Transmission and control strategies for porcine reproductive and respiratory syndrome virus

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Summary

In the monitoring of porcine reproductive and respiratory syndrome virus (PRRSv), knowledge about between-farm transmission dynamics is still lacking. Our objective was to assess the relative contribution of between-farm PRRSv transmission routes through a mechanistic epidemiological model calibrated with PRRSv occurrence, identify risk areas, and estimate the impact of immunization strategies in the disease spread. We developed a mathematical model of PRRSv transmission accounting for spatial proximity, pig movements, and re-breaks in sow farms, parametrized on data collected routinely by commercial pig farms. We then used the model to simulate the weekly frequency of cases and built risk maps, and compared with the observed cases. We simulated the implementation of two immunization strategies (preventive and reactive) to mitigate the between-farm transmission. Our results indicated for sow and GDU farms' local spread on average was above 60%, while for nurseries between-farm movements represented 83% of transmissions and in finisher farms it was distributed almost 50% local and 50% between-farm movement, the model allowed reproduce the weekly frequency of observed cases and the risk maps built allowed the identification of observed cases in the space. The increase in vaccine efficacy was the most important parameter to mitigate between-farm transmission. Also, the implementation of immunization by a preventive and reactive strategy combined had the better result to mitigate between-farm transmission than implement these strategies individually. These immunization strategies had a better performance with the use of rigorous protocols, such as immunization as soon as the farm receives a shipment or increase the detection

coverage in all production types, as well as reduce time of disease detection. This model can be used by the pork producers to improve surveillance activities, enhancing the capacities to early detect circulation not only of endemic disease but also foreign animal diseases (FADs).

KEYWORDS: swine disease spread, transmission dynamics, disease surveillance, mechanistic modelling.

Introduction

Porcine reproductive and respiratory syndrome virus (PRRSv) is one of the most relevant endemic swine diseases in North America causing major economic loss by reproductive failures and reduction of average daily weight (Holtkamp et al., 2013). In recent years the surveillance and control of PRRSv has increased in order to fight the disease (Corzo et al., 2010; Perez et al., 2015, 2019; Emanuela Pileri & Mateu, 2016). Despite the great advances, PRRSv has proven to be difficult to contain mainly because of the continuous between-farms transmission events (Emanuela Pileri & Mateu, 2016). As a consequence, new outbreaks have been reported each year, with epidemics peaks in the colder seasons (Arruda, Vilalta, Puig, Perez, & Alba, 2018; Hermann et al., 2007; Sanhueza, Vilalta, Corzo, & Arruda, 2019).

In the last two decades, several epidemiological studies have tried to explain the between-farm transmission dynamics of PRRSv (Dee, Deen, Burns, Douthit, & Pijoan, 2004; Dee et al., 2003b; Rosendal et al., 2014; Thakur, Revie, Hurnik, Poljak, & Sanchez, 2015). The contact among farms by pig movements and the proximity distance

between positive and negative farms have been described as the main route for PRRSv spread (K. Lee et al., 2017; Silva, Machado, Baker, Holtkamp, & Linhares, 2019; VanderWaal, Perez, Torremorrell, Morrison, & Craft, 2018; Velasova, Alarcon, Williamson, & Wieland, 2012). Similarly, other studies pointed out that sow farms can re-breaks due to PRRSv recirculation mainly by infected and latent sows, environmental contamination and continuous birth of susceptible piglets (Arruda, Friendship, Carpenter, Greer, & Poljak, 2016; Bierk et al., 2001). Despite these findings, the understanding and quantification of PRRSv transmission continues to be a challenge, which has important consequences in timely control of virus circulation and has limited our knowledge about the impact of control measures over the yearly wave of PRRSv cases.

The construction of mechanistic disease spread models have provided a powerful tool to understand disease transmission dynamics between populations (Dubé, Ribble, Kelton, & McNab, 2009; Siettos & Russo, 2013). More recently studies used mathematical models to investigate how COVID-19 spread between populations and had shown to be useful to monitor the epidemic dynamics, evaluating number asymptomatic populations, risk regions, temporal trend and impact of control strategies (Mandal et al., 2020; Park, Cornforth, Dushoff, & Weitz, 2020; Shim, Tariq, Choi, Lee, & Chowell, 2020; Yang & Wang, 2020), information indispensable to organize effective and efficient control plans and calculate the resources necessaries along the epidemic. Similarly, the use of this mechanistic model in swine diseases can provide the same information, thus it possible to increase our knowledge of the disease dynamic to face endemic disease, as PRRSv, or be used to evaluate epidemic and control scenarios for the introduction of

exotic diseases, such a potential African Swine Fever introduction in the U.S. (Brown & Bevins, 2018; Jurado et al., 2019). In this study, we show that a mechanistic spread model can generate valuable information to understand PRRSv transmission dynamics and evaluate control strategies to avoid the continuous between-farm spread. Our objective was to assess the relative contribution of between-farm PRRSv transmission routes through a mechanistic epidemiological model calibrated with PRRSv occurrence, identify risk areas, and estimate the impact of immunization strategies in the disease spread.

Methodology

We developed a discrete-time stochastic model to simulate between-farm PRRSv transmission. The model included two main transmission routes, between-farm pig movements and local transmission as a function of the distance between susceptible and infected farms, named hereafter simply as local transmission. Additionally, we included the probability of the virus to survive inside the farm causing re-break at sow farms (Emanuela Pileri & Mateu, 2016). In the following sections we present i) a description of the susceptible pig population, the between-farm pig movements and reported cases of PRRSv, ii) a description of the mathematical model, projection of risk areas with future outbreaks and how immunization strategies affect the between-farm transmission.

Data Sources

We collected PRRSv occurrences of 2,294 farms from three not commercially-related pig production systems (here coded as A, B, and C), from a US region. Data of

each farm included national premises identification number, production types (sow, nursery, finisher (which included wean-to-finish and finisher farms) and gilt development unit (GDU), pig capacities, and geographic coordinates.

The record of pig movements between farms was used to reconstruct directed weekly contact networks from June 01, 2019 to December 05, 2019. Each pig movement included movement date, farm of origin and destination, number of pigs transported and purpose of movement (e.g., weaning, market). Movement data with missing either farm location, production type, farm of origin or destination were excluded prior to being analyzed. Thus, the movement between 92% of the farms in the study region comprised a total of 73,361 between-farm movements, in the past six months.

The weekly number of PRRSv cases from January 05, 2009 to December 05, 2019 were compiled from two sources i) for cases in sow farms we used the “PRRSv hotlist” which is used and maintained by each production system to keep track of current and new introductions, and ii) for downstream farms, nurseries, GDU, and finishers, we used ORF-5 PRRSv sequences data, which is maintained by the swine veterinarians to monitor PRRSv strain circulation. Briefly, a new sequence is often generated when clinical signs are identified or there is a reason to request one (Jara, Rasmussen, Corzo, & Machado, 2004). Thus, for sow farms we classified each PRRSv occurrence as “new” or “recurrent case” based on the reported dates. Infection that occured within the past 41 weeks from a previous occurrence in the same sow farm was considered a recurrent case, otherwise it was classified as a new case. We based this classification on the average

national time to breeding farms to reach PRRSv stable status, see (Sanhueza et al., 2019) for more details. Similarly, for nurseries, GDUs and finishers farms, we used pig production phase times to define what was a new PRRSv case, where a sequence of PRRSv within 7, 22 and 25 weeks, respectively, was counted towards a recurrent case. The rationale for the intervals used was based on the production characteristics of each farm type, since these production sites are all-in and all-out continuous animal flow, indeed all animals are introduced and removed from a farm within a short period of time.

Between-farm infection dynamics and transmission routes

The between-farm transmission was modeled through a discrete-time stochastic model, using three farm infection status: susceptible (S), undetected infection (U) and detected infection (D) at each time step (Figure 1A). The chosen one week time step matches the frequency at which cases are reported. In this model, susceptible farms were allowed to become infected, with the disease being initially undetected, through two main between-farm transmission routes: infected incoming pigs from infected farms (both undetected and detected) (VanderWaal et al., 2018), and local transmission from nearby infected farms (Silva et al., 2019; Velasova et al., 2012). To model the local transmission force of infection, we used a gravity model, while also accounting for the vegetation surrounding each farm, as a possible barrier to transmission (Arruda, Vilalta, Perez, & Morrison, 2017). Additionally, previous studies have shown that PRRSv can persist undetected within recently infected farms, mainly in sow farms, contaminated environments or fomites (Emanuela Pileri & Mateu, 2016). We thus included in the model a probability of sow farms to re-break with PRRSv within two-year since their last

infection (Perez et al., 2019). The transmission rates from the between-farm pig movements, local transmission and the re-break probability were represented by the beta values βnet, $\beta local$ and $\beta rebreak$ and were fitted to the observed number of PRRSv cases (see model fitting section) (Figure 1B).

Figure 1.

Between-farm pig movements

We used the weekly pig movement to identify contacts between susceptible farms *i* and both infected detected and undetected farms *j*, which were used to estimate infectious force by pig movements in the network (**λ**net):

$$\lambda net_{it} = \beta net * N_{it};\ \forall = 1, \dots, n\ suceptible\ farms, \quad (1)$$

N_i is the number of incoming contacts received from infected farms (undetected and detected) at the time step *t (one week)*.

Local transmission

The local transmission was modeled through a gravity model as follow:

$$a_{ij} = \frac{m_i m_j}{d_{ij}^2}\ , \quad (2)$$

where the attraction force between the farms *i* and *j* was directly proportional to the farms' pig capacity m_i and m_j divided by the squared Euclidean distance d_{ij}^2 between the two farms. In addition, based on some preliminary simulations, we set the maximum range of local transmission to 35km (a_{ij} = 0 when d_{ij} > 35km). Local transmission was

modulated by the enhanced vegetation index (EVI), which was used to quantify vegetation greenness around each farm, here representing a potential barrier that reduced local transmission of PRRSv (Arruda et al., 2017). Thus, susceptible farms at a high EVI location were less likely to be infected via local transmission from nearby infected farms, decreasing the attraction force between m_i and m_j such that,

$$g_{ij} = a_{ijt} * (1 - e_{it})\ ;\ \forall_i = 1, \dots, n\ suceptible\ farms, \tag{3}$$

where g_{ij} is the attraction force including the barrier effect, in which e_i is the barrier index from farm i represented on a [0,1] scale (see SM for additional information). Thus, the local infectious force (***λlocal***) was defined as

$$\lambda local_{it} = \beta local * \sum_{j=1}^{n} g_{ijt}\ ;\ \forall_i = 1, \dots, n\ suceptible\ farms\ , \tag{4}$$

$$;\forall_j = 1, \dots, n\ infected\ farms$$

Sow farm re-break

Exclusively for sow farms, a re-break probability which is computed with the other two forces of infection was included as

$$\lambda rebreak_{it} = \beta rebreak\ ;\ \ \forall_i = 1, \dots, n\ suceptible\ sow \tag{5}$$

$$farms\ with\ historical\ PRRSv\ records\ from\ June\ 2017\ to\ June\ 2019,$$

The transmission dynamics

The total force of infection (**λ**) was calculated as the sum of all infectious forces accounting for the monthly PRRSv seasonality,

$$\lambda_{it} = (\lambda net_{it} + \lambda local_{it} + \lambda rebreak_{it}) * T_{tm}, \tag{6}$$

where λ_{it} is the total infectious force from a susceptible farm *i* and T_{tm} is the seasonality index from the time step *t* in month *m*. The monthly seasonality represents periods of time where the PRRSv transmission is more or less frequent due to pigs' immunity and a coordinated sequence of events related to the weather that may influence the total transmission (Dee et al., 2003b, 2003a). Thus, the seasonality index values were estimated from the moving averages of the monthly frequency of PRRSv cases between 2015 and 2019 (SM Figure 1), which were then scaled between 0.001 and 1. We also include a term that accounts for the farms' ability to remain PRRSv negative (*H*), which modulates the λ_{it}

$$\lambda_{it} = ((\lambda net_{it} + \lambda local_{it} + \lambda rebreak_{it}) * T_{tm}) * (1 - H_{it}), \quad (7)$$

here H takes values between 0 and 1 and represents a reduction in the total force of infection received by the susceptible farms with lower risk of infection (H>0). Thus, we assigned H values greater than 0 only for sow farms without PRRSv cases from July 1, 2009 until June 1, 2019, which were denominated farms with low risk of infection as an initial condition setting in the model. Furthermore, H value was fitted to the observed number of PRRSv cases (see model fitting). Finally, we calculate the transmission probability (Y_{it}):

$$Y_{it} = 1 - e^{-\lambda_{it}}, \quad (8)$$

where the transition probability of a susceptible farm *i* to infected and undetected status at time point *t* is given by Y_{it}.

The detection rate for an infected farm (transition from undetected to detected infection status) is calculated by a detection probability derived from a logistic function

$$f(x) = \frac{L_p}{1 - e^{-k(x-x0)}} \tag{9}$$

where L is the maximum detection probability for PRRSv cases and its value was defined accordingly to the farm production types p. Thus, for sow farms which undergo periodically testing, we assumed L to be 0.95, while in nurseries, finishers and GDU farm, PRRSv reported cases are frequently underestimated due to the lack of clinical signs and samples are rarely collected, as a consequence the probability of detecting cases in these farms is lower compared with sow farms. Therefore, to fit L in each production type based on observed PRRSv cases and an empirical PRRSv prevalence (see model fitting section for more details). Here, $X0$ is the sigmoid's midpoint to detect an infected undetected farm (i.e. which was assumed to be the average time for PRRSv detection), defined in 4 weeks, k is the logistic growth rate, which we assumed to be 0.5 to increase the detection probability after each week and X were the weeks post infections. These values were defined after consulting with veterinarians of the studied production systems, which was also set to 4 weeks to detect an infected undetected farm. The assumption was in agreement with the only publication to authors' knowledge, done in Chile where it was found the virus could have been circulating for at least one month before it was detected (Neira et al., 2017).

In the model we assumed the course of infection according to the farm production type. Thus, an infected undetected sow farm stayed indefinitely infected until it was detected, after detected the farm stayed infected by a predefined time calculated from a

poisson distribution using 41 weeks (average time to stability) as the mean of the distribution (Sanhueza et al., 2019), then the farm transited to susceptible status after its predefined infectious time elapsed in the simulation. On the other hand, due to the all-in and all-out animal flow in nursery, GDU and finisher farms, these return to susceptible status at the end of its production cycle, which means when all its pigs were moved out of its premises.

Initial conditions settings

The initial farms assumed to be infected in the starting point of the simulation where all farms previously infected within a number of days before June first 2019 accordingly farm types as follows: sow 41, nursery 7, GDU 22, finisher 25 weeks. These time intervals correspond to time to stability in sow farms and cycle production time for the other production types, respectively (Holtkamp et al., 2011).

Model fitting

We used an Approximate Bayesian Computation (ABC) method based on a modified Sequential Monte Carlo (SMC) rejection algorithm, which allows us to recover the approximate posterior distribution of the five unknown model parameters Bnet, Blocal, Breinf, H, and L. A set of draws of these five parameters is denominated a “particle" (Beaumont, 2010), and the value was fitted to the observed PRRSv cases for each production type from June 1 until December 5, 2019. For nursery and finisher farms an empirical expected weekly number of cases, derived from an annual prevalence of 30% (production system veterinarians, personal communications), was used. However,

considering the yearly PRRSv seasonality (Arruda et al., 2018; Jara et al., 2004), we divided that empirical prevalence by week according to the seasonal index T calculated previously and by the average number of weeks by month. For example, the expected prevalence for the weeks in December was calculated as $(0.3 \,/\, (T_{December} \,/\, \sum_{m=1}^{n=12} T_m)) \,/\, 4.34 \,;\, \forall_m = January, \ldots, December$.

The sequential algorithm had a two-step rejection procedure. In the first step, the model was fitted to the weekly frequency of cases using eleven summary statistics, see Table 1. In the second step, the sensitivity and specificity of the model to predict true risk areas was evaluated through the comparison between simulated and observed infected farm locations within cells of 10km by 10km (see SM for the sensitivity and specificity calculation). The ABC rejection procedure was ran until the generation of 100 desired particles (N), with a tolerance interval (ϵ) for all metrics as shown in Table 1. Finally, the model was performed using the parameters listed in Table 2.

Model outputs

The model outputs generated were i) the weekly PRRSv number of infected farms, both undetected and detected, ii) the estimated force of infection for each transmission route and farm production type, iii) forecasting risk areas and comparison of simulated and observed infected locations.

To assess the relative contribution of each transmission route, namely between-farm, local and re-breaks in sow farms, we generated 1000 model runs with each

transmission route simulated one at a time. For example, between-farm transmission can be calculated as the total number of farms infected in the runs with only between-farm transmission divided by the total number of farms infected summed across the three transmission routes.

To evaluate the efficacy of the disease spread model to predict the location of future PRRSv cases, the 319 sow farms from our study region were grouped into 154 cells of 10km by 10km, in which the number of sow farms by cell was 1 in median, 3 in the percentile 75% and a maximum of 12 farms. We calculated a risk of PRRSv detection by cell into one week windows based on the output of the fitted model and the inclusion of previous reported cases to avoid their influence in the forecasting. Thus, we calculated the risk of PRRSv detection and new introductions for sow farms between October 30, 2019 and November 06, 2019 (week with the higher number of cases reported, 3 cases) and identified the cell with a risk about the percentile 90 (arbitrarily chosen) as higher risk.

Control strategies

We simulated two possible control strategies that could be implemented, both of them relate to herd level immunization and were aimed at reducing between-farm transmission (Moura et al., 2019). In the first control scenario simulated, referred to as the preventive strategy, the nursery, GDU and finisher farms administer massive vaccination the same week after receiving pig placement. In the second scenario simulated, hereafter named reactive strategy, all farm types administer massive

vaccination the same week after detecting PRRSv. Finally, we considered a third scenario combining the preventive and reactive strategy. Here we assumed twelve different vaccine efficacies (V): 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 30%, 50%, 80% and 90%, implemented as a reduction in the overall force of infection. Also, here we assumed V followed a logistic growth curve and reached its maximum efficacy after 4 week of implementation (Kick et al., 2019). Because information about the length of the herd immunity levels post vaccination continues to be a gap in knowledge, in our formulated scenarios vaccinated pigs maintain protection for 36 weeks, which was based on (Arruda et al., 2016; Evans, Medley, Creasey, & Green, 2010) and an expert opinion study. Thus, for nursery, GDU and finisher farms, herd immunity protected pigs throughout the whole production phase. A brief explanation of the V to reduce the force of infection is available in SM. Each intervention effectiveness was evaluated through the accumulated number of infected farms by production type over the period simulated and compared with the baseline model (V=0). In addition, we evaluated the influence of some complementary protocols to reduce the average number of cases. Thus, for the preventive strategy, we included a delay of 1, 2 and 3 weeks to vaccinate after receiving a pig placement and for the reactive strategy, we included a delay of 1, 2 and 3 weeks to vaccinate after detecting PRRSv, also a lower time for viral detection of 1, 2 and 3 week and stronger detection surveillance of 0.5 and 0.95 probability in nursery, GDU and finisher farms (i.e., reinforce sampling strategies). All these protocols were evaluated through a multivariate linear regression for each control scenario tested.

Results

In table 3 we summarized the farms susceptible and the total number of infected farms by production types. Sow farms showed more cases of PRRSv as expected, while finisher and nursery farms together had around half of the sow cases. GDU farms were less infected and no cases were reported in isolation and boar stud farms. These results need to be interpreted with caution since the volume of cases are directly related to the surveillance effort, in sow farms it often involves weekly testing at weaning or at processing, in which viral detection may vary because of the test options available (Henao-Diaz, Ji, Giménez-Lirola, Baum, & Zimmerman, 2020). To fit the model, 48 cases were identified from June 01, 2019 to December 05, 2019, being those reported in sow, nursery and finisher farms.

The simulations indicated that on average 61% of the sow farms cases were due to local transmission, while 33% and 6% were due to pig movements and re-break, respectively (Figure 2). For nursery farms, 80% of cases were due to pig movements and 20% local transmission, while for finisher movements and local transmission had almost the same relevance with 47% and 53% of cases, respectively. Regarding GDU farms, local transmission was responsible for 99% of the cases.

Figure 2.

The estimated average number of new cases after 26 weeks thought the simulation was 19 (IQR 16-21) for sow farms, 57 (IQR 52-63) for nursery farms, 9 (IQR 8-11) for GDU farms and 100 (IQR 90-110) for finisher farms. The new detected cases estimated by the model followed the same temporal pattern of the observed cases, being the most of

these observed cases equal to the median of the simulations or falling into the interquartile range (IQR) calculated (Figure 3A). Regarding the new undetected cases estimated by the model, nursery and finisher farms were the production types with a higher weekly frequency (Figure 3B), principally in the last two months (November and December), with a maximum of 13 and 28 cases per week, respectively. Contrary, sow and GDU farms had a lower frequency of new undetected cases, with a maximum of 7 and 5 cases per week, respectively.

Figure 3.

In the spatial forecast of the observed cases in sow farms, the model had an average maximum sensitivity of 62% (IQR 56%-83%) when a subset of cells with risk values above percentile 40 was used as a threshold to identify infected observed cells (SM Figure X). For example, the forecasted week had three sow farms with positive PRRSv records located in three different cells (Figure 4A), our model calculated the risk of disease detection for each cell (Figure 4B) and identified the 16 cells with risk above percentile 90 (16 from 154 cells) (Figure 4C). As a result, two of the cells with observed cases were also cells with risk about percentile 90%. Thus, the model was able to detect two of the three reported cases. We used the model to calculate the risk for newly infected sow farms for the simulated week (Figure 4D) and showed the cells with risk above 90% (Figure 4E).

Figure 4.

Control measures

In general, the three scenarios evaluated had a significant lower average cases starting from a vaccine efficacy (*ve*) of 1% ($p > 0.05$), except by sow and GDU farms in the preventive scenario which needed a *ve* of 2% and 3%, respectively (Table 3 and SM Table x and x). Independent of the statistical differences found, the combined scenario had a lower average cases than using the preventive or reactive strategies individually, that was observed along all the *ve* tested and for all the production types (Figure 5). For example, the average total cases along the 26 weeks simulated without control was 185 new cases, the simulations in the combined scenario with *ve* = 5% had a total of 107 new cases (42% less cases compared with no control scenario), while the same *ve* in the preventive scenario had 136 new cases (26% less cases) and the reactive had 139 new cases (25% less cases). The preventive and reactive scenario had similar results in nursery farms along all *ve* tested, but had differences in finisher farms due to lower average cases in the preventive scenario and in GDU and sow farms due to lower average cases in the reactive scenario (Figure 5). Furthermore, it is important to note that the combined and reactive scenario had a considerably lower average cases than the preventive scenario in sow and GDU farms, that difference was easier to observe after a *ve* ≥ 5%.

In table 3 was presented a multivariate linear regression from the combined scenario in function of the *ve* and other complementary control protocols. As expected, immunization was the most important variable to prevent cases as increased *ve* values (Table 3). The protocol with higher importance was a shorter time to immunize the farm

after receiving a pig shipment, however this variable had a high influence only in finisher farms with 2.2 cases prevented when the farm was immunized in the same week after receiving a pig shipment, while in the other production types prevented lees than 1 case. The remaining protocols for this scenario had a low influence to prevent cases in all production types (<0.6 cases prevented). On the other hand, the contribution of these protocols was different when the preventive and reactive strategies were evaluated individually (SM Table 1 and 2). For both strategies the contribution of *ve* was lower than the combined scenario, but still had the highest influence to prevent cases. However, the influence of the protocols to prevent cases was higher than in the combined scenario, being this difference more evident in finisher and nursery farms. For example, in the preventive strategy, finisher and nursery farms had 5.4 and 1.6 cases less if the farms were immunized in the same week after receiving a pig shipment. While for the reactive strategy, increasing the probability detection of PRRSv to 0.95 in all farm types was the most important protocol with 4.3 and 1.6 cases less in finisher and nursery farms, respectively. The other protocols combined in the reactive strategy prevented 3.6 cases in finisher farms and 1.6 cases less in nursery farms if the farms were detected and immunized in the same week of virus introduction.

Figure 5.

Discussion

In this paper, we addressed two important points for the control of PRRSv in the United States, i) we built a disease spread model able to reproduce and quantify between-

farm transmission dynamics. Our results indicated for sow and GDU farms' local spread on average was above 60%, while for nurseries between-farm movements represented 83% of transmissions and finisher farms it was distributed almost 50% local and 50% between-farm movement. ii) We evaluated the effect of PRRSv surveillance and control strategies in reducing the number of new infected farms. The increase in vaccine efficacy was the most important parameter to mitigate between-farm transmission. Also, the implementation of immunization by a preventive and reactive strategy combined had the better result to mitigate between-farm transmission than implement these strategies individually. These immunization strategies had a better performance with the use of rigorous protocols, such as immunize as soon as the farm receives a shipment or increase the detection coverage in all production types, as well as reduce time of disease detection. For this last protocol, our model is able to provide information about the probable location of new cases by the construction of risk maps that could be used for early disease detection.

PRRSv spread model

In our current model, the transmission, surveillance and diagnosis parameters were fitted through the observed cases, previous scientific literature and the expert opinion of local veterinarians about PRRSv, thus we tried to represent a close approximation of what happens in field conditions. We highlight that transmission, surveillance and diagnosis continue to be a stochastic process, while disease was not randomly distributed in space. Our model differs from previous studies modeling PRRSv due most of them focused on model within-farm transmission (Arruda et al., 2016;

Bitsouni, Lycett, Opriessnig, & Doeschl-Wilson, 2019; Evans et al., 2010; Phoo-ngurn, Kiataramkul, & Chamchod, 2019), while other studies modeled between-farm transmission, but without the inclusion of empirical farm' location or pig movements between farms to spread the virus (H. S. Lee et al., 2019; Thakur, Sanchez, et al., 2015). Although, there was a study which used empirical pig movements, this did not include the actual spatial location of the farms (Thakur, Revie, et al., 2015). Also, in the knowledge of the author at the moment to write this manuscript, there was no studies with a model calibrated with historical records of PRRSv cases in pig farms. Thus, our study may provide a more robust result about between-farm transmission of PRRSv.

Our findings indicating a high contribution of local transmission in sow (63%), GDU (99%) and finisher (52%) farms was a controversial result because even proximity distances between farms have been indicated as a risk factor associated with PRRSv (Silva et al., 2019; Velasova et al., 2012), most of the previous studies indicated movements as the main transmission route (Amirpour Haredasht et al., 2017; K. Lee et al., 2017; VanderWaal, Paploski, Makau, & Corzo, 2020). Nevertheless, in our study pig movements also played an important role to infect nursery (88%) farms and had approximately half of the contribution to infect finishers farms (48%). Thus, the transmission due pig movements was still relevant to spread the disease and both transmission routes may be conditioned to the farms' production type. Despite these results, it is necessary to consider that the model used in this study was calibrated trying to identify the areas where PRRSv cases in sow farms were reported. Thus, the rate of the movements, local transmission or re-break increased when any of these routes was able to

explain to a greater degree the spatial distribution of these observed cases. As a result, the cases not explained by movements or re-break were explained by a greater contribution of the local transmission. Also, the local transmission in our model may be filling the lack of other potential transmission routes not included here, such contaminated vehicles, vectors and visitors (Dee et al., 2003a; Pitkin, Deen, & Dee, 2009; Pitkin, Deen, Otake, Moon, & Dee, 2009) and their future inclusion may change the contribution of the transmission routes found in this study.

PRRSv surveillance and control

At the moment, studies evaluating farm level immunity against PRRSv are not available, being the most of the studies focused on animal level immunity and making the comparison with our results difficult. Thus, future studies evaluating farm level immunity will bring valuable information to compare with the model result. The studies evaluating the efficacy of immunization through adapted modified-live vaccine (MLV) at animal level have indicated that due the nature of the virus, characterized by rapid mutation rates and extensive genetic divergence (Cho & Dee, 2006; Kappes & Faaberg, 2015), the current vaccines have not been sufficient to provide complete protection against the emerging and reemerging viral strains (Hou et al., 2020; Lunney et al., 2016). Thus, it is possible to assume that the current vaccine efficacy at farm level is low. Despite that, it has been proved that the use of vaccines reduces PRRSv shedding spread (Jeong, Park, Kang, Park, & Chae, 2017; E. Pileri et al., 2017; Emanuela Pileri et al., 2015), and consequently provides a lower probability of transmission, whereby combined with an

effective implementation strategy could reach better results to contain the disease spread between farms.

Our results showed that the combination of the preventive and reactive strategy had the best performance to reduce the number of new cases than using each of these separately, however this can be associated with a higher vaccination coverage in the farms (Bitsouni et al., 2019; Gandon, Mackinnon, Nee, & Read, 2003). On the other hand, the use of these strategies individually could be also useful, but it is necessary to consider their strengths and weaknesses. For example, the preventive strategy had an advantage against the reactive strategy by immunizing the farms after receiving a pig shipment, whereby infected farms could implement immunization before the disease was detected and reduce its infection force to other farms. Thus, the preventive strategy was aimed to avoid cases mainly caused by animal movements, as a result the farms which had a strong contribution of the movements (nursery and finisher farms) had a lower incidence as *ve* increased than the farms which had stronger contribution of the local transmission (sow and GDU farms). On the contrary, the reactive strategy here simulated aimed to immunize detected farms, whereby the route of transmission of the virus to the farm was not as relevant as in the preventive strategy, instead the virus detection in the farms played a more important role. In this study we assumed that sow farms had a high probability of virus detection (L = 0.95), consequently were more often detected and immunized than the other production types which had a lower probability (L = 0.09). Therefore, in the reactive strategy most of the infected sow farms were vaccinated and its infection force to other farms was reduced, this was highly relevant for the control of PRRSv because sow farms act as super-spreaders in the network due they can reach a high number of farms by their trade contact chain (Passafaro,

Fernandes, Valente, Williams, & Rosa, 2020). Our result suggests that the reactive strategy had equal or better performance to reduce cases in nursery, sow and GDU farms, and slightly worse in finisher farms when compared with the preventive strategy. Therefore, the reactive strategy seems to be a better option to implement, however additional studies are necessary to consider implementing the reactive instead of the preventive strategy. Thus, using both strategies combined seems to be the better option at the moment to control PRRSv between-farm transmission.

The results of the built model can provide weekly reports (maps) of where samples have elevated probabilities of return positive, thus providing information necessary to implement PRRSv control based on target surveillance. In the surveillance of PRRSv in the United States, we found two studies trying to predict spatial risk, one was associated with the Dr. Morrison's Swine Health Monitoring Program (MSHMP), which has contributed to collect data and evaluate the characteristics of this disease in the country, one its products was the construction of spatial risk maps of PRRSv outbreaks using machine learning algorithms with environmental and pig population variables (Vilalta et al., 2017), but without the inclusion of between-farm transmission variables that are crucial to understand the disease spread dynamic. The other study used pig trade network matrices and geographical distance to predict the farm's PRRSv status through a spatio-temporal analysis using Bayesian models with INLA (Amirpour Haredasht et al., 2017); the model had a relatively high accuracy (87%) to predict PRRSv farm status, however used 6-month windows to evaluate the probability of new infection and that is a limiting to use into real-time target surveillance. Other studies outside US tried to predict

PRRSv recirculation within sow farms using conditional poisson models with farm production index associated with PRRSv occurrence with (Fraile et al., 2020), although this methodology did not considered between-farm transmission dynamic, it is an interesting methodology to include in futures step in our model to calibrate the re-break probability in the sow farms. Thus, considering the previous studies developed to predict PRRSv, our model can provide valuable information for target surveillance in real time.

Limitations and final remarks

One limitation of this study is related to how sequences are collected in downstream farms. Since each production system may follow a different protocol while deciding in sending a sample to be sequenced, and this can also vary among the veterinarians of the same company, said that until routine surveillance is not implemented in those farm types, this data may be the best approximation of what has been circulating in finisher and GDU and nursery farms. Another limitation of this study is the fact that we do not consider the influence of viral genetics, we assume that all sequences from the downstream farms are all the same and can be transmitted between-farms at the same probability. It was not the goal of this study to model individual PRRSv strains, but this should be considered in future studies. In addition, we calibrated our model using only the spatial location of sow farms, whereby it may brought a bias in the transmission rates calculated with the ABC, and consequently in the contribution of the transmission routes, thus the future inclusion of the location of cases from nursery, GDU and finisher farms will provide a more robust result, however it will only be possible with a stronger surveillance to detect and report the presence of PRRS in these farms. Regarding the

control, in our model we assumed that vaccinated animals acquire life-long immunity, in the future the heterologous response should be investigated in more detail in regard to its effect in reducing between-farm spread, also due most of the literature about vaccines is available at animal-level, the inclusion of compartmental transmission model at animal-level in our model can allow to incorporate specific characteristics of vaccines.

In summary, our model reveals the transmission dynamic of PRRSv in our study area, identifying the contribution of movements and local transmission to infect individually sow, nursery, GDU and finisher farms. Also, increasing the vaccine efficacy was crucial to avoid the continuous disease spread and its implementation through a preventive and reactive strategy combined could prevent outbreaks in all production types. Thus, this study provided producers and swine veterinarians a better understanding of the disease spread process and which, when and where intervention(s) will better impact the disease transmission chain. Ultimately, our model can be used to improve tactical surveillance activities, enhancing the capacities to early detect circulation not only of endemic disease but also foreign animal diseases (FADs).

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Conflict of interest

All authors confirm that there are no conflicts of interest to declare

Ethical statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page. Since this work did not involve animal sampling neither questioner data collection there was no need for ethics permits.

Data Availability Statement

The data that support the findings of this study are available from the regional veterinary office. Restrictions apply to the availability of these data, which were used under confidentiality agreements.

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Table 1. Summary statistics used in the Approximate Bayesian Computation Sequential Monte Carlo rejection algorithm.

Summary Statistic	Observed Values	Tolerance interval
Total number of new cases detected in sow farms	23	10
Av. weekly number of new cases detected in sow farms	0.85	0.5
Max. number of new cases detected in a week in sow farms	3	5
Total number of new cases detected in nursery farms	17	10
Av. weekly number of new cases detected in nursery farms	0.62	0.5
Max. number of new cases detected in nursery farms	3	5
Total number of new cases detected in finisher farms	8	10
Av. weekly number of new cases detected in finisher farms	0.3	0.5
Max. number of new cases detected in a week in finisher farms	3	5
Total number of expected cases in nursery and finisher farms	155	100
Av. weekly number of expected cases in nursery and finisher farms	5.7	5
Max. number of expected cases in nursery and finisher farms	20	10

Table 2. Transmission parameters used in the disease spread model to simulate PRRSv infection dynamics.

Model parameters	Symbol	Values	Reference
Transmission rate by movements	βnet	0.24	Median values from ABC fitting
Transmission rate by local	$\beta local$	0.003	Median values from ABC fitting
Transmission rate by re-break	$\beta rebreak$	0.0019	Median values from ABC fitting
Farms' ability remain PRRSv stable	H	Sow = 0.53 GDU = 0.27	Median values from ABC fitting
Effective surveillance	L	Sow = 0.95 Nursery, GDU and Finisher = 0.094	Median values from ABC fitting
PRRSv cases seasonality	T	Weekly values calculated	Moving averages
Enhanced vegetation index	EVI	Values by farm each week	https://lpdaac.usgs.gov
Gravity with barrier effect	g	Calculated in each time step	Based on EVI (SM)
Av. time for PRRSv detection	X	4 weeks	Expert opinion
Av. infectious time sow farms	-	41 weeks	(Sanhueza et al., 2019)

Table 3. Number of PRRSv cases by production types, for a time series from 2009-2019 and a subset of cases used in the study

Production Type	Susceptible farms	Total new cases 2009-2019	Subset new cases Jun-Dec 2019
Sow	319 (14%)	1070	23
Gilt development unit (GDU)	187 (8.2%)	50	0
Nursery	468 (20.4%)	648	17
Finisher	1272 (55.4%)	537	8
Isolation	33 (1.4%)	0	0
Boar Stud	15 (0.6%)	0	0

Table 4. Multivariate linear regression from the combined control scenario.

		Sow	Nursery	GDU	Finisher
Cases without control		**19 (16-21)**	**57 (52-63)**	**9 (8-11)**	**100 (90-110)**
Vaccine efficacy [c]	1%	-1.4 (-1.4,-1.5)	-4.3 (-4.1,-4.4)	-1 (-0.9,-1)	-14 (-13.7,-14.2)
	2%	-2.7 (-2.6,-2.8)	-8.1 (-7.9,-8.2)	-1.8 (-1.7,-1.8)	-24.8 (-24.5,-25)
	3%	-3.8 (-3.7,-3.9)	-11 (-10.9,-11.2)	-2.6 (-2.5,-2.6)	-33.9 (-33.7,-34.2)
	4%	-4.7 (-4.6,-4.8)	-13.6 (-13.5,-13.8)	-3.3 (-3.2,-3.3)	-41.7 (-41.4,-41.9)
	5%	-5.5 (-5.5,-5.6)	-15.9 (-15.7,-16.1)	-3.9 (-3.9,-4)	-47.7 (-47.4,-47.9)
	10%	-8.6 (-8.5,-8.6)	-23.3 (-23.1,-23.4)	-6.4 (-6.3,-6.4)	-66.1 (-65.8,-66.3)
	15%	-10.1 (-10,-10.2)	-27.7 (-27.6,-27.9)	-7.6 (-7.6,-7.6)	-74.3 (-74,-74.5)
	20%	-10.9 (-10.8,-11)	-31.2 (-31.1,-31.4)	-8.2 (-8.2,-8.3)	-78.8 (-78.5,-79.1)
	30%	-11.9 (-11.8,-12)	-36.7 (-36.6,-36.9)	-8.8 (-8.8,-8.9)	-84.7 (-84.5,-85)
	50%	-13.3 (-13.3,-13.4)	-45.9 (-45.8,-46.1)	-9.2 (-9.2,-9.2)	-91.6 (-91.4,-91.9)
	80%	-15.5 (-15.4,-15.6)	-54.7 (-54.5,-54.8)	-9.3 (-9.3,-9.4)	-96.8 (-96.6,-97.1)
	90%	-16.4 (-16.3,-16.4)	-56.2 (-56.1,-56.4)	-9.4 (-9.3,-9.4)	-97.9 (-97.6,-98.1)
Delay vaccine after shipment [a]	2 w	0 (0,-0.1)	-0.1 (0,-0.2)	0 (0,0)	-0.5 (-0.4,-0.7)
	1 w	0 (0,-0.1)	-0.3 (-0.2,-0.4)	0 (0,0)	-1.4 (-1.2,-1.5)
	0 w	-0.1 (-0.1,-0.1)	-0.6 (-0.5,-0.7)	0 (0,-0.1)	-2.2 (-2.1,-2.3)
Average time dx [a]	2 w	0 (0,-0.1)	0 (0.1,-0.1)	0 (0,-0.1)	-0.1 (0.1,-0.2)
	1 w	0 (0,-0.1)	0 (0.1,-0.1)	0 (0,-0.1)	-0.1 (0,-0.3)
	0 w	-0.1 (0,-0.1)	-0.1 (0,-0.2)	-0.1 (0,-0.1)	-0.2 (-0.1,-0.4)
Delay vaccine after dx [a]	2 w	-0.1 (-0.1,-0.2)	-0.1 (0,-0.2)	-0.1 (-0.1,-0.1)	-0.3 (-0.1,-0.4)
	1 w	-0.2 (-0.2,-0.3)	-0.3 (-0.2,-0.4)	-0.2 (-0.2,-0.2)	-0.6 (-0.4,-0.7)
	0 w	-0.2 (-0.2,-0.3)	-0.3 (-0.2,-0.4)	-0.2 (-0.2,-0.2)	-0.6 (-0.5,-0.7)
Probability. dx [b]	0.5	0 (0,-0.1)	-0.1 (0,-0.2)	0 (0,0)	-0.1 (0,-0.3)
	0.95	0 (0,-0.1)	-0.1 (0,-0.2)	0 (0,0)	-0.1 (0,-0.2)

*p > 0.05. [a] Base comparison category 3 weeks. [b] Base comparison category 0.09.
[c] Base comparison category 0%. (dx = detection, w = week(s))

Figure Legends

Figure 1. Between-farm PRRSv transmission modelling framework. A) Flow between infection stages; and B) The modeled transmission routes.

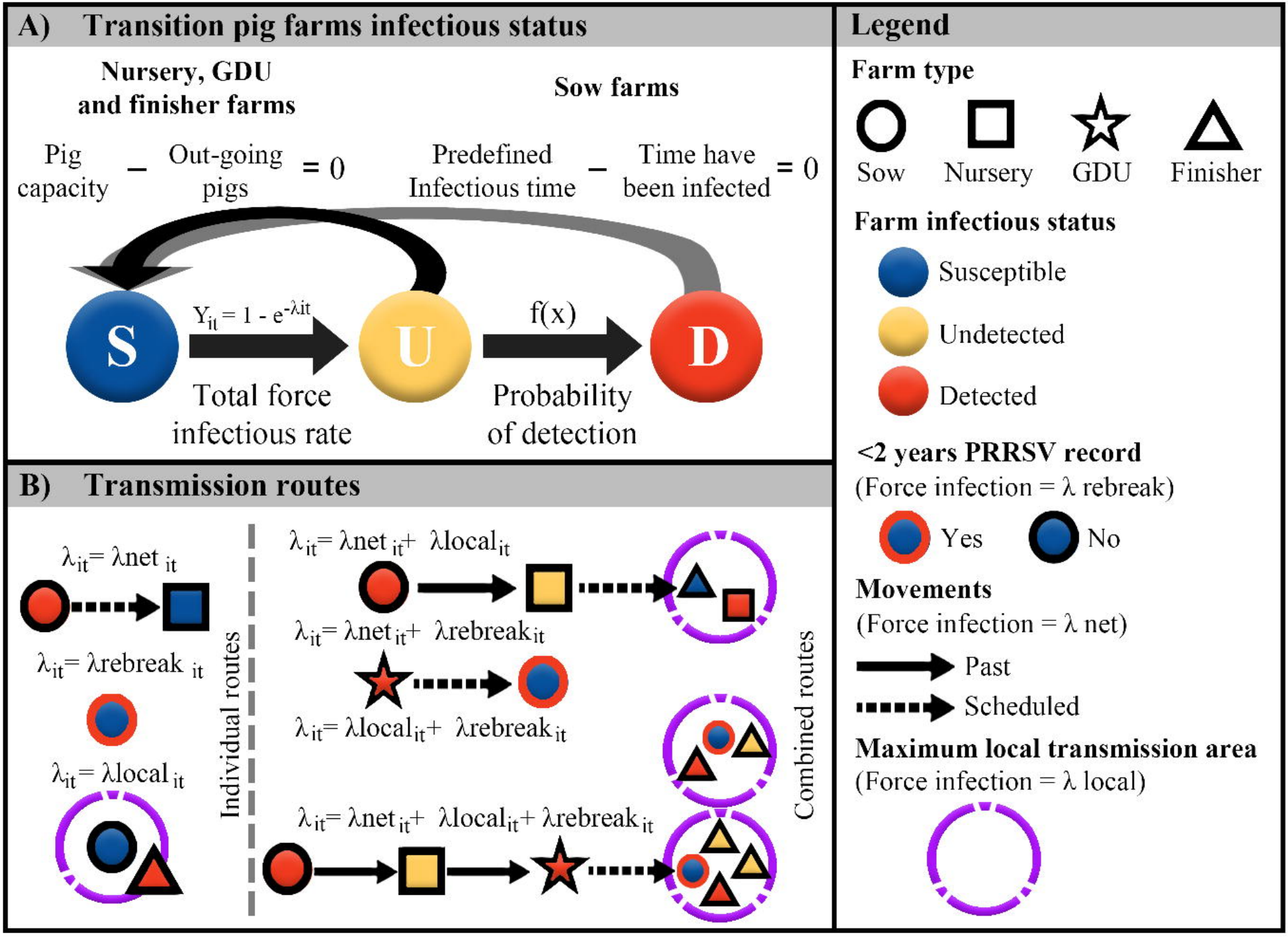
Fig. 2. Infection force by each transmission route and production type. Y-axis represents the proportion of transmission estimated by each transmission route, while x-axis to which week the model was projected to make these inferences.

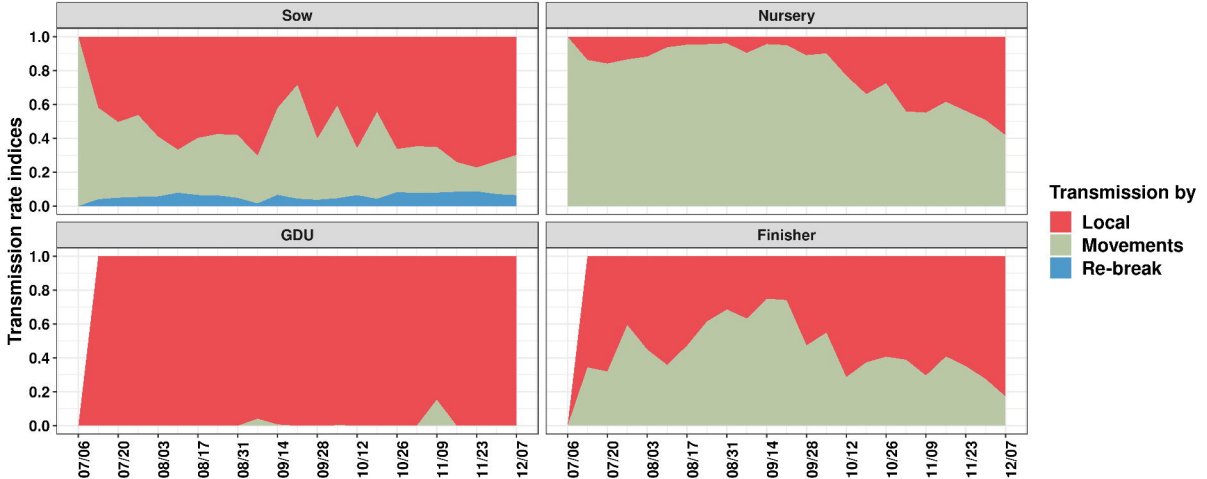
Figure 3. The weekly number of reported and simulated cases PRRSv for sow, nursery, gilt development units (GDU) and finisher farms. **A-top**) Number of observed (in red) and simulated detected PRRSv cases (in grey) and **A-bottom**) the grey line represent the median of the model and shade area the first and third quartile; **B-top**) Number of simulated undetected PRRSv cases and **B-bottom**) the grey line represent the median of the model and shade area the first and third quartile.

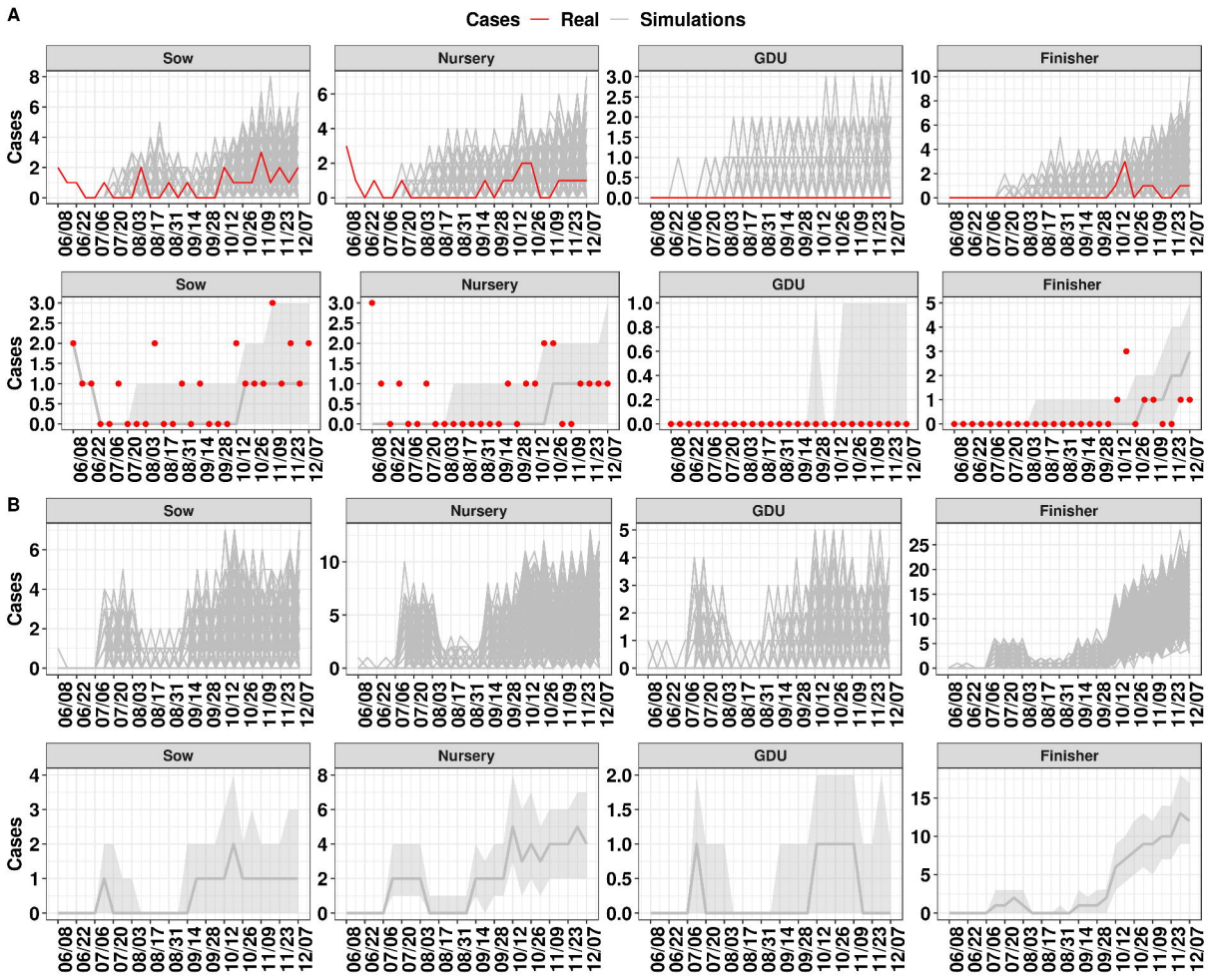
Figure 4. Spatial forecasting of PRRSv in sow farms for a week between October 30, 2019, to November 06, 2019. A) cells with observed sow farms infected; B) risk of PRRSv detection ; C) subset of cells with risk of PRRSv detection above percentile 90; D) risk of new PRRSv introduction; and E) subset of cells with risk of new PRRSv introduction above percentile 90. *(cells with risk = 0 have transparency).

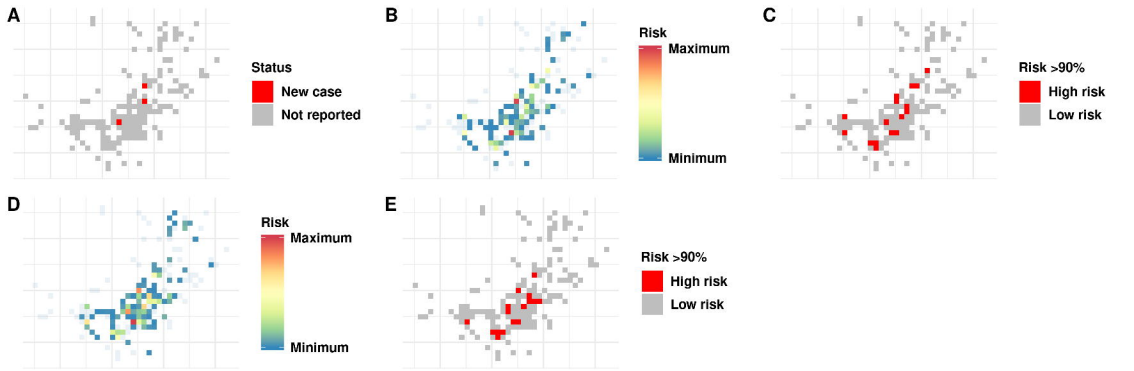
Figure 5. Accumulated number of infected farms along 26 week after the implementation of control strategies. In the graph, the vaccine efficacies are grouped by color, points are

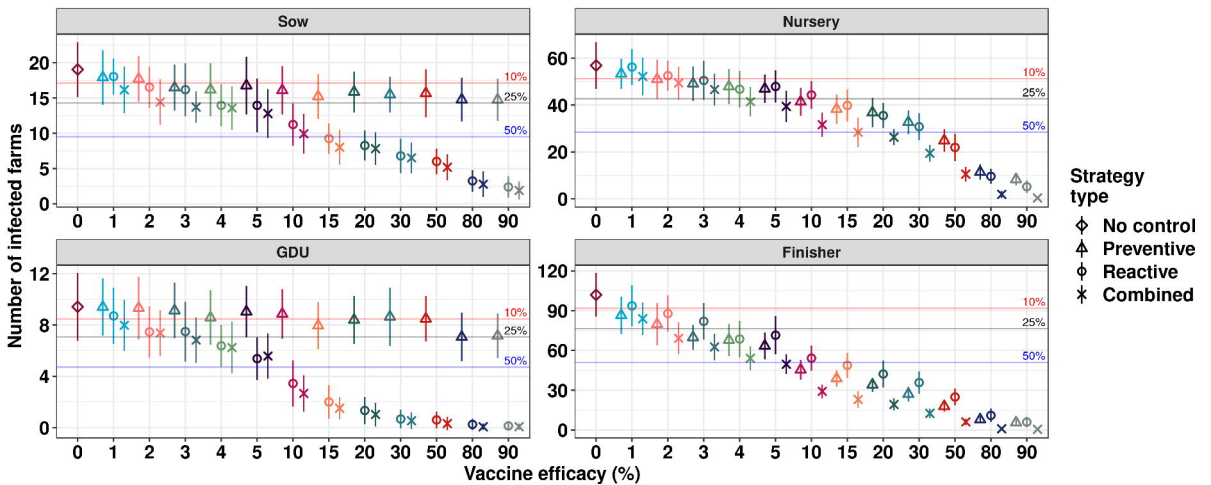
the average cases and their segments represent one standard deviation. For the preventive strategy, farms were vaccinated in the same week after receive a movement, for the reactive strategy farms were vaccinated in the same week after detect positive animals, also the average time of detection was fixed in 4 weeks and the effective surveillance was 0.95 for sow and 0.09 for the other production types (baseline model transmission parameters), for the combined strategy the previous parameters were used.


A) Transition pig farms infectious status
Nursery, GDU and finisher farms
Sow farms
Pig capacity – Out-going pigs = 0
Predefined Infectious time – Time have been infected = 0
S
U
D
$Y_{it} = 1 - e^{-\lambda it}$
Total force infectious rate
f(x)
Probability of detection
B) Transmission routes
$\lambda_{it} = \lambda net_{it}$
$\lambda_{it} = \lambda rebreak_{it}$
$\lambda_{it} = \lambda local_{it}$
Individual routes
$\lambda_{it} = \lambda net_{it} + \lambda local_{it}$
$\lambda_{it} = \lambda net_{it} + \lambda rebreak_{it}$
$\lambda_{it} = \lambda local_{it} + \lambda rebreak_{it}$
$\lambda_{it} = \lambda net_{it} + \lambda local_{it} + \lambda rebreak_{it}$
Combined routes
Legend
Farm type
Sow
Nursery
GDU
Finisher
Farm infectious status
Susceptible
Undetected
Detected
<2 years PRRSV record
(Force infection = λ rebreak)
Yes
No
Movements
(Force infection = λ net)
Past
Scheduled
Maximum local transmission area
(Force infection = λ local)


Sow
Nursery
GDU
Finisher
Transmission rate indices
1.0
0.8
0.6
0.4
0.2
0.0
07/06
07/20
08/03
08/17
08/31
09/14
09/28
10/12
10/26
11/09
11/23
12/07
Transmission by
Local
Movements
Re-break


A
Cases
Real
Simulations
Sow
Nursery
GDU
Finisher
Cases
B


A
Status
New case
Not reported
B
Risk
Maximum
Minimum
C
Risk >90%
High risk
Low risk
D
Risk
Maximum
Minimum
E
Risk >90%
High risk
Low risk


Sow
Nursery
GDU
Finisher
10%
25%
50%
Number of infected farms
Vaccine efficacy (%)
0 1 2 3 4 5 10 15 20 30 50 80 90
Strategy type
No control
Preventive
Reactive
Combined