997514
MV.China2008(01).H1	JN997523 (JN997516)
MV.China2009.H1	JN997527
MV.China2012.H1	KJ136543
MV.Croatia2006.D4	JX126962
MV.Croatia2014.D8	KT337320
MV.France2008.D5	GQ428197
MV.Germany2008.D5	GQ121274
MV.Libya2007.B3	FN594772
MV.SouthAfrica2010.B3	KC305668
MV.Spain2004.D4	FJ869874
MV.UK1994.D4	GQ331933
MV.UK2013.D8	KT732260
MV.UK2014.B3	KT732223
MV.USA1954.A	JX436452
MV.VietNam2000.D5	JF728849
MV.VietNam2014.D8	AB968381

Name of SLAM gene sequence	GenBank accession numbers	Name of Nectin-4 gene sequence	GenBank accession numbers
A.jubatus	XM027048539	*A. melanoleuca*	XM002928747
A.melanoleuca	XM002928437	*B.a. scammoni*	XM007171734
B.a.scammoni	XM007171753	*B. Taurus*	NM001024494
B.bubalis	DQ228868	*B.bubalis*	BC148055
B.taurus	BC114833	*C. jacchus*	XM003735162
C.bactrianus	XM010955648	*C. bactrianus*	XM010955671
C.dromedarius	XM010993089	*C. dromedarius*	XM010993067
C.ferus	XM014562035	*C. ferus*	XM006173954
C.hircus	DQ228869.1	*C. lupus*	NM001313853
C.jacchus	XM002760176	*C. hircus*	MG870289
C.lupus	MG870622	*F. catus*	XM019822297
E.fuscus	XM028129350	*H. sapiens*	NM030916
F.catus	NM001278826	*L. vexillifer*	XM007467114

(Continued)

TABLE 2 | Continued

Name of SLAM gene sequence	GenBank accession numbers	Name of Nectin-4 gene sequence	GenBank accession numbers
G.gorilla	XM004027719	*M. fascicularis*	AB742522
H.sapiens	NM003037	*M.p. furo*	XM004775900
L.obliquidens	AB428366	*O.r.divergens*	XM004407894
L.vexillifer	XM007467101	*O.orca*	XM004284416
M.lucifugus	XM014462802	*O.aries*	XM004002680
M.mulatta	XM001117605	*P.hodgsonii*	XM012184689
M.p.furo	XM004775878	*P.catodon*	XM007112295
N.procyonoides	EU678639	*S.scrofa*	AK397273
N.vison	FJ626692	*T.truncatus*	XM030842125
O.aries	DQ228866	*V.pacos*	XM006215669
O.orca	NM001279809		
O.r.divergens	XM004407883		
P.catodon	XM007124057		
P.hodgsonii	NM001040288		
P.largha	AB428368		
P.leo	XM019433334		
P.t.altaica	XM007092374		
P.vampyrus	XM011373055		
S.scrofa	AK391518		
T.truncatus	XM004327846		
U.maritimus	XM008700683		
V.pacos	XM015249006		
V.vulpes	EU678638		

PPR Infection in Typical Host or Small Ruminants

There were many reports about small wild ruminant species infected by PPRV in the United Arab Emirates (21). On the other hand, white-tail deer challenged with PPRV exhibited clinical signs similar to those in goat (29). Abundant reports of natural infection of PPR disease in gazelles, ibexes, bharals, wild goats (*Capra aegagrus*), wild sheep (*Ovis orientalis*) have also been documented (7, 14, 20, 22, 23, 26, 31). Additionally, Barbary sheep (*Ammotragus lervia*) and Afghan Markhor goat (*Capra falconeri*) died from PPRV infection, which belongs to lineage IV (21). Likewise, in Tibet, China, 19 free-living wild Bharals (*Pseudois nayaur*) showed clinical signs similar to PPR including mucopurulent discharge and severe diarrhea in a pasture nearby where other abnormally dead bharals were prevalent (22). Surprisingly, in India, Chowsingha (*T. quadricornis*), a four horned antelope belonging to the subfamily bovinae and family Bovidae was reported to be affected by PPRV lineage IV (74). Such kind of unusual infection in unusual host requires strong surveillance to strengthen the PPR eradication program. Interestingly six Mongolia gazelles (*Procapra gutturosa*) found dead in a pasture were also discovered to be infected by PPRV lineage IV based on the clinical, serological, and molecular evidences. Above all, an outbreak of PPRV lineage II in Hydropotes inermis (water deer), a rare wild ruminant endemic to China has been reported (32). Experimentally infected West African dwarf goats also showed PPRV virulence (75). Due to the limitations of economic conditions in Africa, prevalence distribution and host range of PPRV have not been well-demonstrated. A recent study showed that PPRV antigen and nucleic acid were detected in specimens from free-ranging dorcas gazelles (*Gazella dorcas*) in Sudan using an immunocapture ELISA and RT-PCR assays (24). Phylogenetic analysis showed that PPRV detected in these gazelles belonged to the lineage IV genotype. With the continuous development of free-animal husbandry, there is a greater chance of interaction between free-living wildlife and domestic species, and it is difficult to monitor PPR in the free-ranging wildlife species thereby increasing the risk of interspecies transmission.

PPR Infection in Wild Animals and Dogs

In addition to infection of PPRV in the large and the wildlife ruminants as described above, unexpectedly PPRV infection was reported in carnivore animals as well (7, 13, 33, 34). PPRV was reported to be isolated from an Asiatic lion (*Panthera leo persica*), and multigene sequencing analysis showed that the strain belonged to lineage IV and was closer to the Indian strains (33). Meanwhile, PPRV genome was recently detected from nasal swabs (3/12) of dogs with CDV, and the sequencing results showed 99% identity with PPRV (34).

PPR Infection in Pigs

Pigs experimentally infected with PPRV lineage II showed characteristic clinical signs of PPR (35). Although the transmission from infected pigs to healthy pigs or from infected pigs to goats is not reported, it might spread from ill-goats to pigs (35). Therefore, pigs are considered as dead-end hosts for PPRV. However, a recent study of a virulent PPRV lineage IV infection in domestic pigs and wild boar showed that PPRV could be transmitted from pigs to goats and pigs and from goats to pigs (36), indicating that pigs could be a possible source of PPRV infection. Therefore, further investigation on the role of suids in the spread of PPRV in field and experimental conditions with different PPRV lineages and strains is very important. Similar studies on natural infection of PPRV in pigs are still missing, while there is no evidence about pigs as a susceptible animals. The experimental infection with PPRV Nigeria75/1 in suckling mice caused clinical signs in 25% of Balb/C and 24% of Cd1, respectively, but not in C57 (37); however, the transmission of virus to mice from susceptible animals has not been reported yet. Recent report on the detection of PPRV RNA in *Culicoides imicola* have indicated that PPRV might be a vector borne disease (38).

Mechanisms for Peste Des Petits Ruminants Virus Interspecies Infection

PPRV has a broad host range in comparison to the closely related MV and RPV, but it does occur in CDV and CeMV which have been reported to be able to cross the species barriers to infect a wide range of hosts (76, 77). For example, CDV in non-dog hosts has been reported in almost all continents. However, the mechanisms beyond this interspecies infection remain unclear. Like other members of morbilliviruses, PPRV glycoprotein HN, which interacts with the cellular receptors, is

necessary for virus attachment. It has been demonstrated that signaling lymphocyte-activation molecule (CD150/SLAM) and poliovirus receptor-like protein 4 (Nectin-4/PVRL4) are two major cellular receptors required for morbilliviruses including PPRV to enter the cells (78). In addition, recently microRNA-218 has been reported to affect PPRV replication by regulating SLAM receptor expression facilitated by HN protein of PPRV in PBMC cells (79). Amino acid variations in the CDV protein which binds cellular receptor may play an important role in species specificity (80). From the evolutionary trees, the evolution of H protein of morbilliviruses appears to be strongly associated with the evolution of the cellular receptor (**Figure 2A**), especially in Nectin-4. The phylogenetic tree of SLAM and Nectin-4 shows that seals (*P. largha*) and walrus (*O.r.divergens*) were located on an evolutionary branch, which indicated that the walrus may be infected with PDV (**Figure 2B**). However, the fact linked with viruses and hosts which caused the divergence or convergence in the phylogenetic trees remained unclear. Two studies showed that the rate of variation of PPRV HN gene is higher than that of the MV H gene (66, 81). In addition, the variation of PPRVHN gene is faster than that of the genome, which may be the result of the ability of PPRV HN to adapt to large host immune pressure. We have previously reported several positively selective sites on PPRV HN (68), while no positively selective site was found in other morbilliviruses including MV. This indicates that PPRV HN protein does not have much higher stability in comparison with other morbilliviruses, which would have a positive impact on a wide range of host adaptation. On the other hand, a recent phylogenomic analysis based on partial N gene of PPRV with limited sequence data showed a close relationship between PPRV strains recovered from wild and unusual hosts of the same geographical region. From the findings that camel-originated strains from Pakistan clustered close enough to those of domestic origin PPRV reported previously from Pakistan and China (82), it can be inferred that host factors may have a critical role in susceptibility to PPRV infection. On the other hand, SLAM receptor was thought to be related to interspecies infection with the morbilliviruses (64, 83). A study reported that PPRV HN has a high affinity to sheep SLAM based on the analysis of interaction energy and interaction surface contact area (68). When the 188–606 amino acids of PPRV HN were aligned with those of MV H, 41.9% sequence identity and 61.1% sequence similarity were observed. Likewise, the 32–140 amino acids of sheep SLAM (sSLAM)-mice SLAM (mSLAM) and hSLAM (human SLAM)-mSLAM showed 63.7 and 87.3% sequence identity and 79.4 and 93.1% sequence similarity, respectively. This high homology among them promoted the use of the crystal structure of the MV H-SLAM complex (83) as a model to analyze the interaction of PPRV HN protein with SLAM receptor. Simulation of PPRV HN-sSLAM complex showed the presence of a large number of hydrogen bonding interactions in the interface of the complex; D507 on PPRV HN made an intermolecular salt bridge with K78 on sSLAM V domain and also had Pi interactions with PPRV HN residues R191, R533, Y553, and SLAM residues F132, H63, K129 (**Figure 3**).

Phylogenetic analysis of the receptors showed that the receptors for human and mouse were the most distant compared to goats (**Figure 3**). Balb/C and Cd1 mice could be experimentally infected by PPRV Nigeria 75/1 strain, but the role of SLAM receptor during PPRV infection in these species is still unknown. If the closest SLAM for evolution has a higher affinity with the PPRV HN, it would be believed that the receptors in other species have also an affinity with the PPRV-HN. Simulation analysis showed that the major binding interface of PPRV HN-hSLAM complex is very similar to that of MV H-SLAM complex (unpublished data). Therefore, we explored the probability of PPRV interspecies infection events from host receptor binding properties using the most distantly related natural hosts of PPRV. Residues I194, D505, D507, D530, R533, F552, and P554 in MV H have been identified as important binding sites for SLAM by multiple mutagenesis studies (84, 85). A comparison of the key amino acids located at the interface of PPRV HN-hSLAM complex showed that residues D505, D507, D530, R533, and F552 were highly conserved in PPRV HN and MV-H proteins (**Figure 4**). A mutagenesis study confirmed that the $\beta4$–$\beta5$ hydrophobic groove of H protein head domain is the binding site for both CD46 and Nectin-4, but this hydrophobic groove was not a key binding site for the viral entry through SLAM, which interacts functionally with the propeller blades $\beta5$–$\beta6$ in MV H (86). Furthermore, this study revealed that hSLAM interacts with an intermolecular β-sheet of PPRV-HN head domain $\beta5$–$\beta6$ involving the key $\beta64$s P191–R195. The mutagenesis and crystal structure study showed that the important residue H61 of mSLAM made a Pi interaction with R533 of MV H, and the contact with E123 of SLAM seemed to stabilize the Pi interaction. Our simulation study shows that R533 of PPRV-HN made a Pi interaction and two hydrogen bonds interact with H61 and E123, respectively. In addition, the crystal structure also showed that R130 had stacking interaction with residue F552 of MV H, while in addition to the formation of Pi interaction, R130 also forms a large number of hydrogen bonds with Y192 and S550 of PPRV-HNw. Considering the receptor, many residues (E50, I60, H61, V63, N77, V82, E123, S127, V128, and F131) are highly conserved in various species. This indicated an affinity of PPRV HN and SLAM of different species by comparing the interaction energy and interaction surface contact area which might help in prediction of the potentiality of the virus to expand to more new hosts species excluding humans.

Besides these factors, Herzog et al. have suggested a relationship between pastoral production and PPRV infection. This study has shown that the animals raised in agropastoral (AP) has seroprevalence rate of 5.8%, whereas 30.7% sero prevalence was observed in pastoral (P) villages in northern Tanzania indicating that even the management system affects the PPRV infection (87). Since unrestricted movements of small ruminants also give rise to massive spread of PPRV as demonstrated in Pakistan by the introduction of disease from infected sheep and goats of Sindh Province (north-west) to Punjab province (central) of Pakistan, health clearance certificate before movement of animals should be emphasized (88).

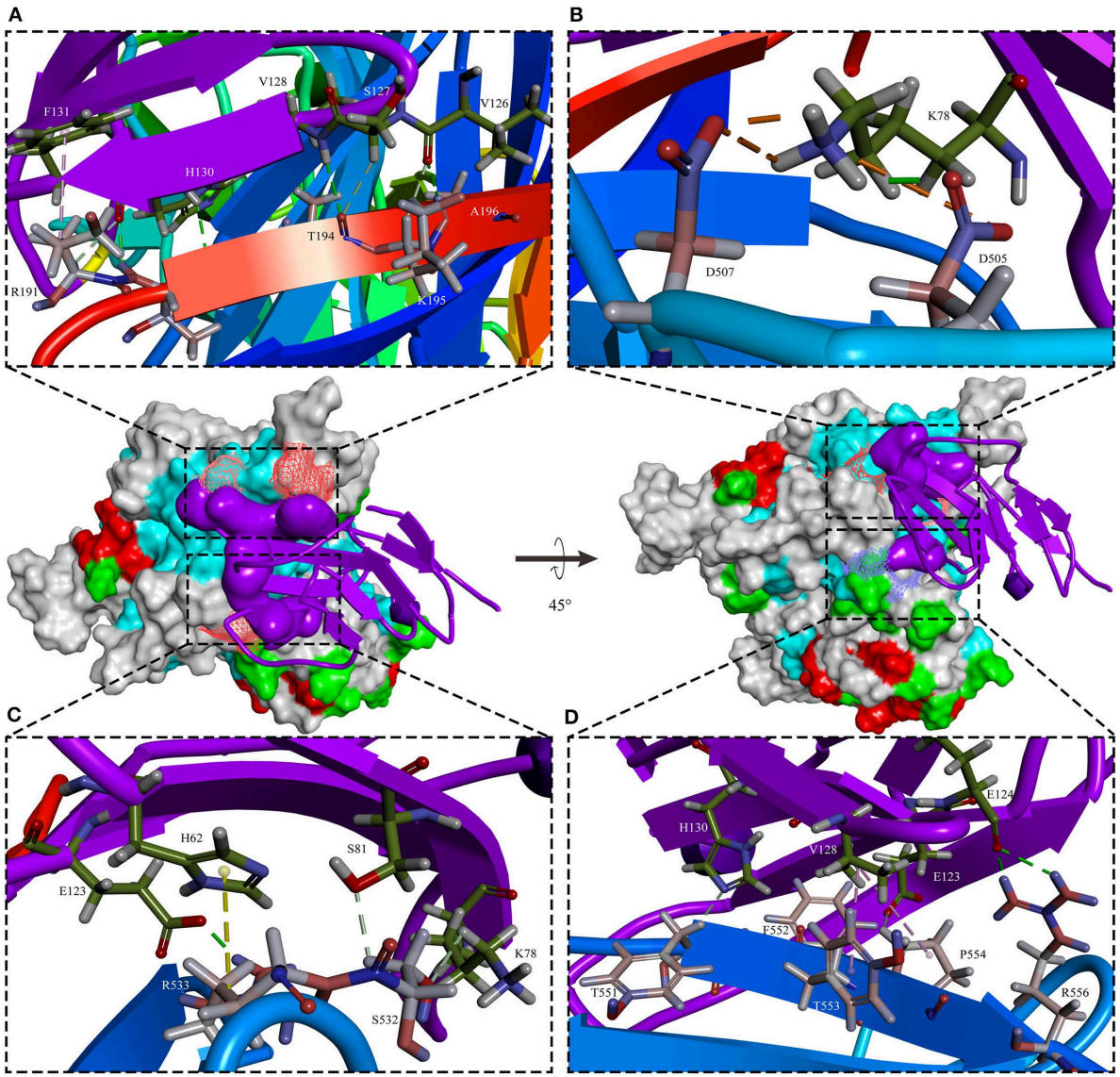

FIGURE 3 | The sSLAM receptor-binding sites with PPRV HNw. The typical β-sandwich structure with BED and AGFCC′ β-sheets of the sheep SLAM (purple) bound to the β4–β6 hydrophobic groove governs in PPRV HNw head domain six-bladed β-propeller head (rainbow colors). In addition to the presence of a large number of hydrogen bonding interactions, D507 on PPRV HNw made an intermolecular salt bridge with K78 on sSLAM-V and also had Pi interactions with PPRV HN residues R191, R533, Y553, and SLAM residues F132, H63, K129. **(A–D)** showed four small segments of the binding interface in PPRV HNw-shSLAM complex.

CONCLUSION

Even though effectively attenuated vaccines have been widely used to protect sheep and goats against PPRV, it remains endemic in several parts of the world. Previous studies suggested that the continual spread of PPRV could be related to the emergence of new PPRV strains and lapses in regulatory control (89), but over the last decades the host range of PPRV has been continuously expanding, and the interspecies infection was reported to occur in many non-natural hosts, which may result in multiple ruminant species reservoirs, leading to the silent spread of PPRV due to interaction of livestock with free-living wildlife. Several reports had raised concerns that global PPRV eradication by 2030 may not be achieved as successfully as RPV (52, 90, 91) partially due to the wide host range of PPRV (92) which should be taken into consideration when the global eradication of PPR is implemented. It was observed that in rural areas where small ruminants and cattle coexist and graze together on the same pasture, cross-species transmission of PPRV from small ruminants to cattle is likely to take place frequently (17). Therefore, understanding the importance and roles of these animals in PPRV transmission and evolution might be crucial for effective eradication of this disease. Particularly, PPRV infection in swine and carnivore requires further molecular

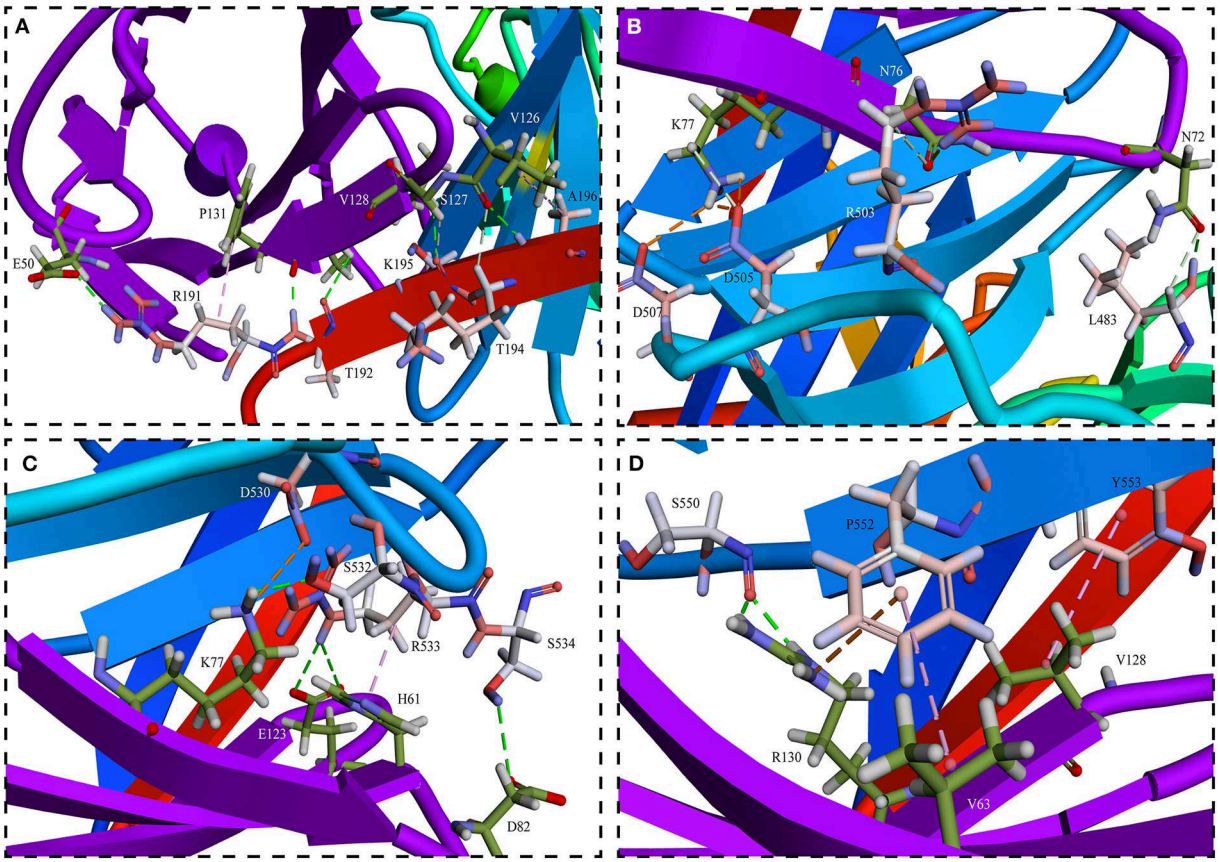

FIGURE 4 | Detailed views of **(A–D)** in the interface between PPRV HNw and hSLAM. **(A)** The interface of PPRV HNw–hSLAM complex, the successional interaction comprised of β-sheet R191-K196 on the PPRV HNw β6 sheets and K126-P131 on the hSLAM G β-sheets made the complex in a more stable state. And R191 of PPRV HNw made the intermolecular Pi interaction with P131 of hSLAM, which might play an important role in stabilizing the PPRV HNw-hSLAM complex. **(B)** The residues D505 and D507 on PPRV HNw made the strong salt bridge with K77 on hSLAM might also play an important role in stabilizing the PPRV HNw–hSLAM complex. **(C)** Key residues D530 and R533 of PPRV HNw made hydrogen bonds and Pi interaction with the residues of hSLAM. **(D)** The strong Pi interaction comprised of residues F552 on PPRV HNw and K64 and R131 on hSLAM. Other residues L483, R503, S532, S534, S550 also made a large number of hydrogen bonds with the SLAM.

and cell biology studies on the ability of PPRV to adapt to multiple host. A phylogenetic tree based on the viral HN and the viral receptors (SLAM and Nectin-4) suggested a stable coevolutionary relationship between PPRV and its hosts. Detailed information about the incidence of natural infection, clinical signs and pathology, and confirmation of the virus in these species as well as their role in the epidemiology of PPRV is still lacking. Additionally, limited viral sequences from these animals are available. Therefore, more viral sequences should be generated representing wild and unusual hosts. Besides comparative sequence analysis, analysis on a range of host factors which may be associated with susceptibility of novel host to PPRV infection should be emphasized. Full elucidation of underlying mechanisms on PPRV evolution in relation to interspecies infection would make a positive contribution to successful global PPRV eradication by 2030.

AUTHOR CONTRIBUTIONS

YD and ZL design of the study, organized the database, and wrote the first draft of the manuscript. MP and RZ organized the part of database and references. YL and ZZ contributed conception and wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Eradication of Peste des Petits Ruminants Virus and the Wildlife-Livestock Interface

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Growing evidence suggests that multiple wildlife species can be infected with peste des petits ruminants virus (PPRV), with important consequences for the potential maintenance of PPRV in communities of susceptible hosts, and the threat that PPRV may pose to the conservation of wildlife populations and resilience of ecosystems. Significant knowledge gaps in the epidemiology of PPRV across the ruminant community (wildlife and domestic), and the understanding of infection in wildlife and other atypical host species groups (e.g., camelidae, suidae, and bovinae) hinder our ability to apply necessary integrated disease control and management interventions at the wildlife-livestock interface. Similarly, knowledge gaps limit the inclusion of wildlife in the FAO/OIE Global Strategy for the Control and Eradication of PPR, and the framework of activities in the PPR Global Eradication Programme that lays the foundation for eradicating PPR through national and regional efforts. This article reports on the first international meeting on, "Controlling PPR at the livestock-wildlife interface," held in Rome, Italy, March 27–29, 2019. A large group representing national and international institutions discussed recent advances in our understanding of PPRV in wildlife, identified knowledge gaps and research priorities, and formulated recommendations. The need for a better

understanding of PPRV epidemiology at the wildlife-livestock interface to support the integration of wildlife into PPR eradication efforts was highlighted by meeting participants along with the reminder that PPR eradication and wildlife conservation need not be viewed as competing priorities, but instead constitute two requisites of healthy socio-ecological systems.

Keywords: wildlife-livestock interface, peste des petits ruminants, small ruminant morbillivirus, global eradication, integrated management, wildlife conservation, one health

INTRODUCTION

Peste des petits ruminants (PPR) is a widespread and devastating disease of domestic and wild artiodactyls caused by peste des petits ruminants virus (PPRV; small ruminant morbillivirus) (1). Among domestic animals, goats and sheep are primarily affected, representing a threat to the primary source of livelihoods for 300 million rural families globally (2), and an estimated US$2.1 billion in economic losses per year (3). As a response, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) endorsed the Global Strategy for the Control and Eradication of PPR (PPR GCES), and launched the PPR Global Eradication Programme (PPR GEP), to eradicate PPRV by 2030 (2, 3). To date, PPR GEP has focused on the surveillance and control of PPR in affected livestock. Although a range of wildlife hosts are known to be susceptible to PPRV (4, 5), the role of wildlife has been assumed, as was the case with rinderpest, to play a minor epidemiological role (6, 7). As a result, PPRV ecology, dynamics, and impact across susceptible artiodactyl communities have not been sufficiently considered (8).

PPRV outbreaks in free-ranging wild artiodactyls can result in severe mortality and threaten wildlife populations and ecosystem stability (9–12), although the full impact on biodiversity conservation remains to be determined. In endemic situations, such as in East Africa, serological responses to PPRV in wildlife indicate widespread spillover at the wildlife-livestock interface, but no overt disease (13). In Asia, PPR outbreaks have impacted wildlife populations, as documented in Mongolia in 2017 with large-scale mortality in the critically endangered saiga antelope (*Saiga tatarica mongolica*) (14). The potential role of wildlife species as maintenance hosts for PPRV in these different ecosystems is unknown. It is also unclear what factors are driving the apparent difference in disease expression between Asian and African wildlife. The expansion of PPR into free-ranging wildlife, continental Asia, and eastern Europe are major concerns that negatively impact biodiversity, dim the vision of a PPR-free world by 2030 (15), and threaten the realization of UN Sustainable Development Goals (SDGs 1, 2, 3, 5, and 15).

In recognition of the threat to PPR eradication, and to galvanize broader support for investigation and action at the wildlife-livestock interface, a meeting, "Controlling PPR at the livestock-wildlife interface," was convened March 27–29, 2019, in Rome, Italy. The meeting was co-organized by FAO, OIE, Wildlife Conservation Society, and Royal Veterinary College, with coordination and support provided by Science for Nature and People Partnership (SNAPP) and the FAO/OIE PPR GEP Secretariat. Invited experts, representing diverse national governments and international institutions, focused on: (1) discussing recent scientific knowledge on PPR at the wildlife-livestock interface, (2) identifying significant knowledge gaps and research priorities on PPRV and wildlife, and (3) drawing lessons learned from PPR control across the ruminant community (wildlife and domestic animals). This article condenses the meeting report and highlights key research and policy priorities, as well as recommendations.

RECENT SCIENTIFIC INSIGHTS ON PPR AT THE WILDLIFE-LIVESTOCK INTERFACE

Recent reviews and case reports have established PPR as a disease of both domestic small ruminants and wild artiodactyls (4, 5, 10–14, 16–23) (**Figure 1**). PPRV continues to expand geographically in unvaccinated susceptible populations of domestic small ruminants, facilitating spillover of virus where domestic and wild artiodactyl species coexist and share resources. PPR caused high morbidity and mortality in the Mongolian saiga antelope, contributing to an 80% reduction of the population, and threatening this subspecies with extinction (9, 14). Clinical PPRV infection has been documented in other threatened wild artiodactyls in Asia. In Pakistan, cases were identified in Sindh ibex (*Capra aegagrus blythi*) (10), and seroconversion was detected in free-ranging domestic yaks (*Bos grunniens*) (24). Recent outbreaks in China involved ibex (*Capra ibex sibirica*), argali sheep (*Ovis ammon*), and goitered gazelle (*Gazella subgutturosa*) (11, 18). Wild goats (*C. aegagrus*) were affected in Iraqi Kurdistan (20), and both wild goats and wild sheep (*O. orientalis/vignei*) were repeatedly impacted in Iran following outbreaks in livestock (12).

In a number of PPRV endemic countries in Africa, there is growing serological evidence of repeated PPRV infection of diverse wildlife species (25), but no overt disease confirmed in free-ranging populations. In Tanzania, sero-positivity was confirmed in African buffalo (*Syncerus caffer caffer*), blue wildebeest (*Connochaetes taurinus*), impala (*Aepyceros melampus*), common tsessebe (*Damaliscus lunatus*), and Grant's gazelle (*Nanger granti*), but with little understanding of the role of these species in PPR epidemiology (13, 26). Other anecdotal reports include seroconversion to PPRV in the West African giraffe (*Giraffa camelopardalis* ssp. *peralta*) in Niger (Chardonnet P., personal communication), and viral detection in dorcas gazelles (*Gazella dorcas*) in Sudan (16). Recent research into atypical hosts for PPRV suggest that domestic pigs and wild boar (*Sus scrofa*), and possibly warthogs *(Phacochoerus africanus*), are competent hosts for the virus, with sufficient viral

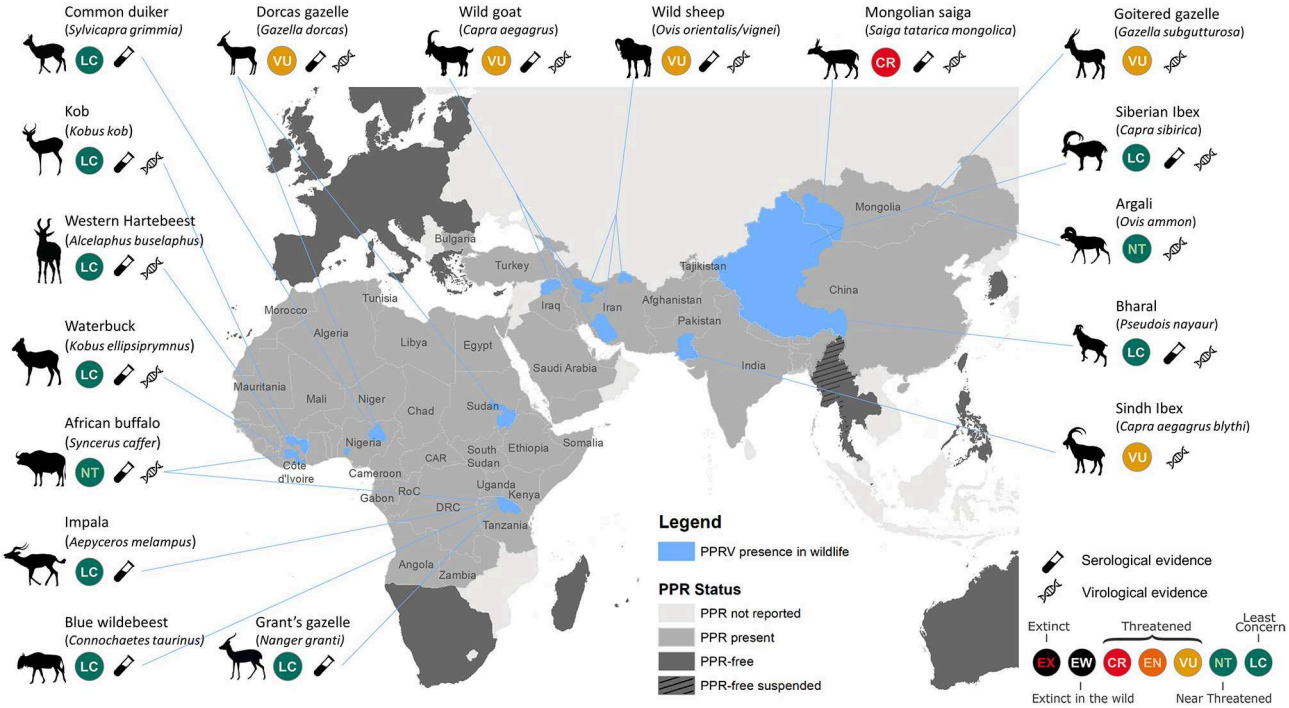

FIGURE 1 | Map illustrating published reports of PPRV detection in free-ranging wildlife species. Data compiled from published reviews and reports (excluding insufficiently documented cases) (4, 5, 10–14, 16–22), official PPR status from World Organization for Animal Health (OIE, www.oie.int/en/animal-health-in-the-world/ppr-portal), and International Union for Conservation of Nature (IUCN) Red List species status (www.iucnredlist.org); CR, Critically Endangered; EN, Endangered; VU, Vulnerable. Areas of PPR detection in wildlife (in blue) are restricted to the states/provinces where wildlife cases were detected. The level of evidence is provided to distinguish serological evidence from virological (i.e., virus isolation, Ag-ELISA, and/or RT-PCR) evidence. PPRV was detected in Argali sheep, Goitered gazelle, and Siberian ibex in both China and Mongolia.

replication and shedding to enable PPRV transmission. Their role in natural systems needs further consideration (27). Multiple reports suggest that dromedaries (*Camelus dromedarius*) are susceptible to PPRV infection and express disease clinically, as observed in Iran, Ethiopia, and Sudan (28–30), though recent PPRV experimental infection trials with camelids resulted in no clinical disease or shedding of PPRV (31). Meeting participants discussed the potential of roe deer (*Capreolus capreolus*) and wild boar facilitating the introduction and spread of PPRV into the European Union, though there is no evidence to suggest that this has occurred.

RESEARCH GAPS AND PRIORITIES

Research gaps and priorities identified grouped into four themes: (1) Diagnostic tools; (2) Risk of PPRV infection in diverse wildlife populations; (3) Epidemiological role of wildlife and impact on wildlife conservation; and (4) Ecological perspectives on PPR at wildlife-livestock interfaces in complex socio-ecological systems.

PPRV Diagnostics in Wildlife

Diagnostic tools for PPRV detection, primarily developed for livestock species, have not been standardized and adequately validated for wildlife. This results in uncertainty regarding the validity of individual-level diagnostics, and most importantly, of population level inference (32). For serological diagnostic tools, a trade-off was highlighted between practicality in most laboratory settings and validation for wildlife species. All available diagnostic options [Virus Neutralization Test, blocking ELISA, pseudotype-based neutralization assays, and PPR-Luciferase Immunoprecipitation System (33, 34)] have value and shortcomings that must be recognized. Moving forward, clear guidelines and standards for application and interpretation of PPR diagnostic tests in wildlife species need to be established. Parallel and replicated testing of samples with multiple diagnostic methods will contribute to our understanding of the respective performance and accuracy of each test (32, 35).

Diagnostic tools to detect viral shedding (e.g., antigen ELISA, qRT-PCR), may facilitate the identification of populations of greatest importance to PPR eradication. Molecular epidemiology using genomic data has the potential to clarify the roles of wildlife in PPRV circulation, direction of transmission at wildlife-livestock interfaces (36), and how viral evolution may alter host range and virulence (37). Thus, high resolution genetic data (i.e., full PPRV gene or genome) from a range of domestic and wild species is needed. In many countries, access to the required sequencing technology is limited, compounded by the difficulty in transporting wildlife samples across international borders due to Convention on International Trade in Endangered Species

of Wild Fauna and Flora, and Nagoya Protocol regulations. Challenges also include practical and ethical requirements associated with obtaining samples from wildlife.

Identifying Risk of PPR in Wildlife Populations

Recognizing that many wildlife species are susceptible to PPRV infection, there are distinct and potentially conflicting criteria for identifying populations requiring additional attention. Wildlife populations of greatest importance to eradication efforts are those populations/communities that contribute to PPRV maintenance and transmission, alone or in interaction with domestic populations. Non-maintenance wildlife populations may be sympatric with, and potentially transmit PPRV to, other wild species with wider ranges and capacity for virus transmission to livestock, thereby acting as bridge hosts (38). Wildlife populations of greatest conservation concern may or may not play an important role in PPR maintenance. However, the impact of PPR in these endangered populations may be devastating, as illustrated by the outbreak in Mongolian saiga (14). Many wild mountain caprine species exist in small fragmented populations, making them highly vulnerable to extirpation as a result of disease outbreaks (9).

Therefore, it is important to consider the entire host community and employ transparent prioritization criteria when allocating resources for PPR research and eradication. Diverse risk assessment approaches, including spatio-temporal risk mapping, can guide prioritization at wildlife-livestock interfaces (39, 40). Participatory epidemiology supports this process, facilitates community engagement, and generates broader support for management decisions (41–43).

The Epidemiological Role of Wildlife and PPR Impact on Wildlife

Information on PPR in wildlife has mainly focused on reporting occurrence in new species, with little data on the virus ecology in these systems (8), the significance for disease control, or threat to wildlife conservation. The small number of samples collected for laboratory analysis during disease outbreaks in wildlife is a further constraint. A greater understanding of the epidemiology of PPRV at the wildlife-livestock interface is required to formulate science-based management options that support eradication efforts and protect biodiversity. Knowledge gaps exist across all steps of the spillover process: susceptibility of wildlife hosts, transmission mechanisms, and the ability of new host species to maintain infection (44).

Assessing the impact of PPRV on the conservation of wildlife populations requires urgent attention. Initial reports of disease impacts on wildlife are often based on direct counts of dead animals, leading to underestimates of impact at the population level (14, 32). Species-specific wildlife survey methods, that account for the probability of detection, must be adopted and applied consistently to support the accurate documentation of PPRV impact on wildlife populations. Integration of this information using dynamic models of within- and between-host transmission will clarify the role of wildlife in PPRV epidemiology, the impact of wildlife hosts on eradication strategies, and the expected short- and long-term impact of PPRV on wild ungulate communities.

The lack of species-specific information on susceptibility, amount and duration of viral excretion, and dynamics of immune response, hinders interpretation of the epidemiological role of diverse artiodactyl species. Experimental infection studies illustrate the value of *ex situ* research in this area (27), acknowledging the expense and ethical considerations of conducting this work. Serological monitoring of vaccinated captive wildlife and atypical host species would provide information about the immunogenicity of available vaccines, and the dynamics of the immune response, which can be used to improve inference from serological data obtained via routine monitoring (45).

There are critical gaps in our understanding of mechanisms of transmission between livestock and wildlife, including the potential for indirect transmission (e.g., via fomites, pasture, feed, water, and mechanical insect vectors). This requires research on viral viability on/in various substrates (e.g., water, soil, mineral licks, hair coat, feces, and carcasses) and under a range of environmental conditions (e.g., temperature, humidity, ultraviolet exposure, water turbidity, and salinity). Detailed descriptions of wildlife-livestock interactions using spatio-temporal analysis can further assess the contribution of these transmission routes to inter-species transmission (46–48), thereby identifying potential prevention and control measures (44).

Most importantly, the participants stressed the need to learn from PPR interventions by including the simultaneous monitoring of wildlife species in pre- and post-vaccination monitoring. Vaccination of livestock in critical ecosystems will create opportunities to answer important questions about the potential of in-contact wildlife/atypical host populations to maintain virus, or the potential for enhanced livestock vaccination to prevent spillover into wild artiodactyls. These opportunities for quasi-experiments have been recognized as crucial for identifying reservoirs of infection in other multi-host systems (49) and need to be identified in advance to benefit our understanding of the dynamics of PPRV between livestock and wildlife/atypical hosts.

Broader Ecosystem-Level Perspective

The meeting participants highlighted the need to look beyond the multi-host epidemiological systems to include a broader examination of the socio-ecological determinants of PPRV dynamics, and ecosystem-level impacts. As PPRV (or other pathogens) drive wildlife populations to local extinction, bottom-up (e.g., on predators) and top-down (e.g., on plant communities) effects must be expected (50), which may considerably alter grazing ecosystems. In systems where PPRV was observed to spillover into wildlife, anthropogenic factors should be considered, including the effects of competition for resources between domestic and wild ungulates due to increasing livestock numbers, or of different livestock management systems. The occurrence, spread, and expression of PPRV may be driven by other environmental, climatic, economic, and social factors, which may not be adequately addressed by conventional disease control approaches (44).

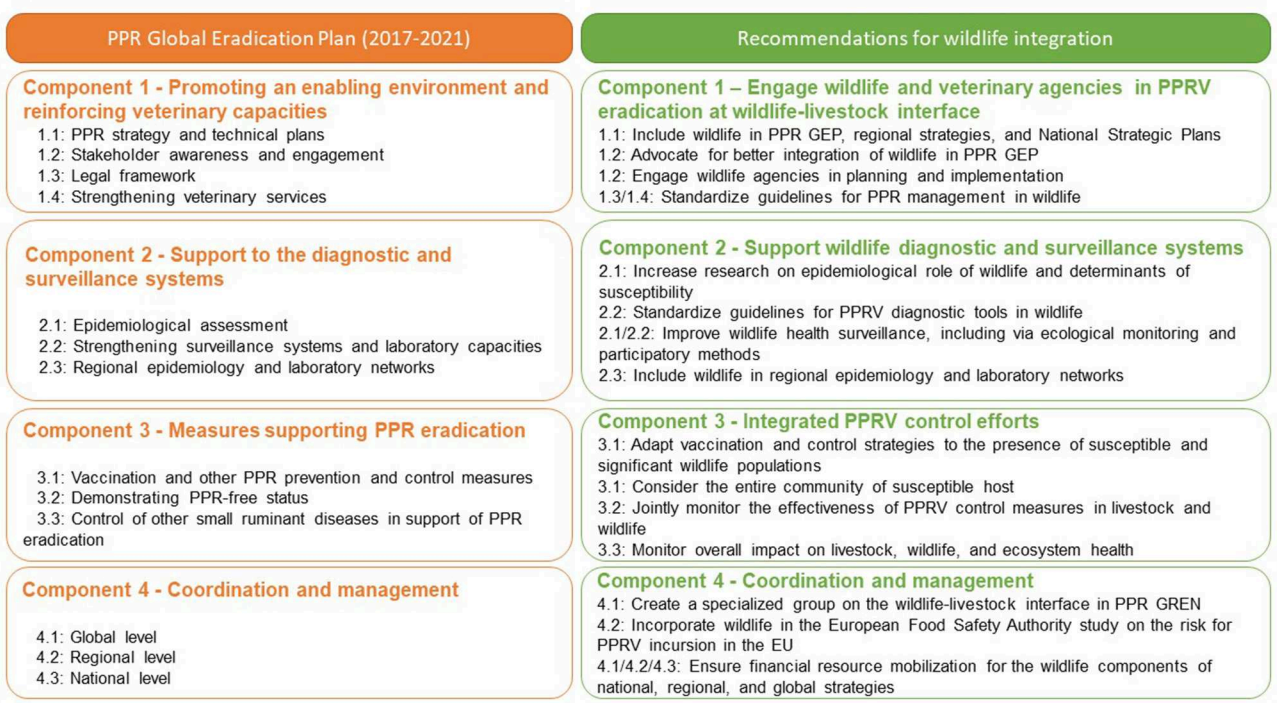

FIGURE 2 | Main components of the PPR Global Eradication Programme (PPR GEP) **(left column)** and suggested additions of wildlife specific activities to the four main components **(right column)**.

Other outstanding questions deserve attention: Is eradication achievable without explicitly including wildlife in control strategies? While the eradication of PPRV in livestock is a desirable outcome, will eradication have a net positive or negative impact for sympatric wild ungulates? May this net impact vary through the different stages of the eradication process? Are there strategies that can optimize control effectiveness, wildlife protection, and long-term socio-economic outcomes? All these questions require multi-disciplinary, trans-sectoral, and collaborative approaches, combining amongst others, veterinary science, epidemiology, ecology, and social sciences with strong community engagement via participatory approaches.

LESSONS LEARNED AND RECOMMENDATIONS

The PPR GEP is a framework with planned activities over an initial 5-year phase (2017–2021) covering four major components designed to lay the foundation for eradicating PPRV (2). Answers to the key research questions outlined above will be required to develop effective PPR surveillance and diagnostic systems (Component 2 of PPR GEP) and to design effective measures supporting PPR eradication (Component 3 of PPR GEP) at the wildlife-livestock interface. Meeting participants observed that the current PPR GEP does not include wildlife species or considerations of impacts on biodiversity (UN SDG 15—Life on Land). Moreover, there is limited information available and a lack of guidelines for policy makers and practitioners on the investigation and control of PPR in wildlife. Consequently, the meeting participants formulated the following recommendations to be addressed now and considered for inclusion in successive phases of PPR GEP (**Figure 2**).

Recommendations for Component 1: Promoting an Enabling Environment and Reinforcing Veterinary Capacities

- Provide policy makers and practitioners with internationally recognized and standardized guidelines for addressing PPR in wildlife. Meeting participants recommended that the Working Group on Wildlife of the OIE and the PPR Global Research and Expertise Network (PPR GREN) draft joint FAO/OIE guidelines for the surveillance, control, and prevention of PPR in wildlife populations[1].
- Integrate wildlife into PPR GCES. The next PPR GEP (2022–2027) document should incorporate wildlife across the four main components of PPR GEP.
- Include wildlife populations in planning of PPR surveillance, control, and eradication activities in National Strategic Plans (NSP) and regional strategies.
- Engage wildlife practitioners (including OIE National Focal Point on Wildlife) and agencies with responsibility for protecting wildlife in PPR GEP training and capacity building

[1] At the time of writing this manuscript, guidelines are in preparation with sections on programme planning and governance, surveillance and outbreak investigation, standardization and data management, laboratory diagnostics, risk assessments, control and prevention options, and risk communication.

initiatives, including the PPR monitoring and assessment tool (PMAT).
- Continue advocating for integration of wildlife into the PPR GCES, including by groups such as the IUCN Species Survival Commission Wildlife Health Specialist Group, to protect biodiversity and the goal of PPR eradication by 2030.

Recommendations for Component 2: Support for Surveillance and Diagnostic Systems

- Establish and share clear guidelines and standards for application of PPR diagnostics tests in wildlife species via OIE.
- Improve wildlife health surveillance systems and systematically conduct thorough wildlife disease outbreak investigations, in particular at the wildlife-livestock interface. Standard ecological monitoring methods, including species-specific wildlife survey protocols, and participatory disease surveillance methods should be expanded to improve our understanding of PPRV at wildlife-livestock interfaces and optimize management strategies.

Recommendations for Component 3: Measures Supporting PPR Eradication

- Identify wild host populations at risk of PPR infection and coordinate between national veterinary and environmental authorities to prioritize targeted vaccination at these wildlife-livestock interfaces.
- Plan and implement vaccination campaigns in concert with communities of livestock owners informed by an understanding of PPRV epidemiology across the ruminant community.
- Assess the immunogenicity/efficacy of PPRV vaccination in susceptible species other than domestic small ruminants.
- Identify science-based alternative management strategies to prevent disease spillover, while avoiding negative impacts on wildlife populations.
- Assess the impact of PPRV control measures by monitoring both livestock and wildlife populations.

Recommendations for Component 4: Coordination and Management

- Establish a specialized group of the PPR GREN on wildlife to promote and support on-going research on PPR at the wildlife-livestock interface[2].
- Support the incorporation of knowledge on PPR at the wildlife-livestock interface in European Food Safety Authority (EFSA) risk assessments for PPRV incursion in the EU.
- Advocate with donors and partners to ensure adequate financial resource mobilization for implementation of PPR GEP (including wildlife components) at national, regional, and global levels.

[2]The wildlife group was formally created at the PPR GREN meeting in Nairobi (13th-15th November 2019). The GREN wildlife group validated the research priorities outlined in this manuscript, stating that adopting a holistic systems approach in PPRV eradication will optimize outcomes for human communities, their livestock, and biodiversity.

CONCLUSION

Recent reports and research at the wildlife-livestock interface make a strong case that wildlife hosts can no longer be ignored in the epidemiology of PPRV. Evidence of transmission between wildlife and livestock may delay PPRV eradication goals. PPRV is also a clear conservation threat to diverse, ecologically important, and often threatened wild species. Strikingly, scientific evidence to formally assess these impacts is lacking across all ecosystems where domestic and wild susceptible hosts coexist. This knowledge gap correlates with a policy gap, as wildlife has until now largely been absent from the PPR GEP framework and National Strategic Plans. We believe that both gaps need to be addressed in order to meet global PPRV eradication goals while protecting global biodiversity. We acknowledge the challenge of resource allocation, but highlight that PPRV eradication and wildlife conservation need not be viewed as competing priorities, but are instead two requisites of healthy socio-ecological systems. This will not only require a better understanding of these systems, but also the long-term commitment, dialogue, and collaboration of diverse stakeholders toward these goals.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AF, CB, AC, GC, PC, MD, TD, MG, RK, JL, JM, SO, SP, SF, ES, JS, CS, J-JS, YV, BT, CW, SZ, and FN contributed significant content to the PPR wildlife-livestock interface components of the meeting. Authors listed as Meeting Participants participated in the meeting and group discussions. AF, RK, CW, FN, and J-JS prepared the initial meeting report. MP wrote the first draft of the manuscript adapted from the meeting report and prepared figures. AF and MP completed the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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REVIEW
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A Review of the Current Status of Peste des Petits Ruminants Epidemiology in Small Ruminants in Tanzania

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Peste des petits ruminants (PPR) is a highly contagious viral disease of sheep and goats with high mortality. The disease is of considerable economic importance in countries such as Tanzania, where small ruminant products are important for sustainable livelihoods. This review assesses current knowledge regarding the epidemiology of PPRV in Tanzania, highlighting the challenges with respect to control and suggesting possible interventions. Thirty-three articles were identified after literature searches using Google Scholar and PubMed. Studies revealed that PPRV is endemic in sheep and goats in Tanzania, although seropositivity has also been reported in cattle, camels, buffalo, Grant's gazelle, wildebeest and impala, but with no clinical manifestation. Three lineages (lineage II to IV) of PPRV have been identified in Tanzania, implying at least two separate introductions of the virus. Diagnosis of PPR in Tanzania is mostly by observation of clinical signs and lesions at post mortem. Risk factors in Tanzania include age, sex, species, and close contact of animals from different farms/localities. Although there is an efficacious vaccine available for PPR, poor disease surveillance, low vaccine coverage, and uncontrolled animal movements have been the bane of control efforts for PPR in Tanzania. There is need for collaborative efforts to develop interventions to control and eradicate the disease. The establishment of a national reference laboratory for PPR, conduct of surveillance, the development of high-quality DIVA vaccines, as well as execution of a carefully planned national vaccination campaign may be key to the control and subsequent eradication of PPR in Tanzania and achieving the global goal of eradicating PPR by 2030.

Keywords: peste des petit ruminants, PPRV, small ruminant morbillivirus, sheep, goats, small ruminant

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INTRODUCTION

Peste des petits ruminants (PPR) is a highly contagious and acute viral disease of sheep and goats, with sub-clinical manifestation in cattle, pigs, and camel. The disease has also been reported in some wildlife species including Dorcas gazelles (*Gazella dorcas*) (1), Nubian ibex (*Capra nubiana*), Laristan sheep (*Ovis vignei laristanica*), and gemsbok (*Oryx gazelle*) (2). The disease is characterized by fever, anorexia, nasal and ocular discharges, sores in the mouth, pneumonia, profuse diarrhea, and often death (3). Reported morbidity and mortality rates have varied between 90–100% and

50–100%, respectively (2). PPR has also been associated with a high rate of abortion in infected goats (4). Consequently, PPR is a major constraint to small ruminant production in Africa (5, 6) and is thus of high economic importance, especially in areas with a high reliance on small ruminant products (7).

PPR is caused by peste des petits ruminants virus (PPRV), species *Small ruminant morbillivirus* (SRMV), a member of the genus *Morbillivirus*, in the family *Paramyxoviridae* (8, 9). It is closely related to other members of the genus, including rinderpest virus, measles virus, and canine distemper virus (8, 10). The virus is highly contagious, easily transmitted by direct contact of healthy animals with the secretions and/or excretions from infected animals, or by contact with infected fomites (2, 11). PPRV exists as one serotype, but sequence analysis of the nucleoprotein (N) gene and the fusion protein (F) gene has revealed four genetically distinct lineages (10, 12). Lineages I and II are mainly found in West and Central Africa; lineage III is found mainly in East Africa, Yemen and Oman; and lineage IV is found across the Arabian Peninsula, the Middle East, southern Asia and recently, in several African territories (10, 13, 14).

The geographical spread of PPR is wide. The disease was first identified in West Africa in the 1940s (15, 16), and has since been observed in North and Central Africa, the Middle East, and parts of East Africa and Asia (17, 18) and Europe (19). In East Africa, PPRV was first isolated in Ethiopia in 1991 (20), although sick goat herds in the Afar region of Ethiopia were suspected to have PPR much earlier in 1977 (21, 22). In Tanzania, PPR was officially confirmed in 2008 (23, 24). However, Karimuribo et al. (23) suggested that the disease had been in circulation in Tanzania for at least 4 years previously, as farmers had reported "rinderpest-like" syndromes in domestic small ruminants, supported by clinicopathological reports and sero-prevalence data. PPR has since been reported in goats, sheep, and camels in Tanzania (25–28).

Similar to other African countries, the impact of PPR on agriculture in Tanzania has wide implications. Agriculture is a mainstay of Tanzania's economy, with approximately one fifth of the agriculture-derived economy emanating from the livestock subsector (29, 30). About 22% of total household income in Tanzania is from livestock rearing, and ∼60% of rural household incomes come from livestock activities (29). Cattle, goats, and sheep constitute a large share of the animals reared by Tanzanian households as sources of protein and livelihood (31), with sheep and goats accounting for about 22 percent of meat consumed in Tanzania (32). Goat and sheep are the species of choice for pastoralists, due to their hardiness and ability to withstand the harsh arid and semi-arid climates. They are mostly kept under extensive management systems with communal grazing and sometimes housing (32).

Currently a global initiative driven by the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) exists to eradicate PPR by 2030 (33). For this to be attainable, it is important to understand the specific epidemiological features of the disease and identify the socio-economic factors that must be considered to stop the transmission of the disease (34). This review is aimed at updating knowledge on the epidemiology of PPR in Tanzania, one of the focus countries for the African Livestock Productivity and Health Advancement (A.L.P.H.A.) initiative, which aims to advance livestock health and productivity in sub Saharan Africa. This article investigates the occurrence and distribution of PPR in Tanzania, the circulating strains, risk factors, economic impacts, control and prevention strategies, and challenges to control of PPR. Additionally, this review aims to identify the challenges and research gaps to inform future control efforts, so that small ruminant production may be improved in this region of East Africa.

METHODS

Literature searches were conducted in PubMed and Google Scholar. Grey literature was obtained using Google Search and the official websites of FAO and OIE (www.fao.org and www.oie.int). The search terms used were "PPR Tanzania" and "Peste des petits ruminants AND Tanzania." All searches were carried out between September 2019 and July 2020. First, title and abstract were reviewed to determine their eligibility. For eligible articles, full text was subsequently reviewed while non-eligible articles were excluded.

Eligible articles were those published about peste des petits ruminants in Tanzania within the last 16 years (2004–2020), published in or translated to the English language. Only articles concerning case reports, reviews, outbreaks, risk factors, economic losses, control measures, and prevalence of PPR in Tanzania were considered relevant. Additionally, conference papers and theses relating to the topic were included if they were not published in a peer reviewed journal at the time of review. Articles were excluded if they had a geographical focus other than Tanzania or focused on a different disease. Editorials, letters to the editor, opinions or commentaries without original data were also excluded. Data extracted from eligible articles included clinical signs, diagnosis, occurrence, distribution and circulating strains, risk factors, economic losses, control, prevention, and challenges of PPR in Tanzania. The process through which articles were sourced, identified, and selected for this review is shown in **Figure 1**.

RESULTS

Selected Studies

Thirty-three articles were eligible for this review, 24 were research articles, and one was a review article (**Supplementary Material 1**). Additionally, there were two conference papers, four theses, and two technical reports.

Clinical signs

Two studies described the clinical signs of PPR in Tanzania and suggest that goats were more susceptible to PPR than sheep, with sheep exhibiting a milder form of the disease (14, 35). The main symptoms of PPR described included anorexia, emaciation, severe depression, fever (40–41°C), diarrhea, muco-purulent nasal, and ocular discharge and erosive and necrotic stomatitis (14, 35). Abortion and nodular lesions were also observed, which were not reported to be common in neighboring Kenya (35).

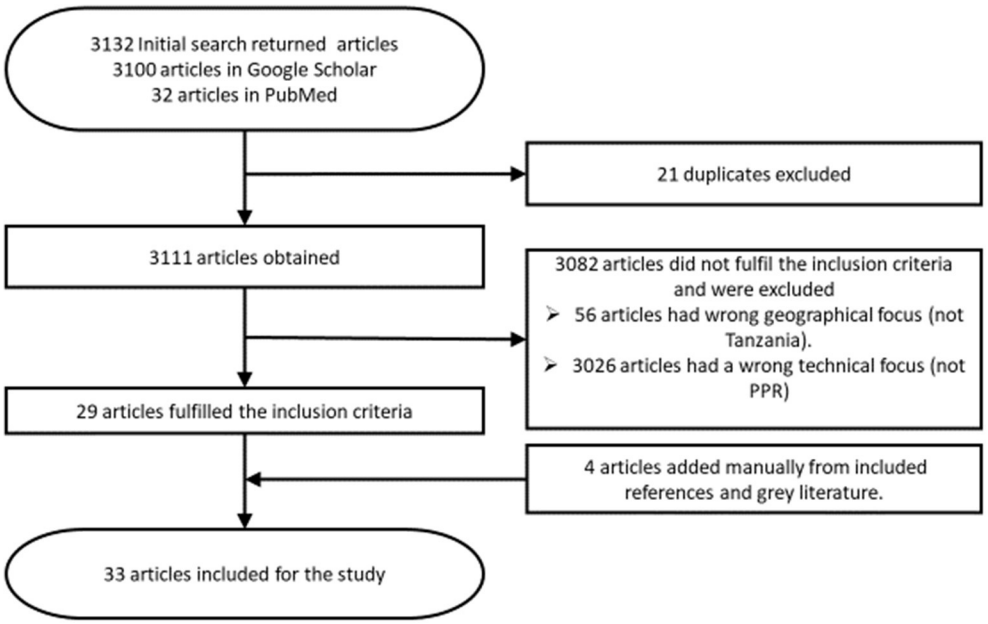

FIGURE 1 | Flow diagram of the systematic review and identification of eligible articles.

Additionally, when performing post-mortem examination of confirmed cases of PPR, Muse et al. (14) observed lung congestion and consolidation, and increased thickness of inter-alveolar walls, indicating pneumonia.

Diagnosis

In the reviewed studies, diagnosis of PPR in Tanzania was mostly by observation of clinical signs and lesions at post-mortem, followed by monoclonal antibody-based competitive enzyme-linked immunosorbent assay (cELISA) for the detection of PPRV antibodies to determine a previous or current infection (26, 36–40, 50). Additionally, some of the studies also utilized confirmatory molecular methods for the detection of PPRV genome (27, 36, 41–43).

Samples collected for testing included swabs of conjunctival, nasal and oral discharges and ulcers, whole blood, and serum samples for serology (27, 36, 41–43). Portions of intestines, lungs, and lymph nodes were also collected and homogenized for the detection of viral RNA (41, 42). Real-time reverse transcription polymerase chain reaction (rRT-PCR), targeting the PPRV nucleoprotein (N) gene, was used to identify the presence of PPRV genome in buffy coat, homogenized tissue samples, and nasopharyngeal and ocular swabs of suspected cases (12, 27, 36, 41–45). Additionally, phylogenetic analysis based on the N gene has been utilized to determine the PPRV lineage and to establish epidemiological relationships (12, 36, 41, 44). The immunocapture enzyme-linked immunosorbent assay (IC-ELISA) for the rapid identification of PPRV antigen (46), recommended by OIE (47), was not reported to have been used in any of the reviewed articles.

Serological tests performed in the reviewed studies were mostly ELISA techniques such as the competitive PPRV specific anti-H monoclonal based ELISA (c-ELISA) as recommended by the OIE (27, 28, 39, 43, 48–50). The c-ELISA detects antibodies to confirm that the animal has been exposed to PPRV at some point in their lifetime. However, due to the vaccines currently used in Tanzania (live attenuated Nigerian strain 75/1 vaccine) these tests are not able to differentiate between previously infected or vaccinated animals (51).

Occurrence and Distribution

Seven studies reported the occurrence and distribution of PPR in Tanzania (12, 24–26, 43, 49, 52). The studies show PPR to be endemic in goat and sheep populations throughout Tanzania, with several outbreaks reported in different regions of the country (26, 43). Limited evidence of PPRV infection has been observed in wild small ruminants (such as dik-dik, gazelle etc.) and these were reported to be restricted to areas in close proximity with livestock in the Serengeti ecosystem of northern Tanzania, indicating a spill over of infection from livestock populations in Ngorongoro district (24, 26, 52). Seropositivity without clinical manifestation has been observed in cattle, camels, buffalo, Grant's gazelle (*Nanger granti*), wildebeest, and impala sampled in Ngorongoro district in northern Tanzania (24, 25, 52).

Outbreak History

Eight of the selected studies discussed events that surround the history of PPR outbreaks in Tanzania. Following the serological evidence of PPRV infection in Kenya and Uganda in 1994, the first nationwide serological screening was performed in Tanzania in 2000. Over 3,000 serum samples were screened for PPRV antibodies using the competitive ELISA (cELISA) and all cELISA results were negative (26, 41). A confirmed

PPR outbreak in Kenya in August 2006, coupled with reports of clinical signs resembling PPR and high mortality amongst sheep and goats in Ngorongoro, northern Tanzania in December 2007 prompted another investigation (36, 49). Clinical and pathological investigations performed in the Ngorongoro district in March 2008 yielded inconclusive results from 112 sheep and goats, whilst serological investigation was negative for PPR (36). As high mortality persisted amongst the sheep and goat populations in Ngorongoro and the neighboring Mara district, a new investigation confirmed the presence of PPR in Ngorongoro in June 2008, where 129/404 serum samples tested positive for PPR antibody (26, 36). Phylogenetic analysis of isolated PPRV from this investigation identified it as a member of lineage III, the most abundant lineage in eastern Africa (36). Spiegel and Havas (53) suggested that the emergence of PPR in Tanzania in 2008 may have been related to the humanitarian crisis in Kenya in 2007, caused by a highly contested election that led to widespread violence and the displacement of citizens into refugee camps in northern Tanzania. This may have contributed to the introduction of PPRV to Tanzania, due to increased transboundary animal and human movement (2). However, retrospective serological analysis performed by Karimuribo et al. (23) using serum samples collected in 2004 suggested the presence of PPRV in northern Tanzania before 2008, and therefore the time of the true emergence of PPR in Tanzania is unknown.

It was believed that PPR was confined to northern Tanzania until 2009 (42). Negative results were observed in retrospective serological analysis performed using archived sera samples collected from small ruminants for Rift Valley fever surveillance in Mtwara and Lindi regions of southern Tanzania in 2007. Although the sampling strategy of this study was not adequate to confirm absence of infection, these results support the theory that PPR may have been introduced in these regions thereafter (54). PPR was first reported in southern Tanzania in December 2009, in Likuna, a village in the southern Newala district, suspected to be transmitted via goats purchased for Christmas and New Year festivities from Pugu livestock market in the outskirts of Dar es Salaam (14, 36). Since then, outbreaks of PPR have been reported in Tandahimba and Newala districts of Mtwara region of southern Tanzania in 2011 (43), in Ngorongoro and Mvomero districts in northern and eastern Tanzania (respectively) in 2012 (41), and in the Loliondo area in Ngorongoro district of Northern Tanzania in 2016 (27).

Sero-Prevalence

The sero-prevalence of PPR in Tanzania was reported in six of the studies performed between 2008 and 2016 and results are summarized in **Table 1**. The national prevalence of PPR was estimated in a study performed using samples collected in 2013 and 2015 as 26.0% with a true prevalence estimated as 27.1% (95% confidence interval: 25.6–28.5%), although prevalence differed widely by region, varying from 2.6% in Katavi region to 67.3% in Arusha and 70.0% in Morogoro (49). Indeed, the authors suggested that the high sero-prevalence observed may have been due to previous PPR vaccination in these regions. A study performed by the same authors in 2016 (27) also observed a high sero-prevalance (74.6%) in Arusha region, however, they reported no history of PPR vaccination, according to records from the District Veterinary Office.

Torsson et al. (50) observed a decrease in the sero-prevalence of PPR from 49.3% in 2014 to 10.0% in 2015, in a study performed at the wildlife–livestock interface in Ngorongoro district in the northern Arusha region, and Ulanga, Kilombero, and Mvomero districts in the south-eastern Morogoro region. The authors attributed the difference in sero-prevalence to vaccination that was performed in the Morogoro and Mtwara regions prior to sample collection in 2014, and therefore it is likely that the high seropositivity was influenced by vaccine-induced antibodies, compared with a population containing more naïve susceptible animals (3–12 months of age) during the 2015 sample collection.

Kgotlele et al. (49) reported that the sero-prevalence of PPR did not differ significantly between goat (26.3%) and sheep (25.2%) populations. However, Swai et al. (48) and Nkangaga et al. (28) observed a significantly higher sero-prevalence in goats when compared to sheep (**Table 1**).

Circulating Strains of PPRV

Only 4/33 of the eligible studies characterized the strains of PPRV present in Tanzania. Kgotlele et al. (41) carried out phylogenetic analysis based on the N gene of PPRV, on nasal and ocular swabs and whole blood samples obtained from PPR cases in northern and eastern Tanzania. They identified lineage III, with a high genetic identity to PPRVs from Sudan and Ethiopia. Jones et al. (45) also identified PPRV lineage III in samples collected in Ngorongoro District in 2015, which clustered with isolates from Uganda, Kenya and Democratic Republic of Congo. Additionally, Misinzo et al. (12) identified lineage II and IV from goats in the 2011 PPR outbreak in southern Tanzania (52). Therefore, this suggests at least three separate introductions of PPR into Tanzania.

Risk Factors

The risk factors for PPRV infection were investigated by eight of the eligible studies, using questionnaires and sero-prevalence data. The risk factors identified as major contributors to PPR occurrence in Tanzania included communal grazing and housing (14, 42, 55, 56); the practice of selling sick animals at cheap prices and bought by livestock keepers for slaughtering in other villages (14); the mixing of infected with healthy animals in markets; and poor access to veterinary services (14).

Torsson et al. (50) reported that female sheep and goats may be at higher risk of PPR than males because they are kept longer on the farms and therefore have a longer risk period for PPRV exposure. Additionally, a higher prevalence of PPR was reported in pastoral (primarily livestock) management systems, compared to agropastoral systems (a mix of crop and livestock) in Northern Tanzania potentially indicating pastoral management as a risk factor (36, 39, 40, 48). Mbyuzi et al. (57) observed a significantly higher incidence of PPR as reported by farmers in the rainy than the dry season. Additionally, Mdetele et al. (58) reported a significantly higher seroprevalence of PPR in semi-arid and coastal agro-ecological zones in Tanzania, when compared to the plateau ecological zones, suggesting coastal, and semi-arid

TABLE 1 | Sero-prevalence of PPR reported in Tanzania.

Article	Location	Region/district	Study period	Overall prevalence (p/n)	Prevalence in goats (p/n)	Prevalence in sheep (p/n)
Swai et al. (48)	Northern Tanzania	Ngorongoro, Monduli, Longido, Karatu, Mbulu, Siha, and Simanjiro districts	2008	45.8% (704/1,549)	49.5% (443/892)	39.8% (262/657)
Muse et al. (43)	Southern Tanzania	Tandahimba and Newala districts of Mtwara region	2011	31.0% (67/216)	35.3%[a]	30.7%*
Kgotlele et al. (49)	Across Tanzania	118 villages in 14 regions across Tanzania	2013, 2015	26.0% (998/3,838)	26.3% (759/2,886)	25.2% (240/952)
Torsson et al. (50)	Northern Tanzania	Ngorongoro district Ulanga district, Kilombero district, and Mvomero district	2014, 2015	46.8% (223/476) (2014), 10.0% (48/481) (2015)	48.3% (115/238) (2014), 10.8% (35/323) (2015)	45.5% (108/238) (2014), 8.2% (13/158) (2015)
Herzog et al. (39)	Northern Tanzania	Arusha and Manyara Regions	2016	21.1% (1580/7,496) (including cattle) 27.6% (1241/4,499) (for goats and sheep only)	28.8% (696/2,419)	26.2% (545/2,080)
Kgotlele et al. (27)	Northern Tanzania	Loliondo area in Ngorongoro district	2016	74.6% (179/240)	75.7% (137/181)	71.2% (42/59)
Mbyuzi et al. (54)	Southern Tanzania	Mtwara and Lindi regions, Tandahimba and Newala districts	2007, 2009	0% (2007), 27.8% (150/504) (2009)	0% (2007), 28.7% (125/434) (2009)	0% (2007), 35.7% (25/70) (2009)
Nkangaga et al. (28)	Western Tanzania	Kasulu, Kibondo and Kigoma in Kigoma region	2011–2012	5.1% (23/450)	4.8% (20/415)	8.6% (3/35)

[a] *Figures were not available for goats and sheep for (43).*
n, number of animals tested for PPRV antibodies.
p, number of animals that were positive for PPRV antibodies.

regions are high risk ecological zones. The practice of grazing sheep and goats in close proximity to or on wildlife grazing areas was also shown to increase the risk of PPR occurrence in wild ruminants (24, 52).

Control and Prevention

PPR control programs initiated by the Tanzanian government were discussed by five of the reviewed studies. Between 2006 and 2008, an estimated 64,661 animals were culled in Tanzania, in attempts to control PPR (59). In response to the incursion of PPR in Tanzania in 2008, the United Republic of Tanzania Ministry of Livestock and Fisheries carried out mass (blanket) vaccination of sheep and goats in the Northern and Lake Zones bordering Kenya through the Vaccination for Control of Neglected Animal Diseases in Africa (VACNADA) project, funded by the European Union Food Facility (37). The VACNADA project achieved 71.1% seroconversion following vaccination, which according to Baron et al. (60), may have been enough to successfully prevent PPR transmission. Despite this, PPR was observed a few months later in southern Tanzania in 2009 and proceeded to spread across the country, including to northern Tanzania (14, 36, 42, 43). Since then several vaccination campaigns have been executed, including in northern Tanzania in 2010 (23), in small ruminants along livestock marketing routes in 2011, and in herds in the area around Mikumi National Park in 2013 (61). The Nigerian strain 75/1 PPR vaccine is often used for PPR control in Tanzania, and other Southern African Development Community (SADC) member countries (26, 41). Karimuribo et al. (23) reported that farmers in Tanzania used antibiotics to treat clinical cases of PPR in their flock.

Challenges for the Control of PPR

Despite numerous vaccination campaigns, PPR has spread throughout most of Tanzania. Two articles outlined the challenges hindering the control of PPR in Tanzania. Torsson et al. (26) highlighted low awareness among small ruminant farmers, traders, and transporters; uncontrolled livestock movements; poor availability of diagnostic tools, poor surveillance and reporting; and a lack of capacity to enforce regulations as major constraints in the control of PPR. In addition to uncontrolled livestock movement, Kivaria et al. (36) reported that poor zoo-sanitary habits by farmers and a lack of proper local and national control strategies are the main factors responsible for the persistence of PPRV in Tanzania.

Economic Impact

The economic losses attributed to PPR in Tanzania were reported by one grey literature report, two theses and a review article. Economic losses may be due to depletion of the small ruminant population, by mortalities associated with the disease, or by culling as a control measure (59). Other economic losses may result from the cost of medication, vaccination, veterinary and labor services, a reduced market value due to poor body condition, and the embargo on livestock markets imposed by authorities (44, 51, 59). A study in 2012 in Tandahimba and Ulanga districts in southern Tanzania found that the outbreaks of PPR reduced the average value of small ruminants by 10%, caused a decrease in flock size, and increased the inputs and risks of small ruminant production (26). This resulted in a loss of potential income and a reduced ability of the flock to support household livelihood (by ∼30%). Consequently, the estimated total loss of income to PPR was estimated to be TZS 335,420 (155 Euro) per household per year, amounting to a cumulative national loss in excess of TZS 200 billion (92 million Euro) per year (26).

DISCUSSION

There is a dearth of literature on the status of PPR in Tanzania, indicated by the low number of eligible articles obtained for this review. Reviewed studies have shown that the incursion of PPR into Tanzania in 2008 may be directly linked with the emergence and spread of PPR in neighboring Kenya in 2006 (53). A pointer to this is the fact that the first report of PPR in Tanzania was an outbreak in Ngorongoro district, bordering Kenya (36, 53), and the strain of PPRV isolated belonged to lineage III, the same lineage predominant in Kenya, and other countries in East Africa at that time (36, 62). Subsequent isolation of PPRV belonging to lineage II and IV (12, 52) suggest that PPRV may have been imported into the country on more than one occasion (12, 36). Lineage II PPRV in Tanzania may have come from Uganda (12, 36), however, the origin of Lineage IV may be difficult to discern as it is widely spread across the world and in East Africa (63). Of the eight countries bordering Tanzania, PPR has been reported in four: Kenya, Uganda, Democratic Republic of Congo and Burundi (64, 65). Indeed, the existence of an informal cross border livestock trade in the eastern and southern African regions (66, 67) presents a continuous risk of PPR incursion, persistence and spread among these countries and beyond (51, 65, 68, 69).

Studies reviewed show that PPR is endemic throughout Tanzania, and it has had devastating effects on the small ruminant population and the livelihoods of pastoralists across the country over the last several years (36). This is attributable to the high transmissibility and morbidity of PPR (2), which has resulted in its rapid spread in small ruminant populations through large areas of Africa and Asia within the past 20 years (70). Evidence of interspecies transmission of PPR has been observed in several studies (1, 71). Munir (72) reported that most epidemics in wild small ruminants appear to originate from nearby infected domestic sheep and goats and although there is no plausible evidence of self-sustaining PPRV infection in wild ruminant populations, the potential importance of wildlife in the epidemiology of the disease cannot be ignored. The endemicity of PPR therefore poses a threat, not only to the pastoralists and their livelihoods, but potentially also to the conservation of wildlife and endangered wild small ruminant species (24, 52, 73).

Events/activities that bring together flocks/herds from different farms/localities or introduce sick animals to healthy ones have been identified as major risk factors for PPR in Tanzania and Kenya (35). These activities include communal grazing and housing, the mixing of infected animals with healthy animals in livestock markets, and the introduction of recently purchased or rustled animals to a herd. Similar risk factors for PPR have been identified by other studies in Djibouti (74), Chad (75), India (76), and Pakistan (77, 78). Poor access to veterinary services was identified as a risk factor for PPR in Tanzania (14), and is the bane of livestock production in most of Africa (79). There is a lack of veterinarians or community animal health workers in rural Tanzania, the hub of small ruminant production (29, 80). Consequently, PPR control in rural Tanzania is not highly prioritized (68).

The yearly economic losses attributable to PPR worldwide are enormous (33). Losses due to PPR identified in this review include: mortalities associated with the disease, reduced market value caused by poor body condition, culling, the cost of medication, vaccination, veterinary and labor services, and the cost of embargo on livestock markets imposed by authorities. These agree with those identified in studies from other PPR endemic countries for example in Ethiopia (81, 82), Kenya (83), India (84), and globally (33). The estimated total national loss of income to PPR (92 Million Euros per year) is a huge burden to the Tanzanian economy and underscores the need to eliminate the disease in the country (26).

Control of PPR may be achieved by culling, confinement of infected animals, biosecurity measures to reduce infectious fomites, refusal of imports of sheep and goats from regions suffering outbreaks, and mass vaccination (85). In addition to mass/blanket vaccination, it is also important to target vaccination and sero-surveillance activities at the borders with other PPR endemic areas/countries, to establish immune belts and prevent importation of outbreaks (86). Since the suspected incursion of PPR into Tanzania in 2008, the disease has continued to spread throughout the country, and is now endemic in most regions, despite vaccination campaigns. Mdetele et al. (37) reported a significant increase in antibody detected between pre- and post-vaccination goat and sheep in Northern Tanzania, which suggests that the vaccine may be effective in an outbreak. It is likely therefore, that the inability of vaccination programs to effectively contain the disease may be attributed to other factors such as poor coverage of vaccination programs, lack of control of livestock movement, and the high fecundity due to the dynamic nature of small ruminant populations (26, 87). Herd immunity levels required for successful prevention of PPR transmission is in the range of 70–90% (60), and previous vaccination campaigns in Tanzania may have fallen short of this estimate. Continuous effort is required to maintain high levels of immunity to prevent transmission, especially in small ruminants with a short generation time and high turnover of new/naïve animals (87). Additionally, interference

of maternal immunity in young animals, poor vaccine quality, and deficiency in the maintenance of cold chain may also cause vaccination failure (82). Consequently, the reasons for vaccine failure and the persistence of disease transmission in Tanzania should be elucidated. Investigations should be encouraged to further evaluate the barriers to vaccine use, and factors that may affect vaccine efficacy and uptake, including the maintenance of cold-chain storage, and the correct administration. Control by vaccination requires that farmers are aware of the benefits, and that they and their veterinary extension advisors appreciate that frequency of vaccination is related to herd dynamics. Additionally, proper animal identification is necessary for traceability, adequate vaccination coverage, and accurate sero-monitoring (88, 89). Establishing herd status through clinical history and serological testing would be advantageous provided that laboratory access and costs can be managed.

Adequate surveillance of PPR is vital for control and to inform vaccination programs, as demonstrated in countries with successful PPR control policies such as Morocco (90). Indeed, the epidemiological studies accessed for this work covered only few districts/areas of Tanzania, leaving huge areas without data on the status of PPR. For this review, searches were done online only, thus theses, articles and reports not available online were not used for this study. Consequently, the methods used to collect data for this review may have resulted in bias in the study locations, and data from certain locations may have been exempted from this study.

A major hinderance to adequate surveillance is the inability of most antibody tests to distinguish between infected and vaccinated animals (91). This may be overcome with the use of vaccines with DIVA (Differentiating Infected from Vaccinated Animals) capability with their accompanying diagnostic tests, allowing for the discrimination of infected and vaccinated animals (10, 91). This is important for proper planning, execution, and evaluation of control programs (86, 91, 92). Additionally, the use of low-cost, easy to use, point of care diagnostic techniques, and alternative non-invasive sample types may improve surveillance (93–95). At present, there is no official national reference laboratory for PPR in Tanzania, however, the Center for Infectious Diseases and Biologicals (CIDB) of the Tanzania Veterinary Laboratories Agency (TVLA) performs routine testing for PPR and has recently joined a twinning project with OIE Reference Laboratories to improve capacity for PPR diagnosis and expertise (96). International collaborations with organizations such as OIE and FAO should be sought, with local efforts to solve this problem if the target of eradicating PPR globally by 2030 is to be achieved.

This review demonstrates the endemicity of PPR in Tanzania that has major socio-economic impacts on pastoralists and agro-pastoralists in the country, and consequently to the local economy. Uncontrolled animal movement, poor vaccination coverage, mixing of herds/flocks from different farms/localities and sick with healthy animals have aided the transmission and persistence of the disease. Interventions are required to control and eradicate PPR in Tanzania which may be achieved by the collaboration of stakeholders, including: farmers, the Tanzanian government, international organizations (such as FAO and OIE), researchers, and multinational veterinary pharmaceutical companies. An effective widespread/national vaccination campaign must be planned and executed; along with policies aimed at improving awareness of the disease, improving diagnostics, surveillance, disease reporting, and controlling livestock movement; to arrest the spread of the virus and stop the disease incursion into neighboring countries, and achieve the global goal of eradicating PPR by 2030.

AUTHOR CONTRIBUTIONS

AE, EM, and RA: conceptualization. AE, RA, EI, and BA: methodology. EI and AO: analysis. EI, BA, RA, AE, AC, AO, EM, and GV: writing and review. AC and GV: funding acquisition. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.592662/full#supplementary-material

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