**Post-vaccination herd immunity against peste des petits ruminants and inter-vaccination population turnover in small ruminant flocks in northwest Ethiopia.**

Andnet Yirgaa, Wudu T. Jemberub\*, Nicholas Lyonsc, Alemseged Gebrua, Fasil Akililua, Jonathan Rushtone

aCollege of Agriculture and Environmental Sciences, Bahr Dar University, P.O. Box 79, Bahir Dar, Ethiopia.

bCollege of Veterinary Medicine and Animals Sciences, University of Gondar , P.O. Box 196, Gondar, Ethiopia

cThe Pirbright Institute, Ash Road, Pirbright, Woking, GU24 0NF, UK

dNational Animal health Diagnostic and Investigation Center, P. O. Box 04, Sebeta, Ethiopia

eInstitute of Infection and Global Health, University of Liverpool, IC2 Building, 146 Brownlow Hill, Liverpool, L3 5RF, UK

\*Corresponding author: Wudu T. Jemeberu (wudutemesgen@gmail.com/wudu.temesgen@uog.edu.et)

# **Abstract**

Vaccination is the main tool for control of peste des petits ruminants (PPR) because of the availability of effective and safe vaccines that provide long lasting protection. However vaccination campaigns may not always provide sufficient herd immunity needed to prevent disease outbreaks because of logistic problems with vaccination such as inappropriate cold chain and vaccine delivery methods, and the rapid population turnover of small ruminants. This study was carried out to assess post-vaccination herd immunity against PPR and inter-vaccination population turnover in small ruminant flocks in Metema district, Northwest Ethiopia where frequent PPR outbreaks occur despite regular vaccination. A total of 412 serum samples were collected from selected small ruminants in 72 flocks (average flock size of 33.4 and standard deviation of 30) above three months of age in three kebeles immediately before a vaccination program. One month after the vaccination using freeze dried live attenuated vaccine, 359 serum samples were collected from randomly selected small ruminants in the same flocks. The collected serum samples were analyzed to determine the seropositivity using a monoclonal antibody-based C-ELISA. The pre-vaccination seropositivity of 72.3% (95% CI: 67.8-76.4) increased to 93.9% (95% CI: 90.9-95.9) post-vaccination (P<0.001). The observed seropositivity following vaccination was above the recommended herd immunity threshold (80%) required to reduce the transmission of infection in the population sufficient to eliminate virus. A survey of sampled flocks six months post-sampling indicated 68% of animals were still present in these flocks. This population turnover reduces the herd immunity to about 64% which is below the required threshold for control. The high level of herd immunity achieved post-vaccination indicates good vaccine quality, cold chain maintenance and effective vaccine delivery in the district’s vaccination campaigns. The decrease in herd immunity associated with population turnover and annual vaccination intervals represents a challenge to effective control and suggests changes to the timing or frequency of the vaccination is required.

**Key words**: *Herd immunity, Metema, PPR, Serum, Sheep and goat, Vaccination*

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# **1. Introduction**

Peste des petits ruminants (PPR) is one of the most important diseases of small ruminants in Ethiopia. It is an acute, highly contagious and frequently fatal disease of sheep and goats caused by PPR virus (PPRV), a member of genus morbillivirus of family *Paramyxoviridae* (OIE, 2012). The PPRV is differentiated into four lineages. In East Africa (including Ethiopia) lineage 3 is present, while lineages 1 and 2 are found in West Africa and lineage 4 in the Middle East and South Asian- sub-continent (Dhar et al, 2002).

Peste des petits ruminants virus has been causing frequent outbreaks in Ethiopia since the 1990’s inflicting high morbidity and mortality in small ruminants (Roeder et al., 1994, Gelagay, 1996). Large scale epidemiological studies indicated that the disease is widely spread throughout Ethiopia (Waret-Szkuta et al., 2008, Megersa et al. 2011). PPR also ranks among the most important diseases of small ruminants in smallholder production elsewhere in the world (Bett et al., 2009). Because of its significance for food security and livelihood improvement in smallholder small ruminants producers worldwide, PPR has been prioritized as the next target for global eradication after the success with eradication of rinderpest in 2011. A global PPR control strategy was launched in 2015 to eradicate the disease by 2030 (OIE and FAO, 2015).

Vaccination is the main tool of PPR control because of the availability of effective and safe vaccines which provide long lasting protection (OIE and FAO, 2015). However cold chain requirements of the commonly used freeze dried live attenuated vaccines and rapid population turnover affects the ability to develop and maintain sufficient herd immunity to control infection. Herd immunity, although may be used in slightly different senses, basically refers to the proportion of immune individuals in a population that reduces risk infection to the susceptible individuals by the presence and proximity of immune individuals (Fine et al., 2011). The proportion of immunes that provide protection due herd immunity may vary depending on the contact structure of the population and transmissibility of the agent. This threshold herd immunity of PPR is set to be about 80% in the global eradication of strategy of PPR (OIE and FAO, 2015). The difficulty of maintaining an effective cold chain in remote rural areas and poor vaccine delivery can compromise development of sufficient herd immunity in the vaccinated population. Moreover, small ruminant populations are characterized by rapid turnover due to births, purchase of animals from other areas, deaths due to various causes and offtake (slaughter and sales). This type of population turnover may rapidly dilute herd immunity acquired from vaccination campaigns thwarting efforts at controlling disease.

Metema district in northwest Ethiopia is endemic for PPR and vaccination is practised by the district veterinary office using freeze dried live attenuated vaccine produced by the National Veterinary Institute (NVI). Even though the disease is endemic and annual vaccination is practised in the area, no prior study was conducted regarding the herd immunity in small ruminants acquired through vaccination and how the post-vaccination herd immunity is affected by population turnover in the inter-vaccination period. The objective of this study was to evaluate post-vaccination herd immunity and measure inter-vaccination population turnover of small ruminant flocks in Metama district and provide guidance on how policy may be optimized to maintain sufficient coverage to control PPR.

# **3. Materials and methods**

## **3.1. Study Area**

The study was conducted in Metema district, West Gondar zone, Amhara Regional State. The district is located in the western lowlands of Ethiopia between geographical coordinates of 12°25′N to 13°8′N latitude and 35°50′E to 36°45′E longitude. The altitude range is from 550-1608 meters above sea level. Metema district has 24 kebeles (sub-districts)., The district has a large livestock population estimated as 393,746 cattle and 152,488 sheep and goats (CSA, 2017). Livestock are kept under extensive production systems in which individual household flocks meet in common grazing and watering points. The district is frequently affected by PPR outbreaks and annual vaccination typically takes place between September and December to prevent disease outbreaks that are usually expected to occur after December when there is more mixing of animals in the grazing fields after harvesting crops.

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## **3.2. Study Population**

The study population was small ruminants (sheep and goats) from three kebeles of Metema district (Wedigemzo, Debico and Simyelesh). The three kebeles were conveniently selected because of the timing of the vaccination campaign during the planned period of the study. These kebeles had different vaccination histories against PPR; small ruminants in Wedigemzo were vaccinated in 2015 and 2016 while sheep and goats in Debico and Simyelesh were vaccinated only in 2015. There was a report of an outbreak of PPR in all kebeles in November 2016.

## **3.3. Vaccination campaign**

The vaccination campaign assessed during the present study was conducted in all the three study kebeles in December 2017. The vaccination was given as part of the regular preventive annual vaccination practised in the district. It was coordinated by the district veterinary office and vaccination was delivered by animal health personnel within each kebele under the supervision of a district veterinarian. The PPR vaccine used was a freeze-dried live attenuated vaccine (Nigeria 75/1 strain) produced by National Veterinary Institute (NVI), Ethiopia. The vaccine was stored at -20°C until vaccination. On the day of vaccination the vaccine was transported in a cool box with ice packs to the vaccination area. In the field, vaccine was reconstituted with normal saline and 1ml of the vaccine was injected subcutaneously into the neck according to the manufacturer’s instructions using a 30ml automatic syringe. Any reconstituted vaccine left after 30 minutes was discarded. All small ruminants over three months of age were targeted for vaccination.

## **3.4. Sampling and sample size for the post-vaccination herd immunity assessment**

Herd immunity was assessed based on proportion positive seroconversion in the vaccinated population. Although seroconversion may not exactly equate to immunity, it is practically used as indicator of immunity, for example, as post-vaccination evaluation tool to monitor success of vaccination in the FAO-OIE global PPR control program (OIE and FAO, 2015). For this study the all small ruminant flocks of the district were considered as a herd for the purpose of determining herd immunity in relation to PPR vaccination.

Serum was collected from small ruminants pre- and post-vaccination in the selected kebeles. Pre-vaccination serum was collected immediately before vaccination from haphazardly selected animals in flocks gathered for vaccination. This sampling method was used to mimic random sampling as strict randomization was not possible in that situation. Flocks from different villages of a kebele were gathered at one vaccination site and sampling was done from two to three vaccination sites in the single kebele and sampling for a single kebele was done in the same day. The sampled flocks were identified by their owner name and address (kebele and village) to trace back them for post-vaccination sampling. The post-vaccination serum was collected 30 days post-vaccination from small ruminants selected again haphazardly in the same flocks by going village to village. The flocks were monitored for occurrence of outbreak during the 30 days of sampling interval period. Expected seroconversion of 50% was used for sample size determination as there was no previous estimate of it in study area. So for confidence level of 95 % and precision level of 5%, a sample of about 384 small ruminants in the study kebeles were targeted for sampling (Dohoo et al., 2012). In practise sample size close to this target was sampled with a little bit larger size (412 small ruminants pre-vaccination from 72 flocks) and a little bit smaller size (361 small ruminants post-vaccination from 61 flocks) as dictated by practicalities in the field. For example in pre-vaccination animals were gathered for vaccination and was convenient to sample the required number of animals but was difficult to access all these flocks again one month after for resampling as they were not gathered for any reason. The average flock size of the sampled flocks was 33.4 with standard deviation of 30.

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## **3.5 Serum collection and testing**

Approximately 5-6 ml of whole blood was collected per animal through jugular vein puncture using a plain vacutainer tube. Blood samples were kept in a slanted position overnight to allow clotting and separation of serum. Serum was decanted into 2ml cryovials and transported in ice cooled box to the University of Gondar veterinary laboratory and stored at -20°C until being sent to National Animal Health Diagnostic Center, Sebeta, for serological analysis. All sera were tested using the ID Screen® PPR competition ELISA test kit (IDVet, CIRAD-EMVT, Montpellier, France). This diagnostic kit is designed to detect antibodies against the nucleoprotein of the PPR virus. The relative specificity and sensitivity of the test with reference to virus neutralization test, OIE prescribed test, was 99.4% and 94.5% respectively (Libeau et al., 1995). The test was performed and interpreted according to the manufacturer’s recommendations (Libeau et al., 1995).

## **3.6. Assessment of the inter-vaccination population turnover in the vaccinated flocks**

To assess the population turnover of the vaccinated flocks, visits were repeated 6 months post-vaccination. The number of animals present in 72 vaccinated flocks in three kebeles were recorded during the vaccination campaign and flock owners were requested to note animals leaving and joining their flocks in the next six months. The reasons for leaving the flocks were categorized as due to death, being sold, slaughter for family consumption, gifts and others (e.g. lost/stolen, killed by predators). The reasons for joining the flocks were categorized as due to birth, purchase or gift. Based on these flock dynamics, the proportion of animals originally recorded that were still present in the flocks at the time of revisit was calculated as the number of animals in the flocks during vaccination minus the number of animals leaving the flocks until the time of revisit divided by the total number of animals present in the flocks at the time of the revisit.

An informed oral consent was obtained from each participating flock owners for serum sampling and monitoring flock dynamics after reading a written explanation on the purpose of the study, the risks and beneﬁts of participation in the study, the right to refuse to participate in the study as well as the conditions of conﬁdentiality regarding the presentation of results. This has been approved by the Institutional Review Board of University of Gondar.

## **3.7. Data Management and Analysis**

Data were entered into a Microsoft Excel spreadsheet, and coded prior to being imported into Stata 14.0 (Statacorp, Texas, USA) for analysis. Descriptive statistics were generated to express level of herd immunity both before and after vaccination and the proportion of vaccinated animals in the flocks. Chi-squared tests were used to determine the statistical significance of the difference between pre- and post-vaccination herd immunity, and inter-kebele difference in pre and post-vaccination herd immunity, and population turn over.

# **4. Results**

**4.1. Vaccination herd immunity**

## ***Pre-vaccination herd immunity***

The level of herd immunity for PPR in the population before vaccination was measured based on randomly selected 412 sheep and goats from 72 flocks in three kebeles (Wedigemzo, Debico and Simyelesh). The overall proportion of seropositive in the three kebeles was 72.3% (95% CI: 67.8-76.4). There was statistically significant difference (*P*<0.001) in the proportion of seropositives between the three kebeles(Table 1).

Table 1. Pre-vaccination seropositivity in small ruminants in the three kebeles of Metema district (N= 412)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Kebele | Time since the last vaccination (year) | No sheep and goats sampled | No of seropositive sheep and goats | Seropositivity proportion (95% CI) | *x2*analysis values |
| Wedigemzo | 1 | 200 | 163 | 81.5% (75.5-86.3) | *x2*=18.4  df=2  *P*<0.001 |
| Debico | 2 | 112 | 76 | 67.9% (58.6-75.9) |
| Simyelesh | 2 | 100 | 59 | 59.0% (49.1-68.2) |
| Total |  | 412 | 298 | 72.3% (67.8-76.4) |

## ***Post-vaccination herd Immunity***

One month after vaccination, sheep and goats from 61 of the vaccinated flocks were sampled and tested for PPR antibody. The other 11 flocks that were sampled pre vaccination were inaccessible for the post-vaccination sampling. From these 61 flocks 359 animals were sampled and the number of seropositives were 337 indicating a post-vaccination herd immunity of 93.9% (95%CI: 90.9-95.9). Although there was slight variation in post-vaccination herd immunity level among kebeles the difference was not statistically significant (*P=0.49*) (Table 2).

Table 2 Post -vaccination seropositivity one month after vaccination in small ruminants in the three kebeles of Metema district (N= 359)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Kebele | No. of sheep and goats sampled | No. of seropositive sheep and goats | Seropositivity proportion (95% CI) | *x2*analysis values |
| Wedigemazo | 199 | 189 | 94.9% (90.9-97.1) | *x2*=1.4  df=2  *P*=0.494 |
| Debico | 107 | 98 | 91.6% (84.6-95.6) |
| Simyelesh | 53 | 50 | 94.3% (83.7-98.2) |
| Total | 359 | 337 | 93.9% (90.9-95.9) |

There was strong statistical evidence of an increase in the proportion of seropositive small ruminants from pre-vaccination to post-vaccination (73.3% versus 93.9%, *P*<0.001). Similarly there was an increase in seropositivity in each kebeles which was also statistically significant (*P*<0.001) (Figure 1).

**Figure 1**: Seroconversion proportion before and after vaccination in the three vaccinating kebeles of Metema district

## **4.2 Inter-vaccination population turnover in small ruminant flocks**

The total population size in the study flocks of the three kebeles six month after vaccination decrease by about 4 % (from 2991 to 2872) of the original size. In the 72 flocks monitored in three vaccinated kebeles, only about 68% small ruminants present in the flocks during vaccination were still present 6 months after vaccination. There was significant variation in the turnover between kebeles (p = 0.01) (Table 3). The main reason for animals leaving flocks was selling (33%) and the main reason for joining was births (90%) (Table 3).

Table 3. The small ruminant turnover during 6 month period after vaccination

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Kebeles (no. of flock monitored) | No. of animals during vaccination | No. of animals left the flocks ( percent out of total leaving the flocks) | | | | | | No. of animals joined flocks (percent out of total joining flocks) | | | | No. of animals 6 months after vaccination | Proportion of vaccinated after 6 months (%) a |
| Death | Slaughter | Sell | Gift | Otherb | **total out** | birth | purchase | Gift | **total in** |
| Debico (25) | **845** | 98 (32) | 67 (22) | 85 (28) | 5  (2) | 50 (16) | **305 (100)** | 290 (97) | 9  (3) | 0 (0) | **299 (100)** | **839** | **0.64** |
| Wedigemza (33) | **1431** | 153 (29) | 83  (16) | 167  (32) | 8  (2) | 109  (21) | **520 (100)** | 388 (90) | 45 (10) | 0 (0) | **433**  **(100)** | **1330** | **0.68** |
| Simyelesh (14) | **715** | 69 (32) | 41 (19) | 91 (42) | 4  (2) | 13 (5) | **218**  **(100)** | 156 (79) | 41 (21) | 0 (0) | **197 (100)** | **703** | **0.71** |
| **Overall (72)** | **2991** | 320 (31) | 191 (18) | 343 (33) | 17 (2) | 172 (16) | **1043**  **(100)** | 834  (90) | 95  (10) | 0  (0) | **929**  **(100)** | **2872** | **0.68** |

# aThe difference between kebels in the proportion of vaccinated after six months was statically significant (χ2 = 8.97, df= 2, p = 0.01**);** b includes lost, stolen and killed by predators.

# **5. Discussion**

Peste des petits ruminants (PPR) is a highly contagious and fatal disease of small ruminants that is endemic in Africa, Middle East and Asian countries. PPR is a major contributor to poverty among the smallholder farmers in rural areas who solely rely on small ruminants as a source of income. Following global eradication of rinderpest, attention has turned to PPR with aims to eradicate by 2030 (OIE and FAO, 2015). Vaccination will be an important tool for PPR control in the endemic situations of developing countries. To achieve the eradication of PPR by the given time frame, the efficiency of vaccination campaigns need to be evaluated. Post-vaccination evaluation of herd immunity enables evaluation of the immunogenicity of the vaccine and the efficiency of vaccine delivery although the impact of the population turnover needs to be taken into account when optimizing vaccine schedules (FAO and OIE, 2015).

In Metema district in Ethiopia, PPR is endemic and annual vaccination against PPR has been practised by using freeze dried live attenuated vaccine. Although the district claimed annual vaccination, the vaccination interval was inconsistent among the kebeles in the district in which some kebeles vaccinate annually while others vaccinated with a longer interval. The present study showed that the level of herd immunity before the current vaccination was 72.3% which might have been acquired either from the prior vaccination or prior exposure to virus through outbreaks in the study areas.

The 72.3% herd immunity found prior the current vaccination seems large. This is in contrast to the finding that the proportion vaccinated six months after vaccination during the current study was observed to decrease to 68%. This might indicate unnoticed and/or unreported recent PPR outbreak prior to the current vaccination that causes high level of seroconversion proportion. Anyway whether or not this pre-vaccination herd immunity is sufficient for preventing outbreak occurrence depends on transmission dynamics of the disease in that population. Epidemiological investigation carried out in smallholder farming systems in Tanzania and Pakistan estimated the basic reproduction number for PPR ranged from 4.0 to 6.9 which indicated a need for a corresponding herd immunity of 75% to 86% to prevent outbreaks in these populations (Zahur *et al*., 2009; Kivaria *et al*., 2013). In the FAO-OIE global PPR eradication strategy, a threshold herd immunity of 80% is targeted (OIE and FAO, 2015). Another study considered a lower threshold herd immunity of 70% based on the experience of controlling PPR in Morocco (Hammami et al., 2016). In a recent study that used a simulation model of a pastoral area in Ethiopia where PPR is endemic, a permanent herd immunity as low as 37% was suggested to be enough to prevent PPR outbreak (Fournie et al., 2018). Considering the 80% threshold herd immunity targeted by the global PPR eradication strategy, the 72.3% herd immunity observed prior to current vaccination was not sufficient to prevent the disease outbreak in the study population. However, there was inter-kebele differences in the pre-vaccination level of herd immunity in which the highest level of herd immunity was recorded in Wedigemzo kebele (81.5%) and the lowest in Simyelesh (59%). The high level of herd immunity in Wedigemzo kebele could be associated with the relatively recent vaccination history in 2016 whereas the recent vaccination in the other kebeles were in 2015. It could also be due to different extent of virus circulation in the three kebeles as there was a history of PPR outbreak in 2016 in all kebeles.

Post-vaccination, the overall herd immunity of the three kebeles increased from 72.3% to 93.9%. This post-vaccination herd immunity was much higher than the recommended critical herd vaccination immunity threshold needed to control transmission of the PPRV in a population. The level of post-vaccination herd immunity observed in the present study was higher than the seroconversion level 61% reported fourteen days post-vaccination in Awash Fentale District of Afar region, Ethiopia (Faris *et al.,* 2012). This difference might be due to short time between vaccination and post-vaccination assessment and/or differences in vaccine delivery. Post-vaccination studies in other countries have indicated high seroconversion rates similar to the present study. In Pakistan, 96% herd immunity was recorded one month after vaccination (Rajput *et al*., 2016) and in Bangladesh, seroconversion level of 100% was reported in experimental goats (Kabir *et al*., 2016). The high level of herd immunity observed following field vaccination in the present study indicates good vaccine quality, cold chain maintenance and vaccine delivery in the district’s vaccination practices.

Given the high specificity of almost close to 100% and relatively lower sensitivity of about 95% of the test used (Libeau et al., 1995), the above reported seroconversion proportions would be lower than the true seroconversion proportion. This further strengthen the conclusion about the ability of the vaccination to induce a very high seroconversions and hence indication of good vaccine and vaccination practices.

The role of potential of exposure to the virus in the observed higher proportion of seropositivity both pre- vaccination and post-vaccination in this study cannot be ruled out as the vaccine or the test used did not differentiate between infected and vaccinated animals (DIVA). Although in the latter case that possibility may be small as the flocks were clinically monitored for outbreak during the time between vaccination and post-vaccination serum sampling and no clinical infection was reported. Development and use of DIVA vaccines or tests will be essential to monitor the success of vaccination in achieving herd immunity for PPR control by differentiating whether the immunity observed during post-vaccination seromonitoring is due to the vaccination or infection. Currently there are multiple efforts in the development of novel vaccine for PPR that fulfill the principles of DIVA through use of molecular techniques (Banyard et al., 2010; Parida et al., 2015). Another issue worth mentioning with regard to the assessment of post-vaccination herd immunity in this study is the correlation between seroconversion as measured by ELISA and protection level. Some experimental studies indicate that humoral immune response well correlates with clinical disease protection (Olaleye et al., 1989, Zahure et al., 2014) and seroconversion is used in post-vaccination evaluation tool to monitor success of vaccination in the FAO-OIE global PPR control program (OIE and FAO, 2015). But it is also known that cell mediated immune mechanism play role PPR immunity (Kumar et al, 2014). Evidence of the degree of the correlation between seroconversion and protection under field condition may be needed to make appropriate inference of herd immunity from seroconversion proportion.

The population turnover in study indicated that only about 68% of small ruminants that were in the vaccinated flocks remained in the same flocks six months post-vaccination. Animals from vaccinated flocks left the flocks mainly by being sold, death and slaughter. For those joining the flocks it was mainly by birth and to limited extent by being purchased. So while animals leaving the flocks are most likely vaccinated ones, those joining were non-vaccinated as they are mainly newborns resulting in the reduced herd immunity when passive immunity wanes in three to four months (Balamurugan et al., 2012). In addition, animals less than three months of age that were not included in vaccination would also lose their maternal immunity as they grow older and this would further dilute the proportion of immunes. On the hand, some the purchased animals may be from vaccinated flocks. The detail of how many of the new-borns would lose their immunity and how many of the purchased animals were vaccinated was not available to determine exactly the proportion of immune animals in the flocks six month after vaccination. However, the 68% of vaccinated animals remaining in the vaccinated flocks after six months roughly indicates the expected herd immunity in population would be about 68% of the 94% herd immunity achieved immediately after vaccination (i.e. 64%). The implication of this finding is that annual vaccination frequency practised in the district is not sufficient to maintain the critical herd immunity needed to prevent PPR outbreaks. However population turnover could vary in different seasons of the year and the timing of vaccination in relation to this seasonality of population turnover may have a critical impact on the maintenance of herd immunity in the inter-vaccination period (Hammami et al., 2016). In the present study the population turnover was assessed after the Easter festival. Easter season is the time of year in Ethiopia when large number of sheep and goats are slaughtered and so the estimated turnover could be the maximum in the entire year. Further studies are needed to evaluate the seasonality of population turnover and the implications for vaccination timing to maintain herd immunity.

**6. Conclusions**

High seroconversion was found with the flocks tested indicating a good herd immunity level for PPR, a finding consistent with reports from other countries. This indicates the PPR vaccines are efficient in inducing immunity and supports a general concept that PPR can be controlled through vaccination. However, the study also found that the flock turnover is rapid and if poorly timed the vaccination will only provide good herd immunity for short time periods. Therefore the frequency and timing of PPR vaccination is a vital consideration in control PPR by vaccination.

**Conflict of Interest**

None

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