An exploration of within-herd dynamics of a transboundary livestock disease: a foot and mouth disease case study

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Abstract

Transboundary livestock diseases are a high priority for policy makers because of the serious economic burdens associated with infection. In order to make well informed preparedness and response plans, policy makers often utilize mathematical models to understand possible outcomes of different control strategies and outbreak scenarios. Many of these models focus on the transmission between herds and the overall trajectory of the outbreak. While the course of infection within herds has not been the focus of the majority of models, a thorough understanding of within-herd dynamics can provide valuable insight into a disease system by providing information on herd-level biological properties of the infection, which can be used to inform decision making in both endemic and outbreak settings and to inform larger between-herd models. In this study, we develop three stochastic simulation models to study within-herd foot and mouth disease dynamics and the implications of different empirical data-based assumptions about the timing of the onset of infectiousness and clinical signs. We also study the influence of herd size and the proportion of the herd that is initially infected on the outcome of the infection. We find that increasing herd size increases the duration of infectiousness and that the size of the herd plays a more significant role in deter-

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mining this duration than the number of initially infected cattle in that herd. We also find that the assumptions made regarding the onset of infectiousness and clinical signs, which are based on contradictory empirical findings, can result in the predictions about when infection would be detectable differing by several days. Therefore, the disease progression used to characterize the course of infection in a single bovine host could have significant implications for determining when herds can be detected and subsequently controlled; the timing of which could influence the overall predicted trajectory of outbreaks.

Keywords: transboundary livestock disease, foot and mouth disease, within-herd dynamics, herd size

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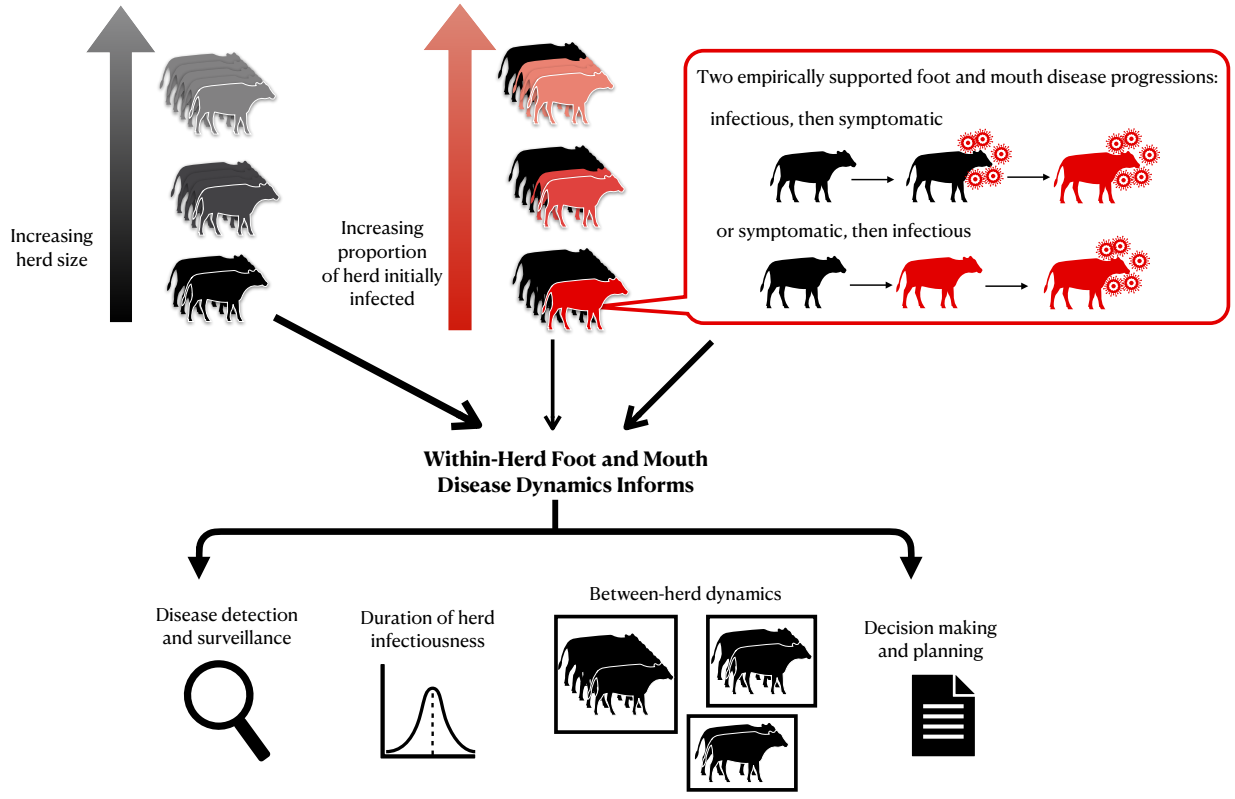
Graphical Abstract



Highlights

- Within-herd dynamics of transboundary livestock diseases affect outbreak outcomes.

- In the FMD system, empirical studies show differing disease progressions in cattle.
- Herd detectability differs by several days depending on assumed disease progression.
- Herd size impacts infectious duration more than number of cattle initially infected.

Introduction

Mathematical models, including agent-based and hybrid models, are part of the toolset that policy makers deploy to inform decisions regarding the potential for outbreaks of transboundary livestock diseases, such as foot and mouth disease (FMD), highly pathogenic avian influenza (HPAI), and African swine fever (ASF) (Webb et al., 2017; Schoenbaum and Terry Disney, 2003; Probert et al., 2016; Keeling et al., 2001; Tildesley et al., 2006; Yoon et al., 2006; Willeberg et al., 2011; Buhnerkempe et al., 2014; Tsao et al., 2014; Savill et al., 2006; O'Neill et al., 2020; Hill et al., 2017; Retkute et al., 2018; Lange et al., 2018; EFSA et al., 2018; Hill et al., 2018). These diseases have the potential to spread rapidly across international borders and cause serious, sometimes catastrophic, economic and agricultural losses in non-endemic countries (Paarlberg et al., 2008; Thompson et al., 2002). Often these models focus on transmission between herds (Keeling et al., 2001; Tildesley et al., 2006; Buhnerkempe et al., 2014; Tildesley et al., 2008; Keeling, 2005; Pomeroy et al., 2015a; Tsao et al., 2019). However, models of between herd spread often make a simplifying assumption that herds are either susceptible or infected. The reality is more subtle as within-herd dynamics impact the force of infection from a herd (Keeling, 2005). Thus, understanding the outbreak trajectory within a herd can provide important information for understanding the biology of transboundary disease systems, including the transmission behavior and the potential for disease detection. This information can also be used to inform decision making and developing policy, and in parameterizing larger between-herd models.

A primary focus of policy intended to mitigate transboundary livestock diseases in non-endemic countries has been to reduce the potential for fast spreading infections. Due to their

fast spread rates, models often make the assumption that once infection is introduced the entire herd or flock, functioning as a single unit, can be considered infected and subsequently infectious. This is a justifiable assumption in large-scale outbreak models because inference is often on large-scale control policies whose implementation occurs over months or weeks compared to the smaller timescale of within-herd dynamics. Additionally, there is often limited data on infection dynamics at this scale (Keeling, 2005). The assumption is also more tractable because it allows herds, flocks or premises to be treated as a single entity. Assuming the entire herd or flock is a single unit is a simplifying assumption but it provides policy makers with metrics of interest about potential outbreaks, including the number of potential herds or flocks infected and the spatial extent. However, some outbreak metrics of interest to policy makers are influenced by within-herd dynamics, particularly overall outbreak duration (Chis Ster et al., 2012; Gilbertson et al., 2022), which is important for understanding potential economic impacts and can be underestimated by models that do not include within-herd dynamics.

Studies exploring the potential impact of within-herd dynamics on outbreak disease progressions are often done using information from data collected in outbreaks, which often includes the day of reporting, the location, control actions taken and, if available, an inferred infection date. These data are invaluable and have been used effectively for numerous studies (Keeling et al., 2001; Keeling, 2005; Tildesley et al., 2006, 2008, 2009; Keeling et al., 2003; Hayama et al., 2012, 2013; Perez et al., 2004b,a; Ward and Perez, 2004; Ferguson, 2001; Ferguson et al., 2001). However, it can be difficult to parameterize within-herd models using outbreak data. One reason for this is there is uncertainty in the estimated date of infection for herds and these data are not always collected during outbreak situations (Keeling et al., 2001; Perez et al., 2004b; Muroga et al., 2012). Additionally during an outbreak, premises that are identified as being infected or at higher risk from infection are often controlled as quickly as possible (Anderson, 2002; Muroga et al., 2012; Perez et al., 2004b), which means that the full progression of infection within a herd or flock is not realized. For instance at

the end of March in the U.K. 2001 FMD outbreak, herds that were identified as infected were supposed to be culled within 24 hours, and those that were identified to be at higher risk (dangerous contacts) were culled within 48 hours (Anderson, 2002), meaning that infected herds were removed from the population before the infection fully progressed through the herd. In endemic settings, serological data are available (Pomeroy et al., 2015b); however, the complex interactions between immunology and the different circulating serotypes can make it difficult to understand the progression of a single strain in an immunologically naive population. Parameterization through serological data also requires repeated sampling through time, which is not always available or feasible.

Another difficulty is that outbreak data available to researchers usually report the entire herd or flock as infected rather than reporting the number of animals that are infected. This means that even with an inferred infection date, there is little information available to understand how the route (e.g. fomite, imported animal) of pathogen introduction impacts the dynamics. For example, it is unknown if a shipment of one or two infected animals into a herd will result in different dynamics than if twenty percent of the herd or flock was infected via local spread (i.e. transmission through a non-shipment related event). Understanding how the number or proportion of the initially infected population within a herd or flock influences disease dynamics could be important for allocating control strategies and understanding both within and between entity transmission.

A factor that can further complicate the parameterization of within-herd models is that estimates of epidemiological parameters from experimental infections are often based on proxies of infectiousness rather than direct observations of transmission (Clancy et al., 2006; Bos et al., 2009; Rohani et al., 2009; Mardones et al., 2010; Charleston et al., 2011; Ypma et al., 2013). Using a coupled experimental design, Charleston et al. (2011) showed that the timing of clinical signs and the onset of infectiousness of FMD in cattle changes depending on the methods used to identify infectious animals (Charleston et al., 2011). Results from a transmission challenge experiment suggest that cattle develop clinical signs shortly before

they are capable of transmitting the virus to other susceptible cattle; however, if cattle are monitored using more traditional measures of viremia in various bodily fluids, the results suggest they are infectious before they show clinical signs. The two differing disease progressions in cattle, one suggested by the transmission challenge experiment, one suggested by traditional measures, could manifest in different dynamics within a herd and could impact the length of time a herd is infectious as well as the detectability assumptions about that herd. The results presented in Charleston et al. (2011) also suggest that FMD progression in cattle may differ from the progression in pigs (Charleston et al., 2011; Stenfeldt et al., 2016; Paton et al., 2018). Uncertainty in the timing of disease stages, such as periods when animals are infectious or showing clinical signs, has also been acknowledged in other transboundary livestock diseases, including HPAI and ASF (Bos et al., 2007; Backer et al., 2009; Guinat et al., 2017). Uncertainty in disease stages, both within a species or among different species, could have ramifications for detection, and possibly control or surveillance, in both endemic and epidemic disease situations. In outbreaks, the time to detection is considered a critical factor in minimizing potential losses (Carpenter et al., 2011; Sánchez-Vizcaíno et al., 2013); therefore, exploring the impact of uncertainty and, in the case of FMD, conflicting findings on the disease stages would be highly beneficial both for policy makers and modeling groups.

In this study, we focus on developing within-herd models for one transboundary livestock disease, FMD, which is a highly contagious virus that infects divided hoofed animals, including important livestock species such as cattle, sheep, and pigs (Haydon et al., 2004). FMD outbreaks are expensive because of the restrictions on trade that are placed on infected countries and the control measures implemented by non-endemic countries (Anderson, 2002; Thompson et al., 2002; Knight-Jones and Rushton, 2013). This makes FMD a policy concern for both countries that are not infected and for countries that are dealing with endemic spread. The United States (U.S.) has not experienced an FMD outbreak in almost a century, and as with many FMD-free countries, preparing for the potential introduction of FMD means having to rely on information gained from outbreaks in other countries; this includes

information on between and within-herd spread. Understanding how within-herd dynamics may be influenced by the factors discussed above will be helpful for informing assumptions about larger-scale between herd processes and control.

For epidemic FMD, it is rare that models focus solely on within-herd dynamics. More often within-herd models are embedded in the larger between-herd models that are of more interest for policy and preparedness. There are a few notable exceptions where within-herd dynamics or transmission have been specifically studied (Chis Ster et al., 2012; Brito et al., 2011; Carpenter et al., 2004). These studies have focused on understanding the role within-herd dynamics or transmission played in previous outbreaks of FMD (Chis Ster et al., 2012; Brito et al., 2011), and improving our understanding of the epidemiology, detection (Chis Ster et al., 2012), vaccination (Brito et al., 2011) and diagnostics (Carpenter et al., 2004). From these studies, it is clear that within-herd dynamics do affect the overall outbreak trajectory or parameter estimates and that there are a number of unknowns associated with understanding within-herd dynamics, including a quantitative exploration of the animals initially infected in a herd (Chis Ster et al., 2012).

Here, we performed a systematic exploration of the impact of herd size, the number of animals initially infected within herds, and model structure (disease progression) to develop a better understanding of within-herd FMD dynamics in cattle. We developed a set of three stochastic compartmental models of within-herd FMD, which are based on the differing assumptions about disease progression that could be made based on experimental studies. By running simulations with these models across herd sizes from 5–10,000 head and initial infection sizes representing 1–25% of the herd, we quantified how these herd characteristics impact the length of time a herd is infectious and potentially contributing to onward spread. Additionally, we investigated the predicted differences in the detectability of infected herds between model structures. The results from these models provide information about the length of time herds of different sizes could be infectious and the impact the inclusion of within-herd dynamics may have on overall outbreak dynamics. By exploring the effect of

disease progression on predictions, these results show that uncertainty in the progression also results in uncertainty in herd detectability which could have impacts on decision making. These results also provide predictions that could be used to inform nation-scale between-herd outbreak models, including assumptions about the reporting of infected herds and possibly the timing of control in relation to onset of infectiousness. Together these results provide information about how herd demographics and assumptions about disease progression impact the predictions about a transboundary disease system and point to the importance of understanding the underlying biology.

Methods

We developed three stochastic compartmental models to study the within-herd dynamics of FMD in cattle. The three model structures reflect the differing disease progression results from empirical studies (Charleston et al., 2011; Mardones et al., 2010) and are all variations on standard susceptible, exposed, infectious, removed (SEIR) models. For all three model variants, we make the assumption that we are dealing with a closed population, such that there are no births, deaths, emigration or immigration. The speed of FMD spread through a herd is on a faster time scale than the processes affecting the herd size and can therefore justify this assumption. We also make the assumption that the cattle herd is immunologically naive, which mimics the situation in an outbreak setting or in an endemic situation with a novel strain, as there is little cross-immunity between strains (Paton and Taylor, 2011).

We assume that FMD will be introduced into a herd through the exposed class, rather than through the infectious class. We make this assumption because it is the first disease stage, and regardless of model variant, the exposed stage is both non-infectious and without clinical signs. Since there is not clear experimental evidence for within-herd FMD transmission being density- or frequency-dependent, we built both transmission types for our three model variants. There is some evidence that between-herd transmission of FMD is density-dependent (Ferrari et al., 2011), and we therefore present the density-dependent versions

of the models in the main text and the frequency-dependent versions in the Supplementary Methods.

The first model, which will hereafter be referred to as the Base model, is an SEIR model (Figure S1). In this model, we assume that cattle are infectious and clinical in the infectious stage, such that cattle become infectious and detectable at the same time. This model represents the simplest assumption regarding relative timing of infectiousness and clinical signs and is therefore useful as a benchmark for comparing with the other two models presented below. Cattle move through the compartments of the Base model as follows:

$$\frac{dS}{dt} = -\beta SI \quad (1)$$

$$\frac{dE}{dt} = \beta SI - \sigma E \quad (2)$$

$$\frac{dI}{dt} = \sigma E - \gamma I \quad (3)$$

$$\frac{dR}{dt} = \gamma I \quad (4)$$

where, S, E, I, R represent susceptible, exposed, infectious, and removed individuals, respectively. The transmission rate is given by β, the transition between exposed and infectious (infectious rate) is given by σ and the recovery rate is given by γ. The stage transition rates for this model and the following two models are in units of days^{-1} (Table S1). Equations 1–4 show density dependent transmission (see the Supplemental Methods for the equations describing frequency-dependent transmission).

The second model, which will be called the Clinical First model, includes an additional compartment for cattle that are showing clinical signs but are not yet infectious. This model follows the results of the transmission challenge experiment conducted by (Charleston et al., 2011). The Clinical First model compartments are: Susceptible, Exposed, Clinical Not Infectious, Infectious & Clinical, Removed (SEAIR) (Figure S2). The model equations are given by:

$$\frac{dS}{dt} = -\beta S I_1 \quad (5)$$
$$\frac{dE}{dt} = \beta S I_1 - \phi E \quad (6)$$
$$\frac{dA_1}{dt} = \phi E - \omega A_1 \quad (7)$$
$$\frac{dI_1}{dt} = \omega A_1 - \theta I_1 \quad (8)$$
$$\frac{dR}{dt} = \theta I_1 \quad (9)$$

assuming density-dependent transmission. The transmission rate, β, is the same parameter as used in the base model. The stages are given by S, E, A_1, I_1, R, where S, E, and R are the same as the Base model and A_1, and I_1 represent the clinical not infectious, and clinical and infectious stages unique to the Clinical First model. The rate of transition from exposed to clinical not infectious is given by ϕ, the rate from clinical not infectious, to clinical and infectious, is given by ω and the recovery rate is given by θ.

The third model will be called the Infectious First model, and follows the results from measures of viremia in fluid. In this model variant, cattle are assumed to be infectious before they show clinical signs. The five compartments of the Infectious First model are: Susceptible, Exposed, Infectious Not Clinical, Infectious & Clinical, Removed (SEIAR) (Figure S3) and is described by:

$$\frac{dS}{dt} = -\beta S(I_2 + A_2) \quad (10)$$
$$\frac{dE}{dt} = \beta S(I_2 + A_2) - \eta E \quad (11)$$
$$\frac{dI_2}{dt} = \eta E - \rho I_2 \quad (12)$$
$$\frac{dA_2}{dt} = \rho I_2 - \mu A_2 \quad (13)$$
$$\frac{dR}{dt} = \mu A_2 \quad (14)$$

assuming density-dependent transmission. The transmission rate, β, is the same parameter as used in the base model. The stages are given by S, E, A_2, I_2, R, where S, E, and R are the same as the base model and A_2, and I_2 represent the infectious not clinical, and clinical and infectious stages unique to the Infectious First model. The rate of transition from exposed to infectious not clinical is given by η, the rate from infectious not clinical, to clinical and infectious, is given by ρ and the recovery rate is given by μ.

All three model variants were parameterized from the empirical cattle study by Charleston et al. (2011) (Table S1). We chose to use this study because it experimentally estimates each model parameter and uses Bayesian inference to estimate uncertainty in each parameter estimate, which is used in the sensitivity analysis described below. Charleston et al. (2011) also allows consistent parameterization methods among models because it coupled a transmission challenge experiment with measurements of viremia in bodily fluids. Whilst the results from the transmission challenge part of the Charleston et al. study are different from results previously reported, the results from the measures of viremia are consistent with previous FMD studies (Mardones et al., 2010; Charleston et al., 2011). The Base model and Clinical First models were parameterized using the transmission challenge experiments; however, in the Clinical First model, the exposed stage is split into two so that there is a distinct stage for clinical but not yet infectious cattle. The Infectious First model was also parameterized using the same experiment, but Charleston et al. (2011) defined the infectious state based on a commonly used proxy for infectiousness: detection of the virus in fluids by PCR. Specifically, Charleston et al. (2011) measured viremia in blood, nasal fluid, and oesophageal-pharyngeal fluid (OPF), which resulted in three estimates for stage durations (Charleston et al., 2011). Therefore, we used three different parameterizations for the Infectious First model, corresponding to the different fluids.

Twelve herd sizes ranging from 5 to 10,000 head were selected based on the category divisions in the NASS Agricultural Census herd sizes (USDA, 2014). For each herd size, infection was seeded with 1%, 5%, 10%, and 25% of the herd initially infected with the

virus. For smaller herd sizes, the initial number of animals exposed at the start of the simulation will either be the stated percentage above or 1 animal, whichever is larger. For larger herds, the initial number of animals exposed will be the stated percentage above or 100 animals, whichever is smaller. All percentages will be rounded to the nearest whole animal, see Table S2 for a complete list of herd sizes and the number of initially exposed animals. All models were stochastically simulated using the adaptive tau-leaping method (Cao et al., 2007) coded in the R programming language (version 3.0.3) with the adaptivetau package (Team, R Core, 2014; Johnson, 2019). We ran 1000 simulations for each combination of model variation, initial condition, and parameter set.

We analyzed the results to estimate the length of time in days herds are predicted to be infectious. For the Base and Clinical First models, this is the length of time cattle remain in the infectious (I and I_1, respectively) class. For the Infectious First model, the length of time animals are infectious is the total length of time they are in either the Infectious Not Clinical stage (I_2) or the Infectious and Clinical stage (A_2). As we are interested in understanding the potential ramifications of when cattle become detectable, for the Clinical First and Infectious First models we also studied the length of time the cattle could be detectable before they are infectious and the length of time cattle could be shedding virus before they are detectable, respectively. For Clinical First model, the length of time before cattle are clinical but not yet infectious, is the length of time they remain in the Clinical Not Infectious stage (A_1). For Infectious First model, we are interested in the length of time cattle are in the Infectious Not Clinical stage (I_2). For each of these quantities of interest we found the median and the 2.5 and 97.5th quantiles.

We conducted a sensitivity analysis to assess the relative importance of herd size, number of initially infected animals, and each epidemiological parameter for the length of time herds are infectious. Using Latin Hypercube Sampling, we generated 1000 epidemiological parameter values for the 4 herd sizes between 100 and 1000 head, and 4 initially infected sizes, resulting in 16,000 parameter sets (Marino et al., 2008). The sensitivity analysis was

localized to the epidemiological parameter ranges based on the 95% credible interval from the Charleston et al. (2011) study (Table S1). We calculated model sensitivity based on the median infection times from 1000 simulations of each parameter set. We define sensitivity as the change in infection time for one standard deviation change in each parameter and use a linear regression to assess the contribution of each parameter as well as interaction terms between parameters (Buhnerkempe et al., 2014; Tsao et al., 2019). We report analyses for each model separately and for the Infectious First model focus on the viremia in blood parameterization sensitivity results.

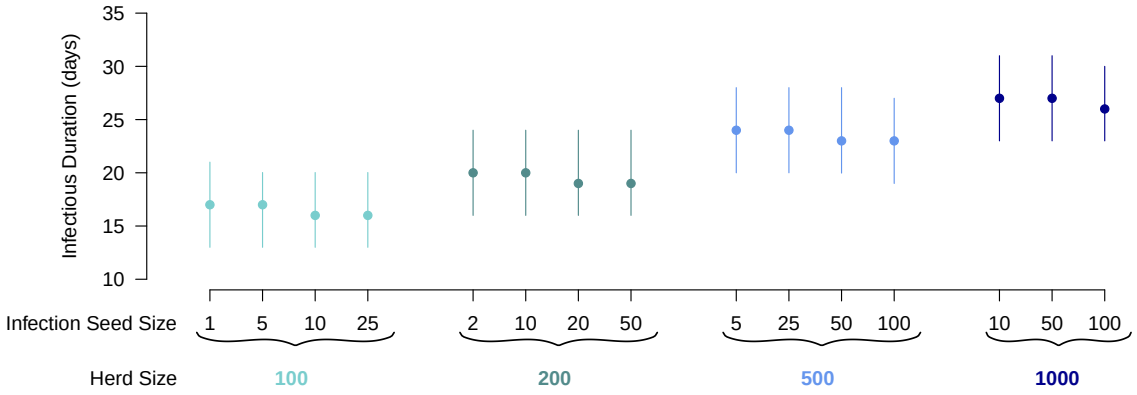
Results

The results from all three model variants, the three parameterizations of Infectious First model and both the transmission types, show that the length of time herds are infectious increases with increasing herd size (Figures 1 & S4-S5). We see very little difference between the results from the density and frequency-dependent transmission versions of the models. Similarly, there are only slight differences between model variants in the predicted length of time herds are infectious. The largest difference in the predicted duration of infectiousness is between the blood parameterization of the Infectious First model and all other model variants and parameterizations. The blood parameterization of the Infectious First model predicts that at larger herd sizes, the length of time the herds will be infectious is lower than the predictions from other parameterizations and model variants, such that the slope of the duration of infectiousness by herd size is lower for the blood parameterization (Figure 1c & S4c).

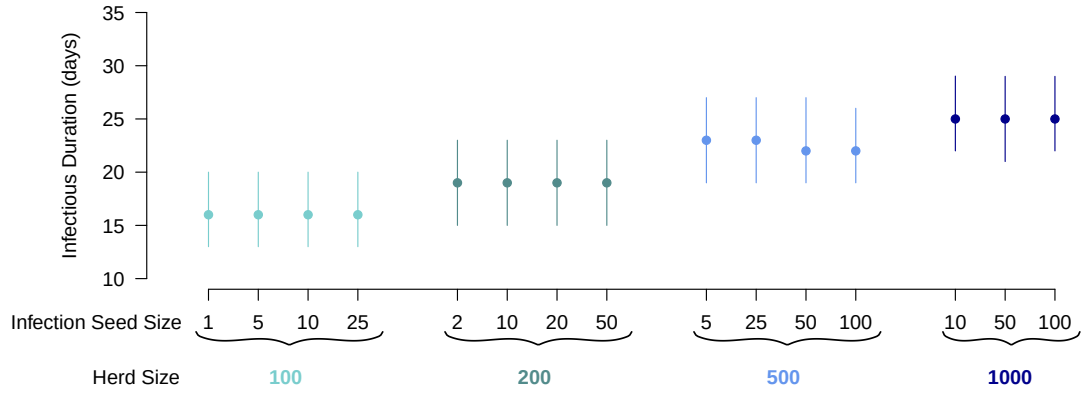
Our results also indicate that the size of the herd is more important in determining the length of time the herd will be infectious than the number of animals initially infected (Figures 1 & S4-S5). This is also supported by results from the sensitivity analysis. Herd size is consistently the best predictor of infection duration while the initial size of the infected population has a minimal effect (Figure 2 & S6). For example, in the base model assuming

1% of a herd is initially infected, an increase in herd size from 100 to 1000 individuals is associated with an increase in the median duration the herd is predicted to be infectious by 10.4 days. An increase in the initially infected size from 1% to 5% is associated with no changes in duration. Epidemiological parameters are also more important than the initial size of the infected population in influencing the duration a herd will be infectious. Longer exposed and infectious periods are associated with longer infection times.

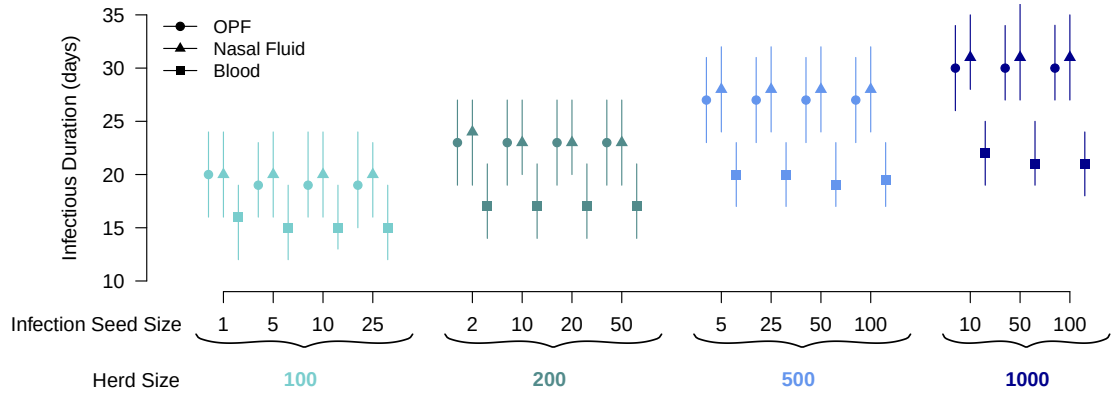
In the Clinical First model, cattle develop clinical signs before becoming infectious, such that the virus may be detectable before transmission begins. Our results indicate that the median estimated length of time that herds could be showing clinical signs but not transmitting is less than half a day for both the density and frequency-dependent models (Figures 3 & S7-S8). The duration that herds show clinical signs is sensitive to epidemiological parameters but not herd size or initial infection size (Figure 4). However, there is more variation at smaller herd sizes than those studied in the sensitivity analysis; the estimated 97.5th quantile for herds of 20 or smaller being 2 days and for herds of 5 being 3 days. The results of the Clinical First model suggest that detecting the infection in cattle herds before the onset of transmission would be unlikely but that the chances increase in small herds.



(a) Base model



(b) Clinical First model



(c) Infectious First model

Figure 1: The length of time in days herds of 100 to 1000 head are infectious assuming density-dependent transmission. The top x-axes show the number of animals initially exposed to the FMD virus and the bottom axis shows the herd size. The Base model results are shown in panel (a), Clinical First model results are in panel (b) and Infectious First model results are in panel (c). On the Infectious First model plot (c), the round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters.

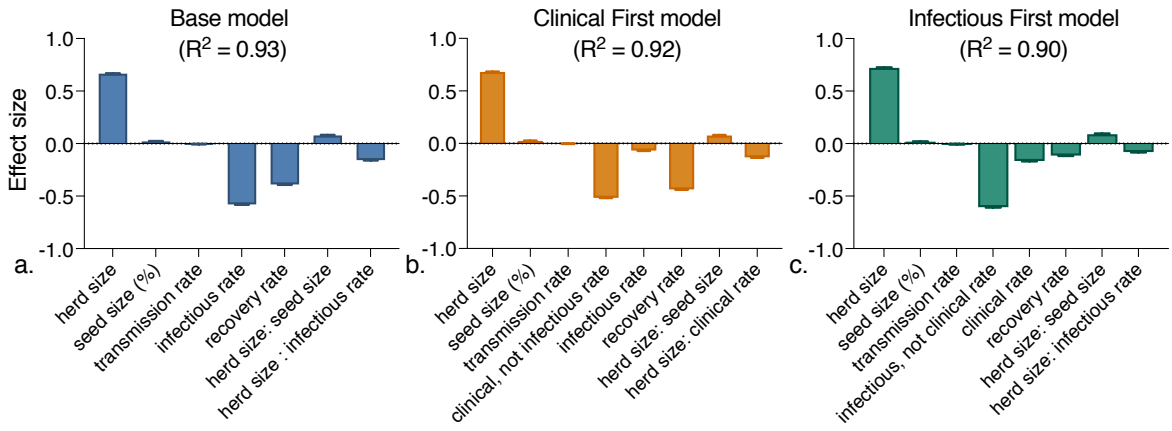


Figure 2: Sensitivity analyses across model parameters. Effect size represents linear regression coefficients and 95% confidence interval for models fit to the median duration a herd is infectious in the (a) Base model, (b) Clinical First model, and (c) Infectious First model assuming density-dependent transmission. We have standardized both predictor and response variables for comparison among parameters.

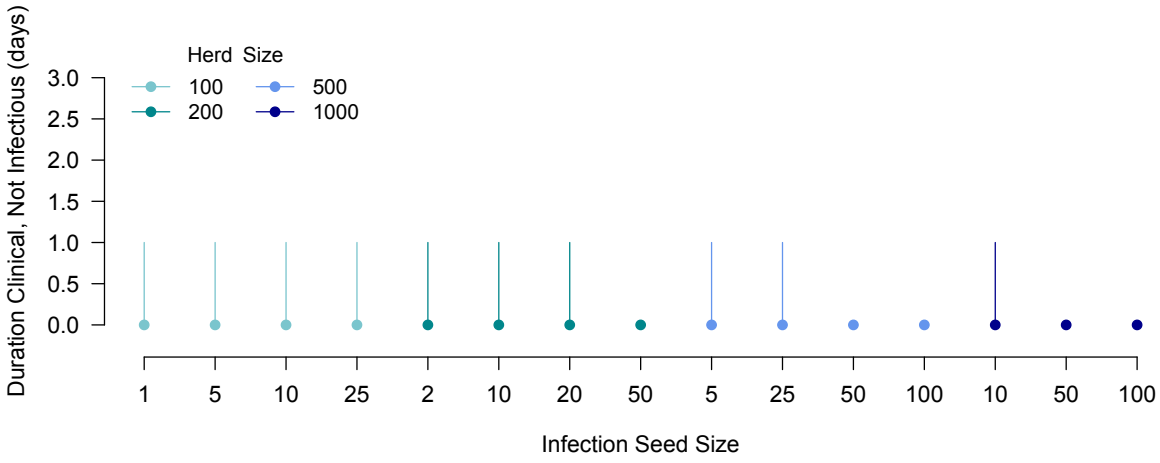


Figure 3: Median length of time herds of size 100 to 1000 head are predicted by the Clinical First model to have cattle with clinical signs that are not infectious assuming density-dependent transmission with the 2.5 and 97.5 quantiles. The x-axis shows the initial size of the exposed population. The color of the points and lines correspond to the herd size, shown in the legend.

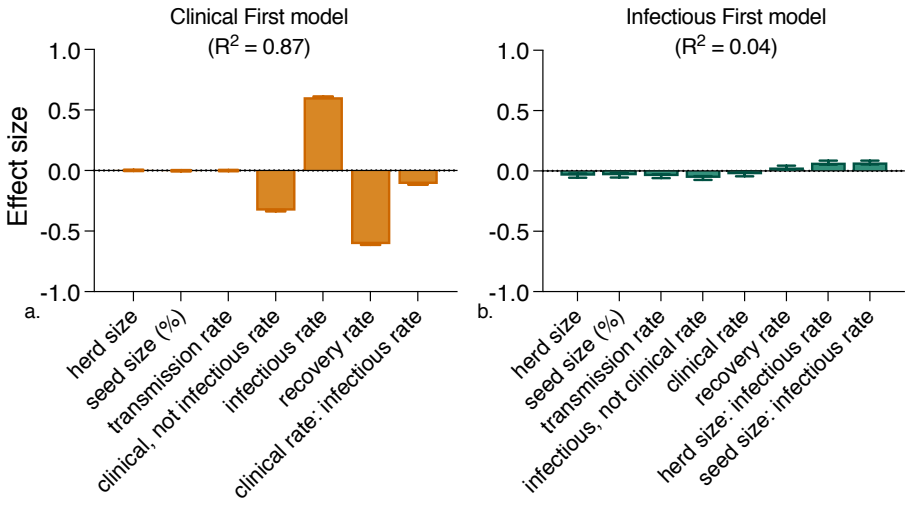


Figure 4: Sensitivity analyses across model parameters for (a) the median length of time herds could be showing clinical signs but not transmitting and (b) the median length of time herds are transmitting the virus without clinical signs. Effect size represents linear regression coefficients for models fit to the median duration a herd is infectious assuming density-dependent transmission. We have standardized both predictor and response variables for comparison among parameters.

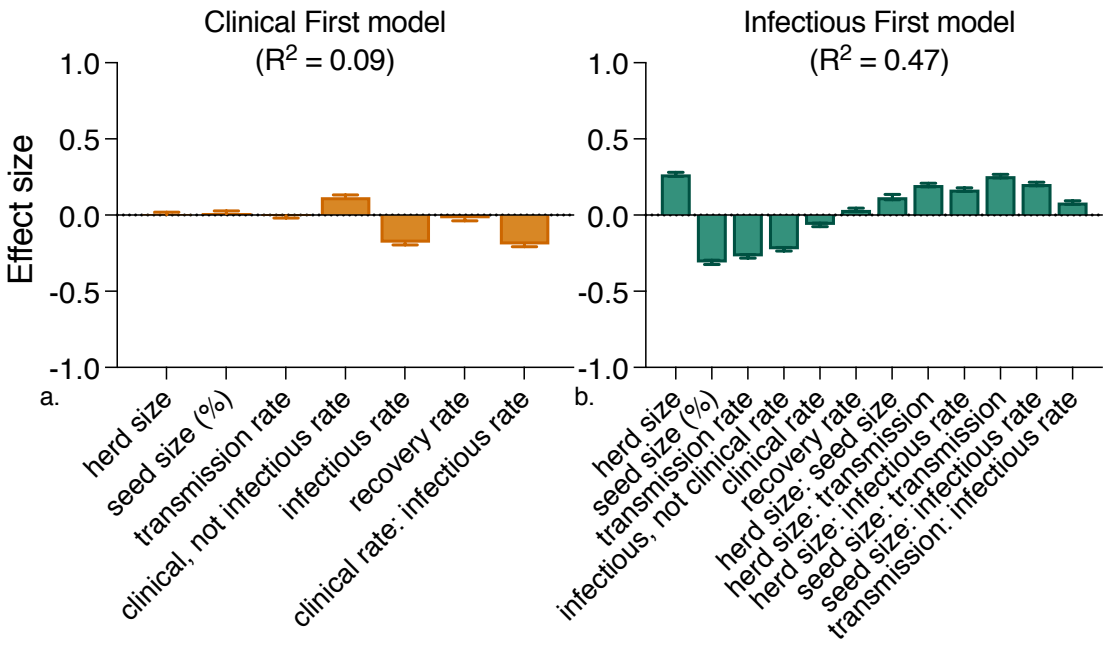


Figure 5: Sensitivity analyses across model parameters for models assuming frequency-dependent transmission. Model sensitivities are displayed for (a) the median length of time herds could be showing clinical signs but not transmitting and (b) the median length of time herds are transmitting the virus without clinical signs. Effect size represents linear regression coefficients for models fit to the median duration a herd is infectious assuming density dependent transmission. We have standardized both predictor and response variables for comparison among parameters.

In the Infectious First model, cattle develop clinical signs after becoming infectious, such that cattle may be transmitting the virus for several days before they are visually detectable. Our results show that the median length of time herds can be transmitting the virus without clinical signs is 2 days for the majority of herd sizes, number of initially infected, and parameterizations (Figure 6 & S9). This also holds for both the density and frequency-dependent versions of this model, though there is a bit more variation in the frequency-dependent case (Figures 6 & S9-S10). The variation in the length of time that herds can be silently transmitting ranges between one and four days, with the variation decreasing as herd size increases (Figure 6 & S9). The duration of transmission prior to clinical signs is less sensitive to epidemiological parameters than the duration of clinical signs but no infectiousness from the Clinical First model. Instead the duration of infectiousness without clinical signs is slightly sensitive to herd size, number of initially infected, the epidemiological

parameters and some of the interaction terms (Figure 4 & 5).

Figure 6: Median length of time herds of size 100 to 1000 head are predicted by the Infectious First model to have infectious cattle that are not yet showing clinical signs assuming density-dependent transmission with the 2.5 and 97.5 quantiles. The x-axis is the number of initially exposed animals. The color of the points and lines correspond to the herd size, shown in left legend. The round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters (right legend).

Discussion

The length of time a herd or premises is infectious is important to decision makers and a parameter common to many livestock disease models (Backer et al., 2009; Buhnerkempe et al., 2014; Bradhurst et al., 2015; Carpenter et al., 2004; Gulenkin et al., 2011; Jewell et al., 2009; Keeling et al., 2001; Tildesley et al., 2006; Tsao et al., 2019; Hayama et al., 2013; Ward et al., 2008). This value is often estimated from outbreak data, which can be difficult because herds are often identified and controlled before the full infection dynamics are observed such that the estimated infectious times may be too short. Using empirical studies to parameterize herd-level infection parameters removes the uncertainty and uncontrolled elements of infection dynamics observed in outbreaks; however, these data are on the individual animal-level, which does not necessarily provide a good estimation of a herd-level duration of infection. Our study provides estimates of the infectious period of FMD at the herd-level when the infection is allowed to run its course without intervention. Our results

suggest that if left uncontrolled, herds can transition from having very few infected animals to many infected animals rapidly. Additionally, once infected, herds may be infectious for several weeks to over a month for larger herds. From these results, we can see that the duration of infectiousness is highly influenced by the size of the herd.

Our results also indicate that the size of the herd is more important in determining the length of time the herd is infectious than the initial size of the infected population regardless of the model variant or the transmission version of the models. The sensitivity analysis also supports the importance of herd size in determining the length of time herds are infectious. This finding suggests that large farms could drive between farm transmission by being both more transmissible and by staying infectious longer and that therefore, from a policy perspective, large farms should be considered for targeted control in the event of an outbreak. This finding also suggests that in larger between-herd spread models, accounting for herd size may be the most important variable for estimating the length of time herds will be infectious and is more important for capturing the dynamics than the number of animals that initiated the infection in that herd. The relationship between initially infected population and duration is extremely hard to estimate from observed data because of the many different factors influencing the outbreak. Additionally, while we estimate herd size to be more important in determining duration than the proportion of the herd initially infected for cattle only premises that are infected at a single time point, in an epidemic setting herds may be infected through multiple routes at different times which has the potential to change the dynamics. Additionally, the presence of multiple species on a single premises may change the interaction between the proportion of the herd initially infected, the herd size and the duration. Within-herd FMD dynamics on multi-species premises may be particularly complex because not all susceptible species have the same disease progression (Charleston et al., 2011; Stenfeldt et al., 2016; Paton et al., 2018).

The duration of the infectious period chosen in models may not have a substantial impact on outbreak scenarios that are well controlled; however, this parameter could have measur-

able impacts on scenarios where control resources are assumed to be limited. In a scenario with a limited control resource, it may not be possible to control herds as expeditiously as when the resource is unlimited. For example, in the event of a delay in culling owing to personnel or disposal constraints, the results from this study could provide an estimate of the length of time herds may continue to contribute to spread. In this study, we do not study potential impacts of transmission from asymptomatic carriers because the transmission risk from these animals has been estimated to be fairly low and potentially context dependent (Parthiban et al., 2015). Therefore, the estimated length of spread does not account for potential carriers, which would be an important consideration in the context of uncontrolled long-term infection dynamics both of FMD and other livestock diseases. Additionally, the application of control measures, which is not studied here, would alter the length of time a herd is infected, either by removing infected animals before the infection has run its course or by changing the susceptibility of a herd through vaccination. However, the estimates provided in this study give an upper bound on the length of time herds are contributing to transmission during the non-carrier phase of transmission. Estimates of the potential length of spread could be used in economic analyses of the cost of allowing animals to remain on a control wait list for specific lengths of time or investing in additional resources to move through the wait list more swiftly. These types of economic and epidemic trade-off analyses are invaluable when creating preparedness plans or estimating the impact different control strategies would have on outbreaks.

The duration that individual herds contribute to transmission will also be important for understanding how the composition of premises contributes to the overall outbreak dynamics. Studies have shown that aspects of demography, including premises clustering, and the number of large farms in a given area, impact the outcome of potential FMD outbreaks (Werkman et al., 2016; Tsao et al., 2019; Gilbertson et al., 2022). Using well informed estimates for the duration of infectiousness for herds of different sizes will help disentangle the impact of herd size on duration of an outbreak within a herd versus the duration of an

outbreak across multiple herds. Depending on the demography, it is possible that a single large farm in isolation will have a shorter outbreak duration than many small farms that all become infected in a transmission chain. Using herd size-specific infectious durations may also be helpful in accurately determining high risk regions or areas because of the livestock demography. This finding that the transmission dynamics of FMD within-herds contributes to the overall outbreak has also been found by previous explorations of epidemic FMD outbreaks (Brito et al., 2011; Chis Ster et al., 2012). Chis Ster et al. (2012) points to the importance of herd size and species composition for understanding the UK 2001 FMD outbreak and how little is known, quantitatively, about the initially infected animals within a herd. The work we present here builds on these results, focusing on a single susceptible species, and shows that the herd size is more impactful to the duration a herd is infectious than the number or proportion of initially infected animals. Additional studies, exploring the interactions among species within and between-herds will be important for fully understanding how within-herd dynamics and livestock demography interact to influence overall outbreak dynamics.

The suggestion that cattle may not be infectious until after they are symptomatic presents an opportunity to catch, and potentially, control the onward spread of FMD very early in an outbreak. Additionally, the onset of clinical signs corresponding closely (less than one day) to the onset of infectiousness, could be used to target efforts in determining which herds could have been infected by the focal herd by narrowing the search window. The results from our simulations suggest that the short time window where cattle are not infectious but are showing clinical signs, does not offer much opportunity of identifying the virus before transmission has begun; the median for all herd sizes is less than one day. However, at smaller herd sizes, there is greater variation in this time period and therefore there is more opportunity for catching it, though logistically the time is short enough that it is still unlikely.

While the Clinical First model suggests that the window of time cattle are symptomatic but not yet infectious is too short for an actionable difference in detection in comparison

to the Base model, it does provide a substantial head start in detection in comparison to the Infectious First model. The Infectious First model, that follows the traditional idea of cattle silently transmitting FMD before developing symptoms, suggests that visual detection is not possible until after several days of viral shedding. The difference between a few days of silent spread (median 2 days, Figure 6 & S9) and simultaneous or closely timed onset of clinical signs and infectiousness could result in substantial differences in assumptions about detection. Rapid detection of FMD outbreaks is considered to be an important aspect of containing spread and mitigating the impacts of the outbreak (Carpenter et al., 2011). Generally in models the first few herds to be infected take longer to be reported than subsequent infections; an assumption that follows data from FMD outbreaks and results from the intensification of surveillance after the outbreak has been officially reported. Models assuming that FMD spreads silently could predict longer detection times and unchecked transmission than those models assuming transmission with clinical signs. Given the importance of the FMD disease progression in determining herd detectability and outbreak dynamics, additional research on the timing of infectiousness and clinical signs would be beneficial. Additionally, empirical research suggests that unlike cattle, pigs do transmit FMD before developing clinical signs (Paton et al., 2018; Stenfeldt et al., 2016). Research into the biological aspects of FMD infection across serotypes and susceptible species, and more broadly into the timing of disease stages in other transboundary livestock diseases would be useful for informing decision making and parameterizing mathematical models. Additional research is of particular importance for diseases that infect more than one species because these can, as has been found with FMD, have differ between susceptible species (Charleston et al., 2011; Paton et al., 2018; Stenfeldt et al., 2016).

The results we present here are based on simple compartmental models exploring within-herd infection dynamics of FMD independently of between herd transmission, control or immune dynamics. The simplicity of the model limits our ability to fully study the potential impacts of the different model assumptions, parameters, and herd sizes on overall outbreak

trajectory. Additionally, the models presented here are for a single species and FMD infects multiple important livestock species. As a result of this, we were not able to study the potential dynamics of mixed species herds. The cattle only scenario does however cover the most commonly observed outbreak scenario as 72.1% of FMD outbreaks internationally have been in cattle only (USDA APHIS VS Center for Epidemiology and Animal Health, 2017). Additionally, approximately 71% of FMD outbreaks in non-endemic countries have been first suspected in cattle (McLaws and Ribble, 2007). To the best of our knowledge, cattle are the only livestock species, at least so far, where the silent spread portion of the FMD infection has been brought into question (Charleston et al., 2011; Paton et al., 2018). If the almost concurrent appearance of clinical signs and transmission is unique to cattle, then herds that are mixed or consist solely of non-cattle divided hoofed species would silently transmit the virus and detection on these premises would be delayed. Another assumption we make is that herds are uniformly mixing. While we feel this assumption is justifiable because of the high degree of infectivity, we do recognize that there are certain production types (e.g. U.S. dairy) that could lead to non-uniform mixing. In such situations, the differences resulting from assumptions regarding onset of infectiousness and detectability may have greater impacts on the predicted results than those presented here. The models used in this study are limited in scope, but they still provide information that can point to additional studies and new avenues of research. These models could also be easily adapted to study other livestock species susceptible to FMD.

The implications of the difference in potential for detection on overall outbreak trajectory and the potential for control are beyond the purview of this study; however, it is a very interesting finding that could be studied further by larger between-herd models. As mentioned in the previous paragraph it is unclear if cattle are the only species affected by FMD that can be detected before or at the same time as infectiousness begins. Should it be found for FMD or more broadly for any livestock infection that certain species are detectable earlier in infection than others, it opens up new possibilities for surveillance and control strategies.

For example, one common control tactic in highly infectious agricultural pathogens, is to assign a higher risk status for herds that have had an epidemiologically relevant contact with infected herds. Higher risk herds are controlled preemptively or given more stringent movement restrictions than lower risk herds (Tildesley et al., 2009; Perez et al., 2004a). In situations where certain species transmit silently and others do not, control prioritization of high risk herds could be optimized taking this information into account.

The importance of within-herd dynamics to overall outbreak dynamics is not always apparent, particularly in non-endemic settings where herds are fully susceptible and the spread between them is rapid. However, there are a number of aspects about FMD that cannot be understood in the absence of within-herd dynamics. In this study, we used a series of compartmental models to gain a better understanding of how changes to the most basic assumptions, such as the ordering of the infection stages, can alter the predicted within-herd dynamics of FMD. Our findings suggest that regardless of the model structure and type of transmission, herd size is more important in determining the length of time herds remain infectious than the size of the initially infected population. We also found that the differences in disease progression lead to a two day difference in detectability; which results either in silent spread or detection concurrent with transmission. The magnitude of this difference could have interesting implications for larger between-herd transmission models and could influence surveillance and response plans. The information gained from this study can be used to inform herd-level parameterizations for models and provide a basis for incorporating herd demography data into outbreak simulations to guide future surveillance and response plans. Additionally, the results of this study demonstrate the importance of understanding the within-herd dynamics of fast-spreading livestock diseases and could be applied to other systems, such as HPAI and ASF.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material for

An exploration of within-herd dynamics of a transboundary livestock disease: a foot and mouth disease case study

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Supplemental Methods

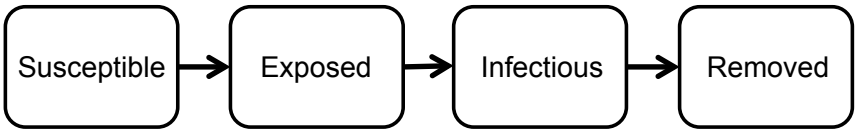


Figure S1: Base model structure. The within herd cattle population is closed and moves sequentially through four compartments: Susceptible, Exposed, Infectious, and Removed.

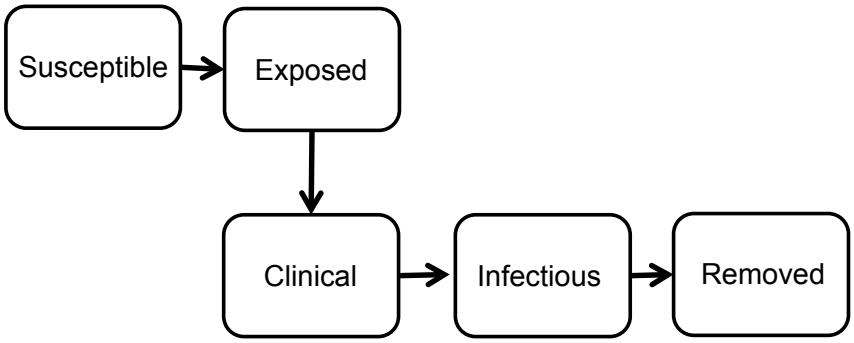


Figure S2: Clinical First model structure. The within herd cattle population is closed and moves sequentially through five compartments: Susceptible, Exposed, Clinical, Not Infectious, Clinical And Infectious, and Removed.

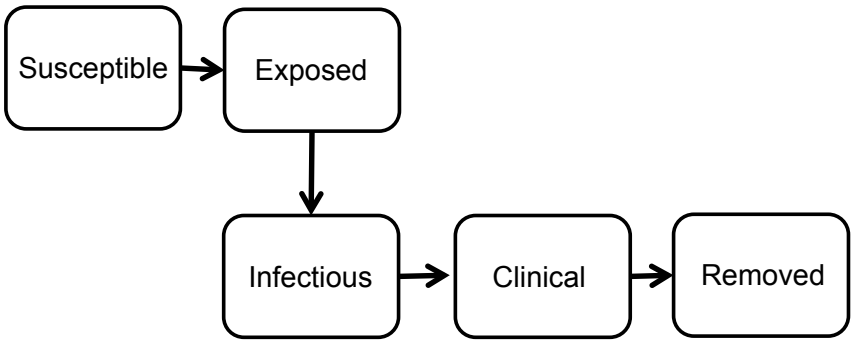


Figure S3: Infectious First model structure. The within herd cattle population is closed and moves sequentially through five compartments: Susceptible, Exposed, Infectious, Not Clinical, Clinical And Infectious, and Removed.

The three model variants were also run with frequency-dependent transmission. The base model variation is given by the following equations.

$$\frac{dS}{dt} = \frac{-\beta SI}{N} \tag{S1}$$

$$\frac{dE}{dt} = \frac{-\beta SI}{N} - \sigma E \tag{S2}$$

$$\frac{dI}{dt} = \sigma E - \gamma I \tag{S3}$$

$$\frac{dR}{dt} = \gamma I \tag{S4}$$

$$N = S + E + I + R \tag{S5}$$

Where, S, E, I, R represent susceptible, exposed, infectious, and removed individuals, respectively. N represents the total number of animals in the population. The transmission rate is given by β, the transition between exposed and infectious is given by σ and the recovery rate is given by γ.

The frequency-dependent version of the Clinical First model, which describes the situation where cattle develop clinical signs before they become infectious, is given by:

$$\frac{dS}{dt} = \frac{-\beta S I_1}{N} \tag{S6}$$
$$\frac{dE}{dt} = \frac{-\beta S I_1}{N} - \phi E \tag{S7}$$
$$\frac{dA_1}{dt} = \phi E - \omega A_1 \tag{S8}$$
$$\frac{dI_1}{dt} = \omega A_1 - \theta I_1 \tag{S9}$$
$$\frac{dR}{dt} = \theta I_1 \tag{S10}$$
$$N = S + E + A_1 + I_1 + R \tag{S11}$$

The transmission rate, β, is the same parameter as used in the base model. The stages are given by S, E, A_1, I_1, R, where S, E, and R are the same as the base model and A_1, and I_1 represent the clinical, not infectious and clinical and infectious stages unique to the Clinical First model. N represents the total number of animals in the population. The rate of transition from exposed to clinical, not infectious is given by ϕ, the rate from clinical, not infectious, to clinical and infectious, is given by ω and the recovery rate is given by θ.

The Infectious First model, in which cattle become infectious before clinical signs, with frequency-dependent transmission is described by the following equations.

$$\frac{dS}{dt} = \frac{-\beta S (I_2 + A_2)}{N} \tag{S12}$$
$$\frac{dE}{dt} = \frac{-\beta S (I_2 + A_2)}{N} - \eta E \tag{S13}$$
$$\frac{dI_2}{dt} = \eta E - \rho I_2 \tag{S14}$$
$$\frac{dA_2}{dt} = \rho I_2 - \mu A_2 \tag{S15}$$
$$\frac{dR}{dt} = \mu A_2 \tag{S16}$$
$$N = S + E + I_2 + A_2 + R \tag{S17}$$

The transmission rate, β, is the same parameter as used in the base model. The stages are given by S, E, A_2, I_2, R, where S, E, and R are the same as the base model and A_2, and I_2 represent the infectious, not clinical and clinical and infectious stages unique to the Infectious First model. N represents the total number of animals in the population. The rate of transition from exposed to infectious, not clinical is given by η, the rate from infectious, not clinical, to clinical and infectious, is given by ρ and the recovery rate is given by μ.

The herd sizes and the size of the initially infectious cattle on a premises are shown in Table S2. Each model variant and herd size and initial exposed population size were simulated 1000 times.

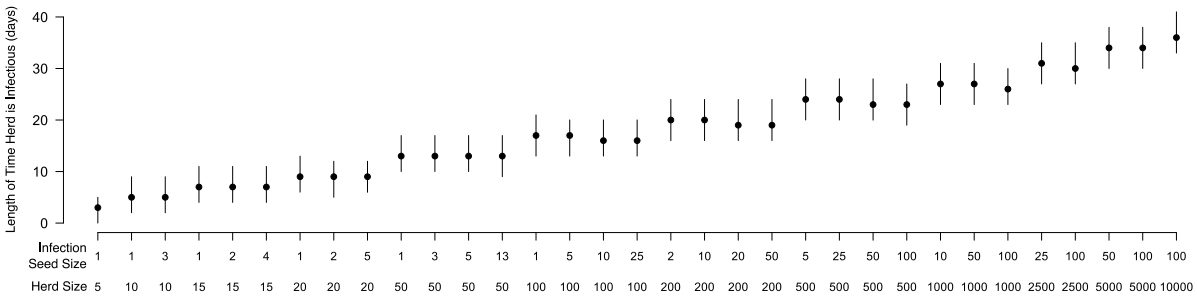
Table S1: Parameter Values

Model	**Parameter**	**Description**	**Value**	**Range**
Base model	β	Transmission Rate	21.84	0.34–141.62
	σ	Infectious Rate (Days^{-1})	0.22	0.32–0.14
	γ	Recovery Rate (Days^{-1})	0.77	3.33–0.21
Clinical First model	β	Transmission Rate	21.84	0.34–141.62
	ϕ	Clinical, Not Infectious Rate (Days^{-1})	0.25	0.34–0.17
	ω	Infectious Rate (Days^{-1})	1.92	6.25–0.77
	θ	Recovery Rate (Days^{-1})	0.77	3.33–0.21
Infectious First model OPF	β	Transmission Rate	21.84	0.34–141.62
	ν	Infectious, Not Clinical Rate (Days^{-1})	2.17	5.56–1.19
	ρ	Clinical Signs Rate (Days^{-1})	0.27	3.6–0.19
	μ	Recovery Rate (Days^{-1})	0.22	0.27–0.18
Infectious First model Nasal Fluid	β	Transmission Rate	21.84	0.34–141.62
	ν	Infectious, Not Clinical Rate (Days^{-1})	0.39	0.59–0.22
	ρ	Clinical Signs Rate (Days^{-1})	0.65	0.75–0.57
	μ	Recovery Rate (Days^{-1})	0.20	0.30–0.12
Infectious First model Blood	β	Transmission Rate	21.84	0.34–141.62
	ν	Infectious, Not Clinical Rate (Days^{-1})	0.43	0.67–0.26
	ρ	Clinical Signs Rate (Days^{-1})	0.58	0.69–0.43
	μ	Recovery Rate (Days^{-1})	0.41	0.48–0.37

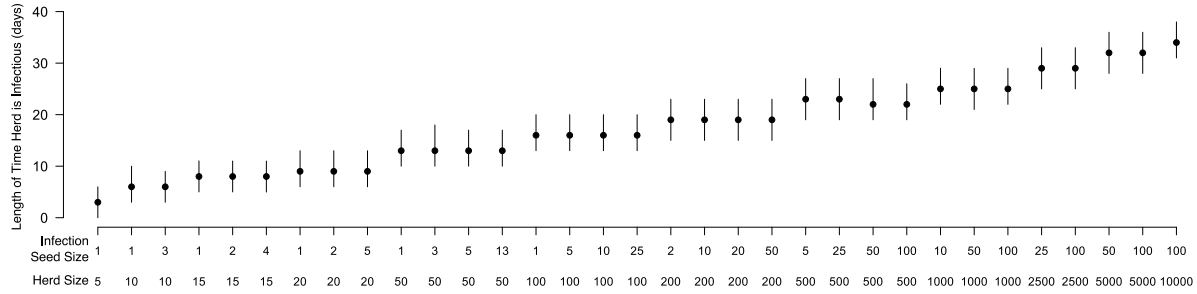
Table S2: Herd sizes and number of animals in the herd infected at the start of the simulations.

	Percent Infected			
Herd Size	1%	5%	10%	25%
5	1	1	1	1
10	1	1	1	3
15	1	1	2	4
20	1	1	2	5
50	1	3	5	13
100	1	5	10	25
200	2	10	20	50
500	5	25	50	100
1000	10	50	100	100
2500	25	100	100	100
5000	50	100	100	100
10000	100	100	100	100

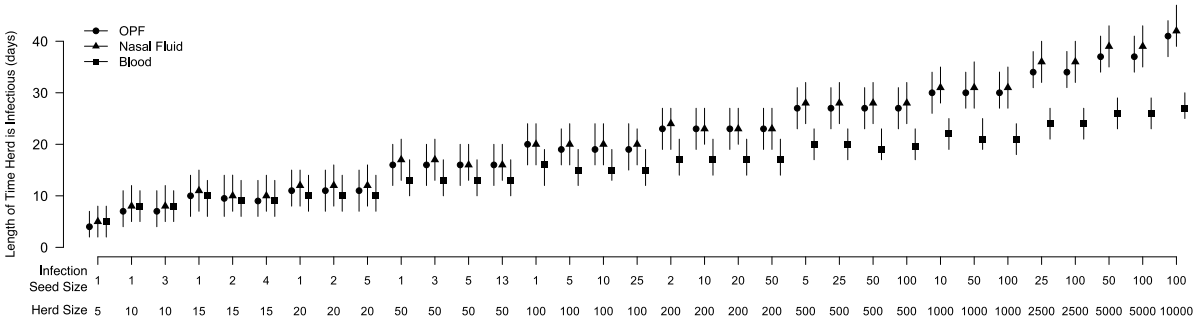
Supplemental results



(a) Base model

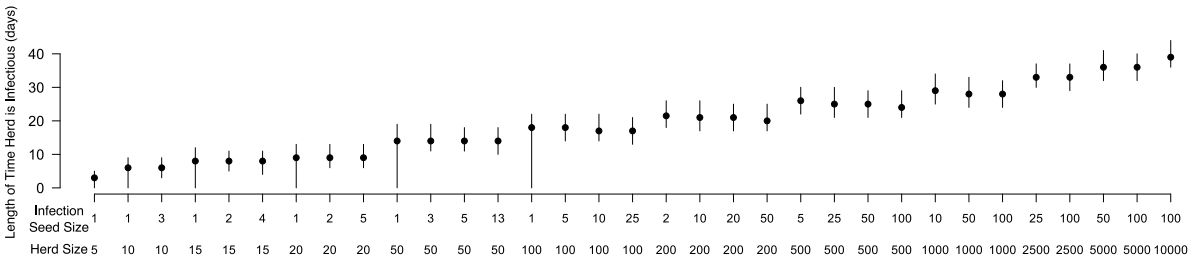


(b) Clinical First model

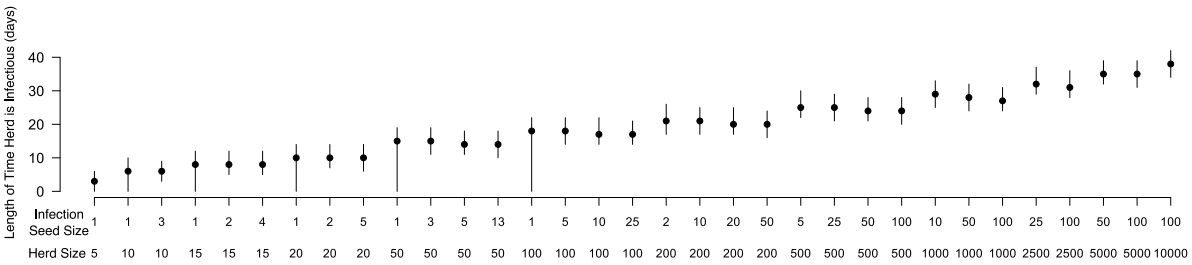


(c) Infectious First model

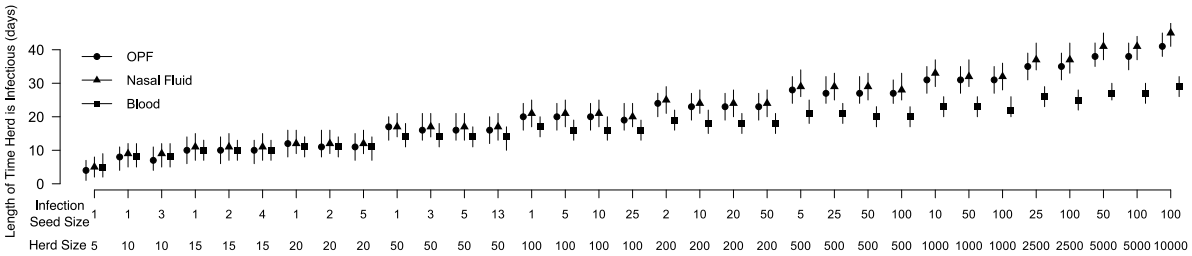
Figure S4: The length of time in days premises are infectious assuming density-dependent transmission. The x-axes show the size of the herd before the period and the number of animals initially infected with the FMD virus (after the period). The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd. The base model results are shown in panel (a), the Clinical First model results are in panel (b) and the Infectious First model results are in panel (c). On the Infectious First model plot (c), the round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters.



(a) Base model



(b) Clinical First model



(c) Infectious First model

Figure S5: The length of time in days premises are infectious assuming frequency-dependent transmission. The x-axes show the size of the herd before the period and the number of animals initially infected with the FMD virus (after the period). The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd. The base model results are shown in panel (a), the Clinical First model results are in panel (b) and the Infectious First model results are in panel (c). On the Infectious First model plot (c), the round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters.

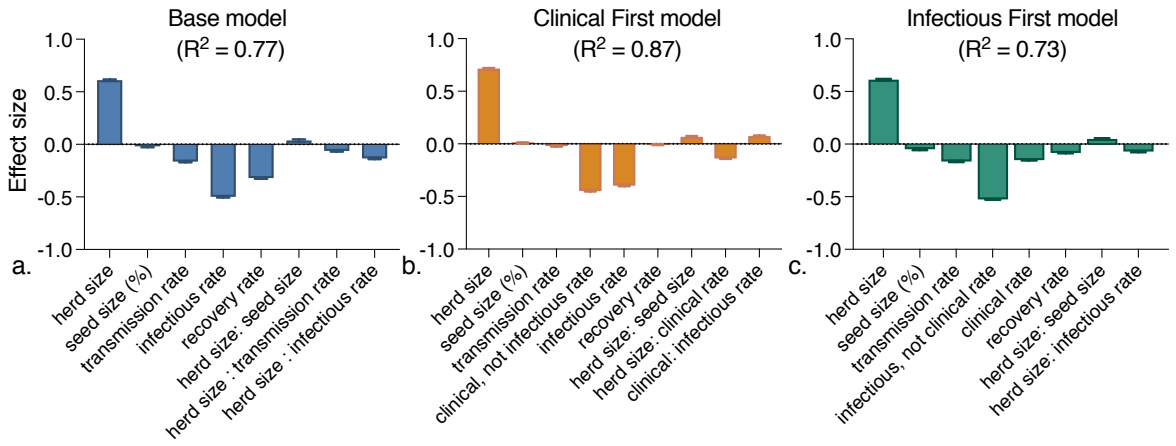


Figure S6: Sensitivity analyses across model parameters for models assuming frequency-dependent transmission. Effect size represents linear regression coefficients for models fit to the median duration a herd is infectious in the (a) Base model, (b) the Clinical First model, and (c) the Infectious First model assuming frequency-dependent transmission. We have standardized both predictor and response variables for comparison among parameters.

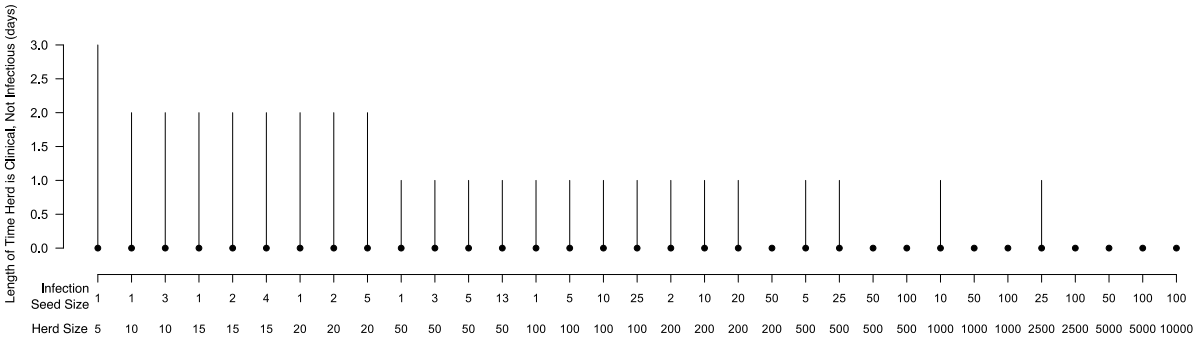


Figure S7: Median length of time premises are predicted by the Clinical First model to have cattle with clinical signs that are not infectious assuming density-dependent transmission with the 2.5 and 97.5 quantiles. The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd.

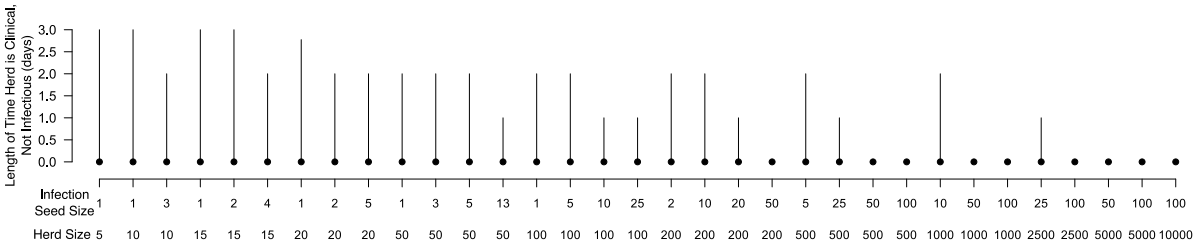


Figure S8: Median length of time premises are predicted by the Clinical First model to have cattle with clinical signs that are not infectious assuming frequency-dependent transmission with the 2.5 and 97.5 quantiles. The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd.

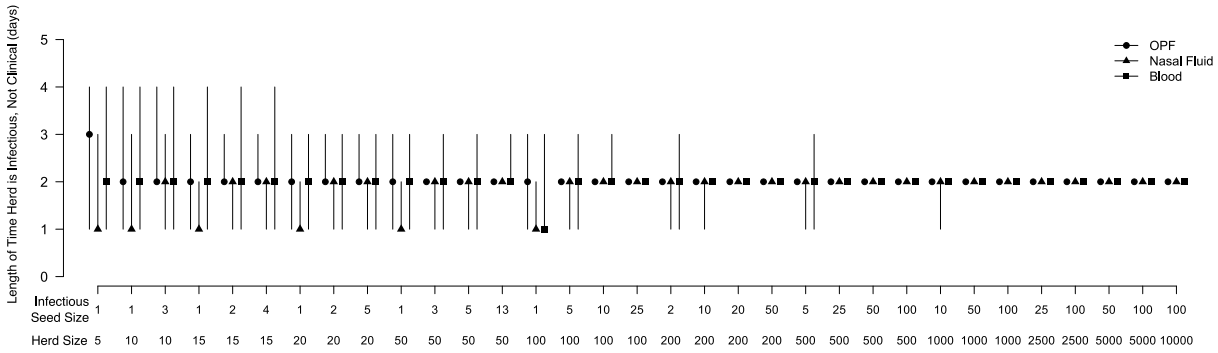


Figure S9: Median length of time herds are predicted by the Infectious First model to have infectious cattle that are not yet showing clinical signs assuming density-dependent transmission with the 2.5 and 97.5 quantiles. The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd. The round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters.

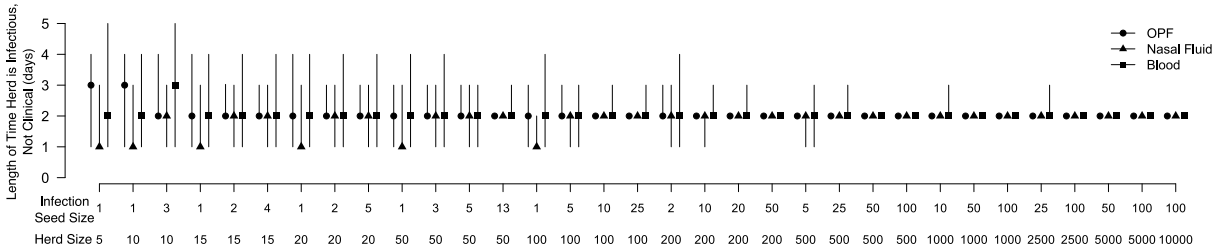


Figure S10: Median length of time herds are predicted by the Infectious First model to have infectious cattle that are not yet showing clinical signs assuming frequency-dependent transmission with the 2.5 and 97.5 quantiles. The top x-axis is the number of animals that are initially infected and the bottom x-axis is the total number of animals in the herd. The round points show results using OPF parameters, triangle points show results using nasal fluid parameters and square points show results using blood parameters.