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Modeling Peste des Petits Ruminants (PPR) Disease Propagation and Control Strategies Using Memoryless State Transitions

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Abstract

Peste des Petits Ruminants (PPR) is an infectious disease affecting goats and sheep. PPR has a mortality rate of 80% and a morbidity rate of 100% in na ïve herds. This disease is currently of concern to Afghani goat and sheep herders as conditions in Afghanistan are conducive to the disease becoming an epidemic. PPR is similar to Rinderpest, but is not as well studied. There is a lack of empirical data on how the disease spreads or effective large-scale mitigation strategies. We developed a herd-level, event-driven model of PPR, using memoryless state transitions, to study how the virus propagates through a herd, and to identify effective control strategies for disparate herd configurations and environments. This model allows us to perform Sensitivity Analyses (SA) on environmental and disease parameters for which we do not have empirical data and to simulate the effectiveness of various control strategies. We find that reducing the amount of time from the identification of PPR in a herd to the vaccination of the herd will radically reduce the number of deaths that result from PPR. The goal of this model is to give policy makers a tool to develop effective containment strategies for managing outbreaks of PPR.

Keywords

Peste des Petits (PPR), SEIR modeling, disease control strategies, memoryless state transitions, Poisson process, disease diffusion

1. Introduction

Peste des Petits Ruminants (PPR) is a virulent virus which first affected goats and sheep in sub-Saharan Africa then recently in the Middle East and southern Asia (Roeder et al., 1994; Shaila et al., 1996; Silva et al., 2011). PPR has different strains ranging from mild to severe and has a clinical resemblance to

Rinderpest (Roeder et al., 1994; Zahur et al., 2009). PPR is highly contagious, with severe variations of this disease exhibiting a 70%-80% mortality rate with most animals dying 10-12 days after becoming symptomatic (Diallo et al., 2007; Baron et al., 2011). Secondary infections with PPR are common and can increase mortality to 100% (Kitching, 1988). Studies show that the disease can spread quickly through a herd resulting in a large number of fatalities (Roeder, 1999; Mbyuzi et al., 2014). Dr. Roeder's study of an outbreak in a goat herd in Addis Ababa, Ethiopia observed a mortality of 60%, 20 days after the initial infected animals were identified, with a herd originally numbering over 1,400 (Roeder et al., 1994). A mathematical model of PPR disease propagation in ruminant herds is important for understanding how the disease spreads in disparate herd configurations and environments and for identifying strategies to mitigate the spread of the disease (Rossiter & James, 1989; Schloeder & Jacobs, 2010).

The lack of firsthand observations on how PPR spreads through a herd underscores the need for a model to address uncertainty in parameter values. A model allows us to perform Sensitivity Analysis (SA) on environment and disease parameters for which we do not have empirical data. Sensitivity Analysis (SA) is a common scientific modeling technique used to understand uncertainty in parameter estimation (Sacks et al., 1989; Arendt et al., 2012).

There are many techniques and frameworks used to model infectious diseases. Two common techniques are (a) Ordinary Differential Equation (ODE) modeling, and (b) stochastic lattice modeling. In a deterministic (ODE) SEIR framework, the number of individuals in each infection-related state is calculated via a set of ODEs that accounts for average transition rates between states (Li et al., 1999). This method models the evolution of the population as a whole, not the specific infection-related evolution of an individual (Boccara & Cheong, 1992). Magal and Ruan (2014) show traditional SEIR models ignore population changes, such as births and natural deaths (Magal & Ruan, 2014). Stochastic lattice models, also known as an automata network, couple a state-evolution process similar to that in the ODE model with a spatial location representation (Rhodes & Anderson, 1997; Fuentes & Kuperman, 1999). A key assumption in stochastic lattice models relates to the disease process in a given individual. Namely, these models commonly use transition probabilities to test if an individual has moved into the next state during a given time period. Thus, the time the individual was in the current state is ignored, making these models memoryless.

In this paper, we describe an event-driven memoryless model of state transitions. We represent individual animals as a herd, because the animals move together and are exposed to the same environments. A set of matrixes describes the discrete state variables characterizing the demographics and condition of animals in the herd. We model disease progression as a Poisson process, in which transition rates depend solely on the beginning and ending states and not on the time the animal entered the state. A Poisson process is a continuous-time random process in which events happen with a constant probability per unit time (Cannizzaro et al., 1978). An exponential distribution describes the interval times and events are assumed to be independent. This memoryless process allows the state of

the herd to be represented using state space counts rather than individual state enumerations. The model is parameterized to explore uncertainty in herd structure, diffusion of the disease within a herd, and the effectiveness of control strategies.

The benefit of this model over traditional ODE and stochastic lattice models is that, for larger populations, storing the state of each animal is burdensome. Depending on the number and character of state variables, it is more efficient to use the marginal sums of individuals in different states to represent the population. Using a Poisson process provides the ability to represent each state transition independently of past transitions, thus reducing the computational complexity of state transitions. The Poisson process also allows us to describe the transition rates as occurring continuously and independently at a constant rate.

2. Model Design

Our model uses a set of matrixes describing discrete-state variables to define the characteristics of the animals in the herd and the condition of the herd with respect to PPR disease states. We define the following one-dimensional matrix of demographic states: young, pregnant, nanny, and non-pregnant. The sum of all demographic states is the population of the herd. We define another one dimensional matrix of disease states pre-susceptible, susceptible, exposed, infectious, recovered, and dead. Our disease states are modeled after the traditional SEIR model with the addition of a pre-susceptible disease state. We added a pre-susceptible disease state because young animals, less than 4 months old, have a neo-natal immunity to PPR. The first five disease states sum to the population of the herd.

This model has three main processes: disease diffusion, disease state transition, and control strategies. A process will evaluate a set of possible future state transitions specific to that process. Since we use a memoryless state transition engine, each process defines state transitions as rates. The model evaluates all possible future state transitions and implements the next transition. After the transition, the model evaluates all possible future states and chooses the next transition to implement. The use of memoryless states, or a Markov assumption, provides a simple, convenient mechanism for state transitions.

2.1 Disease Diffusion

We use a mixing cell model to describe the diffusion of a disease within a herd. Two important factors of disease diffusion are the probability of a non-infected animal being infected via contact with an infectious animal and the contact rate of the herd. The probability of spreading the disease to uninfected animals is determined by the transmission rate of the disease for a given disease state. The contact rate describes the environment of the herd and defines how interconnected a single animal is to the rest of the herd. A higher contact rate indicates the herd is geographically concentrated whereas a lower contact rate indicates the herd is geographically dispersed.

One of the most important equations in the model describes the process by which individual animal's transition from a susceptible disease state to an exposed disease state. The equation for the exposed transition rate, N_E is defined as,

$$N_E = \frac{(M_E * C * \sum E * \sum S) + (M_I * C * \sum I * \sum S)}{\sum P} \quad (1)$$

where M_E is the exposed disease state transmission probability, C is the contact rate defining the interactions per unit time of a member of the population with other members of the population, $\sum E$ is the number of exposed in the population, $\sum s$ is the number of susceptible in the population, M_I is the infected disease state transmission probability, $\sum I$ is the number of infected in the population, and $\sum P$ is the total number in the population.

2.2 Disease State Transition

Disease propagation is modeled as transitions from one disease state to another using a Poisson random process. We use a set of transition probabilities, λs, to determine when an individual transitions from one state to another. These transitions can be described as the probability per unit time that an animal in each state will move to each of the other states. Each transition probability is a random number draw x from an exponential distribution with a density function

$$f_x = \frac{1}{\beta} e^{-x/\beta}, \quad (2)$$

where β is a scale parameter of the distribution and is the reciprocal of the rate parameter λ. The value β represents the expected value of the next transition time.

The transition time for an animal transitioning from an exposed disease state to an infected disease state is defined as

$$\beta_{EI} = \frac{1}{(\lambda_{EI} * \sum E)}, \quad (3)$$

where λ_{EI} is the average rate at which a single animal transitions from an exposed disease state to an infected disease state and $\sum E$ is the current population of the herd in an exposed disease state.

The transition time for an animal transitioning from an infected disease state to a recovered disease state is defined as

$$\beta_{IR} = \frac{1}{(\lambda_{IR} * \sum I)}, \quad (4)$$

where λ_{IR} is the average rate at which a single animal transitions from an infected disease state to a recovered disease state and $\sum I$ is the current population of the herd in an infected disease state.

The transition time for an animal transitioning from an infected disease state to a dead disease state is defined as

$$\beta_{ID} = \frac{1}{(\lambda_{ID} * \sum I)}, \quad (5)$$

where λ_{ID} is the average rate at which a single animal transitions from an infected disease state to a dead disease state and $\sum I$ is the current population of the herd in an infected disease state.

2.3 Mitigation Strategies

Vaccination is an effective means of controlling PPR (Diallo, 2006). Mass vaccination is not

economically feasible in Afghanistan due to the cost of vaccinations and the geographic and cultural challenges of Afghanistan. A successful mitigation strategy, considering these limitations, is targeted vaccinations. Herds are vaccinated against PPR when the disease is detected in a herd. Vaccination of a herd after the first identification of PPR infection is effective in containing the spread of the disease within a herd and to other herds (Qin et al., 2012). There are a variety of vaccines available to veterinarians with most vaccines conferring immunity for at least three years, which is longer than the economic life of ruminants (Sen et al., 2010). Traditionally, PPR vaccines have a shelf-life of around two weeks. Newer, thermostable vaccines are being developed intended to extend the shelf-life of the vaccine, making it more accessible in remote regions (Sen et al., 2010; Silva et al., 2011). PPR immunity is not hereditary and therefore herd immunity decreases exponentially since the time of the last herd vaccination.

A mitigation strategy has three phases: first, the identification of infectious animals in a herd; second, serological testing to confirm PPR; and third, herd vaccination. Each of these phases takes an unknown amount of time. The time to identify sick animals depends on the number of symptomatic animals in a herd and the number of staff monitoring the herd. The time to confirm PPR via a laboratory test is dependent upon the availability of a veterinarian, the method used to serologically test for PPR, and the reliability of such tests. Finally, the time it takes to vaccinate a herd is dependent upon the availability of a veterinarian and the vaccine. Our model has the ability to consider each of these conditions as a separate process or we can represent the time to vaccination as a single parameter. For the purpose of this paper, we are distilling the mitigation process down to the time it takes from the identification of the first symptomatic animal to the vaccination of the herd.

3. Model Calibration

3.1 Sensitivity Analysis

Once the mathematical model was written, we needed to understand the parameter interactions, valid parameter ranges, and how to identify parameters that most contribute to a reduction in herd deaths due to a PPR outbreak. We identified the key independent and dependent variables and performed a sensitivity analysis on those parameters whose values were uncertain. Sensitivity Analysis (SA) is the study of how uncertainty in a mathematical model's output can be apportioned to the uncertainty in the model parameters (Matthies, 2007). SA is useful for understanding how a model functions, the significance of parameter values and ranges, and the importance of random processes. Input/output effects for stochastic models such as the model used in this paper, are difficult for traditional SA approaches to describe. To deal with problems like this, we use a Gaussian Process (GP). GP has the distinct advantage of producing well-constructed probabilistic outputs and is known for its ability to model computer output that can be represented as a stochastic process (Storlie et al., 2009).

To perform a sensitivity analysis, we first identify parameters we want to study, define parameter ranges, and randomly sample parameter values from the defined ranges. Table 1 describes the four

parameters on which we performed a sensitivity analysis, and their respective ranges. contactRate is a parameter representing the environment or density of a herd. tUntilVaccination is a parameter which represents the number of days from the identification of PPR in a herd to herd vaccination. lDetectInfected is a surveillance parameter used to determine how long it will take to find a PPR infection in a herd. A Latin Hybercube Sampling (LHS) scheme was used to generate 1000 plausible parameter values. Ten simulations were made for each parameter sample, each using a different random number seed, to explore the effects of stochastic processes on the outcome.

Table 1. Parameters for Sensitivity Analysis

Parameters	Range	Type	Description
contactRate	[0-1.5]	Double	Number of contacts per unit time between any animal in the herd and another animal.
lDetectInfected	[.1-1]	Double	The probability per unit time that a herder will locate a symptomatic animal.
tUntilVaccinated	[1-60]	Double	The time it takes to vaccinate a herd after the identification of a symptomatic animal.
pVetEffectivenessVaccine	[.20-1]	Double	The effectiveness of the veterinarian at administering a vaccine (i.e., the percent of animals successfully vaccinated).

Table 2 shows the results of a regression analysis using a GP on the four parameters defined above. A variable, *fraction dead*, was used as the dependent variable, which is the fraction of the herd that died of PPR. The main effect can be described as the total variation due to a specific parameter. Additionally, the interaction effect measures the proportion of variability that is due to the specific interaction between the two input variables, while the presence of interactions between two independent variables indicates a correlation between the effects produced by those two variables. As can be seen in Table 2, both contactRate and tUntilVaccination account for over 90% of the total sensitivity which tells us that those two parameters have the most influence on the dependent variable, *fraction dead.* The sensitivity analysis helps policy makers determine how to effectively utilize resources. Based on this analysis, policy makers should first work on improving the response time of control strategies and less time on improving surveillance and veterinarian effectiveness, since the response time, modeled as tUntilVaccination, has a significant effect containing PPR in a herd.

Table 2. Regression Analysis Using a Gaussian Processes

Parameter	Total Sensitivity	Main Effect	tUntilVaccination Interaction	contactRate Interaction	lDetectInfected Interaction	pVetEffectivenessVaccine Interaction
tUntilVaccination	0.34	0.17		0.157	0.01	0.01
contactRate	0.59	0.42	0.15		0.01	0.01
lDetectInfected	0.04	0.01	0.01	0.01		0.02
pVetEffectivenessVaccine	0.06	0.01	0.01	0.01	0.02	

3.1.1 Contact Rate

The parameter contact rate (contactRate) governs the diffusion of the disease through a herd. There is considerable uncertainty on how to represent herd interaction and how a disease diffuses through the herd. There are not enough empirical observations to understand how PPR spreads through a herd in various herd configurations/environments. A robust parameter sweep of contact rate is a way of representing bounding conditions for disease diffusion.

The range of values for the contact rate was estimated by simulating uncontrolled disease spread through a population of 1000 animals. Simulations of contactRate sweeps indicated that the disease started to spread when contact rate was 0.5 and quickly spread though the herd when contact rate was 1.5. This range was therefore adopted in our primary analyses of control strategy effectiveness. The lower bound for contact rate simulates a sparse environment of low herd density, whereas the upper bound for contact rate simulates an environment of high herd density.

3.1.2 Time Until Vaccination

Time until vaccination (tUntilVaccination) is another important independent variable which represents the time it takes to vaccinate a herd once a symptomatic animal has been identified in the herd. This parameter can be used by policy makers in determining which mitigation strategies will be effective given how long they will take to implement. To better understand time until vaccination, we ran 1000 simulations only varying that parameter. We found plausible ranges for the parameter were 0-60 days. This parameter is used to indicate a fast or slow control strategy.

Now that we have studied the two highly influential parameters independently, we understand better how they influence the dependent variable, fraction dead. This knowledge allows us to find parameter values which agree with empirical data when empirical data is available. Next we need to study these parameters together since the SA showed that contact rate and time until vaccination have a high degree of interaction. We will study these parameters in the example section of this paper (see section 4.1).

4. Results

4.1 Example

We illustrate this model by configuring a study designed to model the effect of varying response times in environments which are geographically concentrated and geographically sparse, represented by the parameter contact rate. We configured a herd with 1000 animals; two animals were initially added to the exposed disease state, two animals were initially added to the infected disease state, and the remaining animals were in the susceptible disease state. For this simulation, we varied the contact rate from 0.5-1.5 and time until vaccination from 0-60 days. An LHS scheme was used to generate 1000 plausible parameter values for contact rate and time until vaccination. Ten simulations were made for each parameter sample, each using a different random number seed. We chose to study contact rate and time until vaccination because the regression analysis described above in section 3 indicated the model is most sensitive to these two parameters. The parameters for disease transmission and disease diffusion can be found in Appendix B. Table 3 lists the simulation parameters.

Table 3. Simulation Parameters

Parameter	Description	Value
herdSize	The number of animals in a simulated herd	1,000
lDetectInfected	Probability per unit time that an infected goat will be identified	0.677
nExposed	Number initially exposed to PPR	0
nInfected	Number initially infected with PPR	2
pVetEffectivenessVaccine	Percent of animals successfully vaccinated	100%
contactRate	Value to determine how much contact each animal has with the rest of the herd	LHS Generated [0.5-1.5]
tUnitlVaccinated	Time to herd vaccination (days) once PPR has been identified	LHS Generated [0,60]

Figure 1 is a scatterplot of PPR fraction dead and the time until vaccination. Each point is a simulation result. We applied a liner fit to determine how strong the correlation is between the time it takes to vaccinate a herd and the fraction of the herd which dies from the outbreak. The r-squared value is only 0.19 indicating there is not much correlation between these two variables. This was a bit surprising as we expected a higher correlation. The sensitivity analysis indicated the model is sensitive to time until vaccination leading us to believe there is an interaction effect between time until vaccination and contact rate.

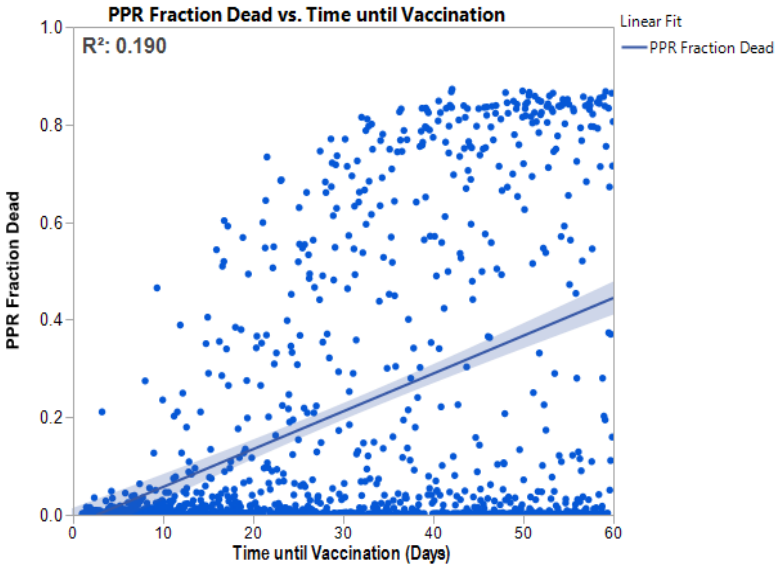

Figure 1. Scatterplot of PPR Fraction Dead versus Time until Vaccination

Figure 2 is a scatterplot of PPR fraction dead and the contact rate. Each point is a simulation result. We applied a linear fit to determine how strong the correlation is between herd density and the fraction of the herd that dies from the outbreak. The r-squared value is only 0.415 indicating there is some correlation between these two variables, but still not as strong as we were anticipating. We will look next at the interaction between the two independent variables in an effort to find a better understanding of the factors that control the dependent variable.

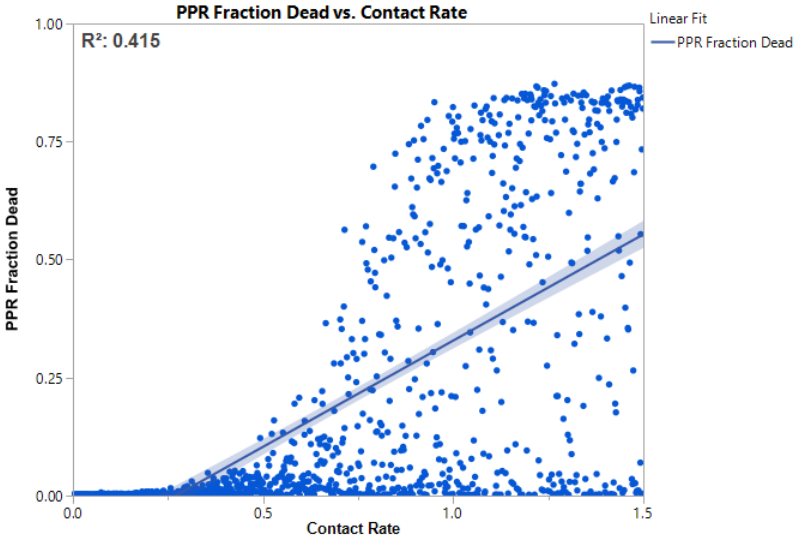

Figure 2. Scatterplot of PPR Fraction Dead versus Contact Rate

Figure 3 is a scatterplot of PPR fraction dead and the time until vaccination with contact rate binned and overlaid by color. Each point is a simulation result. This figure clearly shows there are interaction

effects between our two independent variables, which is necessary for understanding before creating criteria for a mitigation strategy. Figures 1 and 2 illustrated the results of a single independent variable on the dependent variable without being able to illustrate the interaction effects, thus the low r-squared values for the linear fits. This three-variable representation provides a clearer picture of the interactions between time until vaccination, contact rate, and PPR fraction dead. The contact rate in bin 4 has an r-squared value of 0.67 and the contact rate in bin 5 has a r-squared value of 0.61 indicating the outbreak is strongly correlated with geographically denser herds and delays in vaccinations.

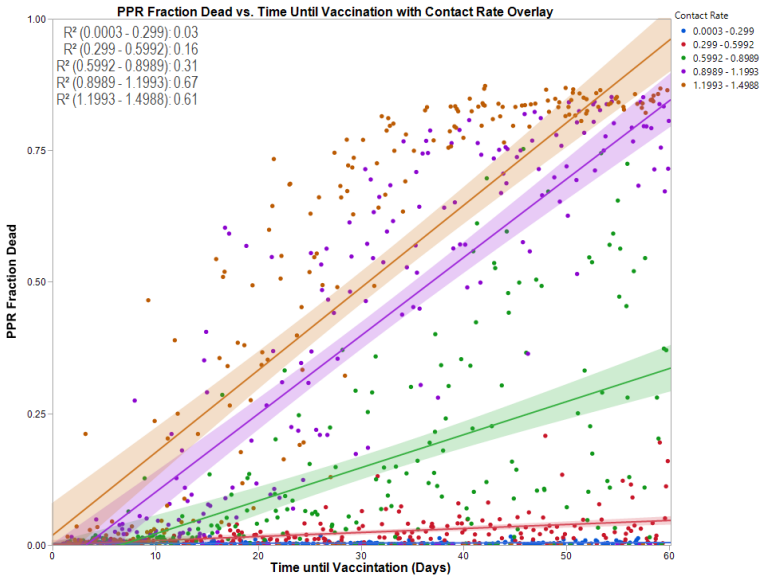

Figure 3. Scatterplot of PPR Fraction Dead versus Time until Vaccination with Contact Rate Overlay

The results of this analysis show that the most effective targeted vaccination strategy is at locations were herds are geographically dense (markets, shared water sources, etc.). Irrespective of the identification of any PPR, this strategy would be the most effective at containing a PPR outbreak. An effective mitigation strategy to reduce the impact of a PPR outbreak must take into account local constraints. There are limited resources in Afghanistan (e.g., Veterinarians, sample processing supplies and facilities, and vaccines), so a targeted vaccination strategy, as opposed to a total vaccination strategy, is the only available option. This strategy is not dependent on surveillance or identification of PPR in the herd before vaccination, since those parameters were shown to have less impact on the reduction in PPR herd deaths (see Table 2).

5. Conclusions

A lack of empirical studies on PPR and effective control strategies necessitates a mathematical model of PPR for policy makers to understand how PPR spreads through a herd, the uncertainty of disease parameters and herd configurations, and to determine which mitigation strategies will be most effective

in mitigating an epidemic. This model can be used to quantify uncertainty in disease diffusion, disease propagation, and mitigation strategies by providing effective ranges of containment under disparate conditions. The use of a memoryless model of state transitions allows us to store the margin sums of state variables instead of the state of individual animals allowing for a more computationally efficient model for larger populations. The representation of disease transitions as a Markov process allows those rates to be described independently of other transition rates and helps quantify uncertainty in disease transition parameters.

A Sensitivity Analysis (SA) on the input parameters allows us to look at which independent variables have the greatest effect on the dependent variables and which parameters have the highest interaction effect. The results of the SA show that the independent variables contact rate and time until vaccination are both highly influential, representing over 90% of total model sensitivity, on the dependent variable, fraction dead. In addition to being highly influential as independent variables, the SA shows that contact rate and time until vaccination both have a high degree of interaction with one another. These SA results led us to perform parameters sweeps of contact rate and time until vaccination both as independent variables and as interacting independent variables.

For illustrative purposes, this paper presents a simple study to model the effect of varying response times in environments which are geographically concentrated and sparse. The results of the study show that the environment contact rate is an important factor in determining the mitigation strategy to prevent or mitigate an epidemic. Geographically dense herds with a contact rate of (.9-1.12) are highly correlated R^2(0.67) with the time it takes to vaccinate a herd in determining how many of the herd would die from a PPR outbreak. In environments where there is a high degree of interaction among the animals such as locations where animals congregate (i.e., water sources, markets), a quick response is necessary to prevent the disease from becoming an epidemic, resulting in high mortality rates. However, in environments where there is a low degree of interaction among the animals such as grazing locations, response times can be longer while still avoiding an epidemic.

The results of the study show that the higher the herd interaction the faster the control strategy needs to be. As the parameter time until vaccination is increased, indicating a slower control strategy, the probability of having a higher fraction of a herd death increases. Conversely, when contact rate is low, indicating a spare environment, a slower control strategy is similarly effective. The simulation results can be used to define criteria for mitigation policies.

This model shows promise for policy makers to model control strategies for containing a PPR outbreak and selecting the most effective control strategies for disparate environments of herd configurations and locations. This model is not limited to PPR, but can be configured to model any type of communicable disease. Future work on this model includes adding movement and interaction among different population groups to determine how a disease spread spatially and to explore how endemic reservoirs of diseases are maintained.

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Appendix A

Model Parameters

Parameter	Description	Range
Simulation		
runID	Unique identifier for a simulation	Integer
Seed	Random number seed	Integer
herdSize	Initial size of the herd	Integer
contactRate	Value to determine how much contact each animal has with the rest of the herd	[0-2]
Birth Process		
startTimeBirthSeason	The time birthing season begins relative to the start time of the simulation	[0-∞]
sigmaBirthSeason	1 Sigma for the birthing season	[0-∞]
annualDeathRate	Annual death rate for the herd	[0-1]
pPregnant	Percent of the herd which is pregnant	[0-1]
pYoung	Percent of the herd which is young	[0-1]
Disease - PPR		
pVaccinated	Percent of the herd initially vaccinated against PPR	[0,1]
nExposed	Population initially exposed to PPR	[0-∞]
nInfected	Population initially infected with PPR	[0-∞]
Surveillance Process		
lDetectInfected	The probability per unit time that a herder will locate an infected goat, which will trigger a vet call. A value of 0 will never trigger a vet call	[0-1]
Control Process		
tUntilVaccination	The time it takes to vaccinate a herd after the identification of a symptomatic animal	[0-∞]
Veterinarian		
pVetEffectivenessVaccine	The effectiveness of the veterinarian at administering a vaccine (i.e., the percent of animals successfully vaccinated)	[0-1]

Appendix B

PPR Disease Parameters

Parameter	Description	Value
M_1	Infected disease state transmission rate probability per unit time	0.05
λ_{EI}	Average time for a single animal to transition from exposed to infected	0.2
λ_{IR}	Average time for a single animal to transition from infected to recovered	0.025
λ_{ID}	Average time for a single animal to transition from infected to dead	0.2225