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Disentangling the influence of livestock vs. farm density on livestock disease epidemics

AMANDA J. MEADOWS,[1,]† CHRISTOPHER C. MUNDT,[1] MATT J. KEELING,[2] AND MICHAEL J. TILDESLEY[2]

[1]*Department of Botany and Plant Pathology, Oregon State University, Cordley Hall, 2701 SW Campus Way, Corvallis, Oregon 97331 USA*
[2]*Department of Biological Sciences, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL UK*

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Abstract. Susceptible host density is a key factor that influences the success of invading pathogens. However, for diseases affecting livestock, there are two aspects of host density: livestock and farm density, which are seldom considered independently. Traditional approaches of simulating disease outbreaks on real-world farm data make dissecting the relative importance of farm and livestock density difficult owing to their inherent correlation in many farming regions. We took steps to disentangle these densities and study their relative influences on epidemic size by simulating foot-and-mouth disease outbreaks on factorial combinations of cattle and farm populations in artificial county areas, resulting in 50 unique cattle/farm density combinations. In these simulations, increasing cattle density always resulted in larger epidemics, regardless of farm density. Alternatively, increasing farm density only led to larger epidemics in scenarios of high cattle density. We compared these results with simulations performed on real-world farm data from the United States, where we initiated outbreaks in U.S. counties that varied in county-level cattle density and farm density. We found a similar, but weaker relationship between cattle density and epidemic size in the U.S. simulations. We tested the sensitivity of these outcomes to variation in pathogen dispersal and farm-level susceptibility model parameters and found that although variation in these parameters quantitatively influenced the size of the epidemic, they did not qualitatively change the relative influence of cattle vs. farm density in factorial simulations. By reducing the correlation between farm and livestock density in factorial simulations, we were able to clearly demonstrate the increase in epidemic size that occurred as farm sizes grew larger (i.e., through increasing county-level cattle populations), across levels of farm density. These results suggest livestock production trends in many industrialized countries that concentrate livestock on fewer, but larger farms have the potential to facilitate larger livestock epidemics.

Key words: disease model; epidemic; foot-and-mouth disease; host density; livestock disease; simulation experiment.

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† **E-mail:** amanda.meadows@oregonstate.edu

INTRODUCTION

Pathogen invasions pose global threats to human and animal health (Daszak et al. 2000), biodiversity (Mack et al. 2000), and food production (Brasier 2008, Hatcher et al. 2012) and are a significant burden on the global economy (Thompson et al. 2002, Pimentel et al. 2005). Therefore, it has become increasingly important to understand factors contributing to the epidemic impact of invading pathogens. For highly contagious diseases affecting livestock such as highly

pathogenic avian influenza, classical swine fever, and foot-and-mouth disease (FMD), host density is a key factor that contributes to epidemic risk and can dictate the control measures necessary to contain the epidemic (Ferguson et al. 2001, Boender et al. 2007, 2008). For example, simulation studies of FMD outbreaks in various countries demonstrate that when outbreaks occur in areas of high host density, livestock movement bans and culling infected farms are insufficient to stop epidemic spread, and more aggressive control measures such as vaccination or preemptive culling are required (Keeling et al. 2003, Le Menach et al. 2005, Tildesley et al. 2012, Hayama et al. 2015). A common goal of disease spread models is to estimate epidemic risk and scenario-plan the best control measures, so many simulation studies are performed on real-world farm data (or approximations of real-world data) to estimate epidemic size under varying control regimes (e.g., Tildesley et al. 2006, Ward et al. 2009, Hayama et al. 2015). These studies provide valuable information regarding the epidemic risks and control strategies in those areas and provide a clear link between host density and the severity of livestock epidemics.

The spread of highly contagious livestock diseases is sensitive to two aspects of host density, which are rarely considered independently: farm density and livestock density. Epidemic data reveal two patterns which suggest these two aspects of density act to influence the spread of livestock disease: (1) There is a strong spatial component to inter-farm transmission, where the probability of infection decreases with increasing distance from an infected source and (2) farms holding more livestock are more susceptible to infection during an outbreak (Keeling et al. 2001, Bessell et al. 2010, Muroga et al. 2012, Boender et al. 2014, Chaudhry et al. 2015). Farm density will influence the distance between farms, while livestock density will influence the number of animals on farms. The pathogens causing these diseases are rapidly transmitted among animals on the same farm and control measures are typically applied at the farm-level, so disease transmission models often consider the farm the unit of infection (e.g., Keeling et al. 2001, Truscott et al. 2007, Boender et al. 2008). The emphasis is on modeling transmission between farms, but attributes of the farm such the number of animals held on the premises can influence the likelihood of inter-farm transmission (e.g., Keeling et al. 2001, Truscott et al. 2007).

Clearly, both aspects of host density play a role in determining the severity of an epidemic, but their relative contributions to epidemic size and risk are rarely considered. This could be because farm and livestock densities are typically correlated in real-world agricultural settings (e.g., USDA 2007; Appendix S1: Fig. S1). However, livestock production in many industrialized countries is becoming increasingly concentrated on large, commercial farms (Robinson et al. 2014). This trend will alter the relationship between farm and livestock density in many areas, so there is a growing need to understand how each aspect of host density contributes to epidemic risk and severity. This may help policymakers and livestock producers plan locations and sizes of new farms that minimize disease risk and provide information that could guide research of alternative control strategies.

Traditional approaches of simulating disease outbreaks on real-world farm data make dissecting the relative importance of farm and livestock density difficult owing to their inherent correlation. Here, we take steps to disentangle these densities and study their relative influences on FMD epidemics. We control for the correlation between farm and livestock density that is typical of real-world farm data by constructing hypothetical farm populations based on ranges of county-level estimates of farm density and livestock density seen in United States cattle farming systems. These hypothetical populations utilize factorial combinations of (1) the number of farms in a county, (2) the number of livestock in a county, and (3) the area of the county. Our factorial design yields a range of farm/livestock density combinations at the same spatial scale they are available in the United States. We simulate FMD outbreaks on these hypothetical data and on data taken from counties within eight US states, representing different geographical regions of the country. To obtain a range of farm and cattle densities from US farm data, we selected six counties within each state for FMD simulations, choosing the county with the highest and median value for each of the following categories: number of farms, number of cattle, and mean farm size (in terms of cattle/farm). We compare the results of these two simulation

studies to evaluate whether cattle density and farm density, calculated at the aggregate county level, are predictive of the size of the outbreak and to weigh the relative importance of importance of these two density measures.

Methods

The model

The model used in this paper was originally developed in by Keeling et al. (2001) to predict FMD spread after movement restrictions were in place during the 2001 epidemic in the UK and has since been adapted to model FMD outbreaks in the United States (e.g., Tildesley et al. 2010, 2012). This model treats the farm as the unit of infection, classifying farm premises as susceptible, infected, infectious, or culled, meaning within-farm dynamics are excluded and all animals on the same farm are assumed to have the same disease status. This is a reasonable assumption if farming practices are relatively similar to the UK because the virus is rapidly transmitted among livestock on the same farm. The rate at which an infectious farm i infects a susceptible farm j is given by:

$$\text{Rate}_{ij} = N_i^q T_q \times N_j^p S_p \times K(d_{ij})$$

N_i is the number of cattle on farm i, S_p and T_q, respectively, measure the species-specific susceptibility and transmissibility for cattle (see Appendix S2 for methods used to determine these values), d_{ij} is the distance between farms i and j, and K is the distance-dependent transmission kernel, estimated from contact tracing (Keeling et al. 2001). Power-law parameters p and q account for a sublinear increase in susceptibility and transmissibility as cattle numbers on a farm increase (Tildesley et al. 2008, Appendix S1: Fig. S2). We assume that farms are infected for 5 d before becoming infectious and then are infectious for 7 d before being reported and culled.

Although FMD can infect other cloven-hoofed livestock such as sheep, pigs, and goats, we focus our modeling efforts on cattle farms. Among FMD-susceptible livestock species, cattle dominate the U.S. system except for a few regions (e.g., North Carolina) where pig farming is highly concentrated (USDA 2007). Differences in host biology among livestock species and in farming practices among production sectors can alter the transmission kernel and farm-level susceptibility (e.g., Bates et al. 2001, Dickey et al. 2008), possibly altering epidemic outcomes. However, we address this uncertainty by performing sensitivity analyses on kernel and susceptibility parameter (see *Parameter sensitivity analyses* below).

Transmission kernel

We modeled the local spread of the virus via multiple transmission routes (e.g., trucks, airborne transmission, and farm personnel) via the use of a distance-dependent transmission kernel (Keeling et al. 2001). The local transmission kernel is a monotonically decreasing function displaying power-law-like behavior:

$$K = \frac{a}{D_0 + \frac{d_{ij}^{\alpha}}{K_w}}$$

where a determines the height of the kernel, D_0 is the kernel offset parameter, which approximates the radius of the initial source of infection (Mundt and Leonard 1985), d_{ij} is the distance between infected farm i and susceptible farm j, α determines the shape and kurtosis of the kernel (Chis Ster and Ferguson 2007), and K_w determines the scale (or width) of the kernel (Tildesley et al. 2012). The kernel, in this form, was estimated from the 2001 UK FMD epidemic when $K_w = 1$ (Chis Ster and Ferguson 2007). Higher values of K_w correspond with greater extent of local spread, while higher values of α correspond with a thinner kernel tail (Appendix S1: Fig. S3). For all simulations, we set $a = 0.1$ and $D_0 = 0.1$, which is approximately the radius (km) calculated from the mean farm area for cattle farms in the UK (Department of the Environment, Food and Rural Affairs [DEFRA]).

Factorial manipulations of cattle and farm populations

We performed factorial manipulations of number of farms and cattle in a county to determine the relative importance of farm density and cattle density to FMD epidemic severity. To alter farm and cattle density, we chose initial county-level cattle populations (20,000, 50,000, 100,000, 200,000, and 350,000) and then increased the

number of farms in the county that the cattle were distributed among (100, 500, 1000, 2000, and 3000). We considered all possible combinations of cattle and farm populations and further altered farm and cattle density by crossing each cattle/farm combination with two county areas: 2500 and 5625 km^2. This yielded 50 scenarios of cattle and farm density (Fig. 1). The county areas chosen correspond to the range of county sizes of those counties we selected (Appendix S1: Table S1) for FMD simulations on U.S. data (U.S. simulations will be described in a later section), as do the resulting cattle and farm densities from each combination of cattle population, farm population, and county area (Fig. 1).

Simulating FMD outbreaks on factorial manipulations of cattle and farm density

For each modeling treatment, we distributed farm locations in a 50 × 50 or 75 × 75 county area, pulling each farm's XY coordinate from a uniform random distribution. This method does not account for any spatial heterogeneities that might be characteristic of real-world farm data. Kernel parameterization can subsume some of the spatial structure of the hosts (Tildesley et al. 2010), so we perform sensitivity analyses on kernel parameters to compare qualitative model predictions as these parameter values vary. Each farm was assigned N number of cattle, pulled from an exponential distribution with a mean corresponding to the mean farm size for that treatment. To ensure the total number of cattle among all farms summed to the desired county-level cattle population, we multiplied each farm-level cattle population by a scaling factor calculated by dividing the desired population by the sum of the cattle population across all farms. We simulated 50 epidemics of this scenario by seeding five random farms with infection and tracking the number of secondary farms and cattle infected, considering this one replicate. For the next replicate, we re-assigned farm locations and farm sizes and performed another subsequent 50 epidemic simulations. In total, we performed 10 replicates of each modeling treatment. Performing replicates allowed us to speculate whether we can expect patterns to hold across heterogeneous farming landscapes. We will refer to these as "factorial simulations" throughout the remainder of the paper.

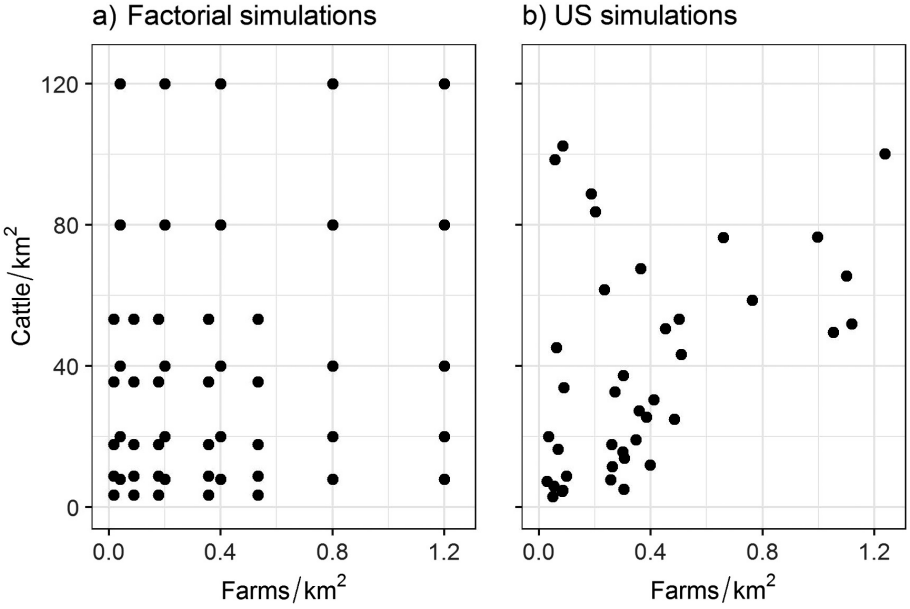

Fig. 1. The relationship between county-level farm density and county-level cattle density in the host demography scenarios used in (a) factorial and (b) U.S. simulations. Factorial simulations were run on hypothetical combinations of county-level cattle and farm populations, while U.S. simulations utilized the county-level reports of cattle and farm populations from the US Census of Agriculture (USDA 2007).

Simulating FMD outbreaks in U.S. states

Although the range of farm and cattle densities used in the factorial simulations were drawn from the levels seen across the United States, simulating outbreaks in a discrete, square county area may not produce the same patterns of epidemic spread and severity as seen in real-world scenarios. Though previous work suggests that conditions in the outbreak focus (e.g., host susceptibility and size of the focus) can influence the severity of the subsequent epidemic (Estep et al. 2014, Severns et al. 2014), it is possible that demography in surrounding counties influence the extent of the epidemic (Tildesley et al. 2012). Moreover, examining outbreaks that are confined to a small county area restricts dispersal of the pathogen and might not reveal patterns of dispersal that are driven by the kernel tail. Therefore, we investigated the consequences of initiating FMD epidemics in US states (Colorado [CO], Florida [FL], Kentucky [KY], Missouri [MO], Oregon [OR], Pennsylvania [PA], and Texas [TX], and Wisconsin [WI]), representing different geographical regions of the country and with varying farm demography patterns including cattle density, farm density, and average farm size. Since we are interested in the relative importance of farm density vs. cattle density, we seeded epidemics in the county with the highest and median number of farms, number of cattle, and mean farm size within each state (Appendix S1: Table S1). We only chose the maximum demography values for Oregon because median values were too low to produce any significant outbreaks. Farm and livestock numbers in the US are reported by the USDA National Agricultural Statistics Service (NASS) at the county level, so precise farm locations and sizes are unknown. However, NASS reports the number of farms by size category (1–9, 10–19, 20–49, 50–99, 100–199, 200–499, and 500+ cattle). The farm data used here were populated from the 2007 Census of Agriculture by randomly allocating locations to farms within a county and deaggregating the NASS county-level farm size data as per Tildesley et al. (2012). We initiated outbreaks by seeding five random farms within the specified county with FMD. Although initial infections are seeded within an index county, we include all farms in the state as potential susceptible hosts. We will refer to these simulations as "US simulations" hereafter.

Parameter sensitivity analyses

The simulations outlined in the previous sections begin by using the assumption that a hypothetical U.S. FMD outbreak would behave similarly to the 2001 UK epidemic, and used the parameters estimated from the Cumbria hotspot region during the UK epidemic (Keeling et al. 2001, Table 1). However, disparity in farming practices, livestock demography, and control measures enacted in response to an outbreak will likely result in different parameter values than those estimated in the UK. Since the values of the corresponding U.S. epidemiological parameters are unknown, we conducted sensitivity analyses on kernel (K_w and α), susceptibility (^{p}), and transmissibility (^{q}) parameters to explore how variation in these parameters impacts model predictions (Table 1). Kernel shape (α) and width (K_w) parameter values, which govern the risk of infection by distance between susceptible and infectious farms, may be influenced by regional differences in contact structure (e.g., movement of animals and fomites between farms). Susceptibility and transmissibility may vary regionally due to farming and biosecurity practices. Despite

Table 1. FMD model parameter values and ranges for sensitivity analyses.

Simulation set	Parameter	UK value	Range (increment)	Description
(a) Factorial simulations	α	2	2–3 (0.0.25)	Shape of transmission kernel
	K_w	1	1, 2, 4	Scale of transmission kernel
	p	0.41	0.2–0.8 (0.2)	Non-linear effect of farm size on susceptibility to infection
	q	0.42	0.2–0.8 (0.2)	Non-linear effect of farm size on transmission potential
(b) US simulations	α	2	2–3 (0.1)	Shape of transmission kernel
	K_w	1	1, 2, 4	Scale of transmission kernel

Note: FMD, foot-and-mouth disease.

uncertainty in the exact scaling relationship between the number of animals on a farm and farm susceptibility/transmissibility, we assume a positive relationship between animals on a farm in susceptibility/transmissibility (Table 1). For example, a previous study performed in central California found that large beef cattle and dairy farms (>250 cattle) experienced higher direct (e.g., incoming livestock shipments) and indirect contact (e.g., contact between livestock and personnel or equipment from outside the farm) rates than small farms (<250 cattle; Bates et al. 2001). The latter is particularly important after the start of an epidemic, when animal movement bans are in place. We were most interested in determining how sensitive the impacts of farm and cattle density on epidemic outcomes would be to variation in these parameters. We performed sensitivity analyses of the kernel parameters (K_w and α) for both factorial (50 cattle/farm density combinations $\times$ 3 K_w $\times$ 5 α = 750 scenarios of FMD outbreaks) and U.S. simulations (41 seeding counties $\times$ 3 K_w $\times$ 5 α = 615 scenarios of FMD outbreaks). However, due to logistical and model run-time constraints, we only performed susceptibility (q) and transmissibility (q) sensitivity analyses on factorial simulations when the kernel width was twice that estimated from the 2001 UK epidemic (K_w = 2) and when the kernel shape parameter (α) was 2, 2.5, and 3. These sensitivity analyses resulted in an additional 2400 scenarios of FMD outbreaks (50 cattle/farm density combinations $\times$ 3 α $\times$ 4 p $\times$ 4 q).

Model output and variable importance analyses

We utilized generalized linear mixed models (GLMs) to assess the linear effects of input variables and their interactions on the epidemic impact in factorial and U.S. simulation scenarios. For factorial simulations, we separately considered the proportion of farms and the proportion of cattle infected in the focus county as the epidemic impact. However, because we did not confine epidemics to the focus county in U.S. simulations, we modeled the proportion of farms or cattle infected in the entire state in the U.S. scenario. We used a binomial GLM to test the effect of farm density, cattle density, the kernel width parameter, and the kernel shape parameter, plus each possible two-way interaction of farm density, cattle density, and the kernel width parameter on epidemic impact. We excluded interactions with the kernel shape parameter because its impacts were relatively weak compared to the kernel width parameter (Table 2). We recognize that some input variables have non-linear effects on model outcomes but use these results in combination with variable importance analyses to assess the relative influence of cattle density and farm density under different scenarios of pathogen dispersal (i.e., different values of kernel parameter values).

In order to assess the relative importance of cattle density and farm density on the size of epidemics, as well as to assess whether the relative importance shifts depending on kernel parameter values, we compared model-averaged parameter estimates (Galipaud et al. 2017). We separately considered the number of farms infected and the number of cattle infected as our response variables and the performed separate analyses for factorial and U.S. model output. For each response variable, we fit a global binomial GLM with cattle density, farm density, the kernel

Table 2. Results from variable importance analyses to rank the relative importance of cattle density (CD), farm density (FD), the kernel width parameter value (K_w), and the kernel shape parameter value (α) to the size of FMD epidemics (in terms of the proportion of farms infected).

	Factorial simulations				US simulations			
Parameter	Subset Estimate	Subset Rank	Full Estimate	Full Rank	Subset Estimate	Subset Rank	Full Estimate	Full Rank
CD	2.596	1	2.596	1	0.047	4	0.009	4
FD	−0.343	4	−0.343	4	0.536	2	0.536	2
K_w	0.668	2	0.668	2	2.423	1	2.423	1
α	−0.149	3	−0.078	3	−0.292	3	−0.275	3

Notes: FMD, foot-and-mouth disease. Shown are the model-averaged parameter estimates of both subset and full averages for the factorial and the U.S. simulation results. Variable importance is ranked (1 being the most important) by the magnitude of the parameter estimate.

width parameter value, and the kernel shape parameter value as the predictor variables. We did not include interaction terms in the global model. We generated the full subset of models from the global model using the dredge function in the R package MuMIn (Barton 2016) and then obtained model-averaged parameter estimates using the mod.av function. We compared both full-model-averaged parameter estimates (averaged over all possible subsets, so the coefficient of a variable is 0 in models where it is absent) and subset averaged estimates (only averaged over models where the variable appears), typically finding the ranking of variable importance did not change between the two methods. Because we expected that kernel parameters might influence the relative importance of cattle density and farm density, we also repeated this information–theoretic process within each level of the kernel width parameter.

Lastly, we repeated the variable importance and GLM analyses for the simulations testing the sensitivity of model outcomes to variation in the susceptibility and transmissibility power-law parameters. These parameters can shift the relative influence of cattle density; when ^{p} is closer to 0, the number of animals on a farm has much less influence on inter-farm transmission than when ^{p} is closer to 1 (Appendix S1: Fig. S2). We provide more methodological details on the analysis of sensitivity output in Appendix S2: methodological details. All analyses were performed in R version 3.3.2 (R Core Team 2016).

Results

Factorial simulations

Binomial GLM results.—The factorial simulations revealed a nuanced interplay between the predictor variables and the proportion of farms infected, as signified by several significant interactions (complete model output available in Appendix S1: Table S2A). There was a significant farm density × cattle density interaction (slope = 0.05, SE = 0.018, $P = 0.006$), suggesting the effect of farm density on the proportion of farms infected increases with cattle density. The simulations reveal patterns suggesting the occurrence of significant epidemics is more dependent on cattle density than farm density. Since we are comparing simulations performed on a range of farm population sizes (100–3000), we define a significant epidemic as an outbreak that results in 10% of farms infected, rather than a set number of farms. Significant epidemics were not present below a county-level cattle density threshold, regardless of farm density, although the threshold was dependent on kernel parameters (Fig. 2). After the cattle density threshold was met, increasing farm density further increased epidemic impact. Increasing the kernel width parameter (the extent of spread) lowered the cattle density threshold necessary for significant epidemics and increased the severity of the epidemics that occurred (cattle density × K_w; slope = 0.041, SE = 0.006, $P < 0.001$). Increasing the value of kernel shape parameter resulted in smaller epidemics (slope = −1.55, SE = 0.447, $P < 0.001$). We also considered the number of cattle infected, as opposed to the number of farms, as the epidemic impact. The number of cattle infected followed the same relationship with the predictor variables as the number of farms infected (see Appendix S1: Table S2A for model output).

Variable importance analyses.—We ranked the importance of cattle density, farm density, the kernel width parameter value, and the kernel shape parameter value by comparing the effect size of their standardized model-averaged effect sizes (Table 2a). Cattle density was the most influential variable, with over 2.5 times the effect of the next most influential variable, the kernel width parameter. This pattern remained consistent within each level of the kernel width parameter (Appendix S1: Table S3A).

US simulations

Binomial GLM results.—We simulated FMD epidemics in several U.S. states, initiating outbreaks in the county with the highest and county with the median number of farms, the highest and the median number of cattle, and the largest and the median average farm size (Appendix S1: Table S1), and track the state-wide epidemic impact. As in the factorial simulations, the relationship between the number of farms infected state-wide and the predictor variables was multifaceted (complete model output available in Appendix S1: Table S2B). There was a cattle density × farm density interaction (slope = −0.044, SE = 0.021, $P = 0.036$), suggesting the effect of farm density on the proportion of farms infected state-wide deceased with increasing cattle

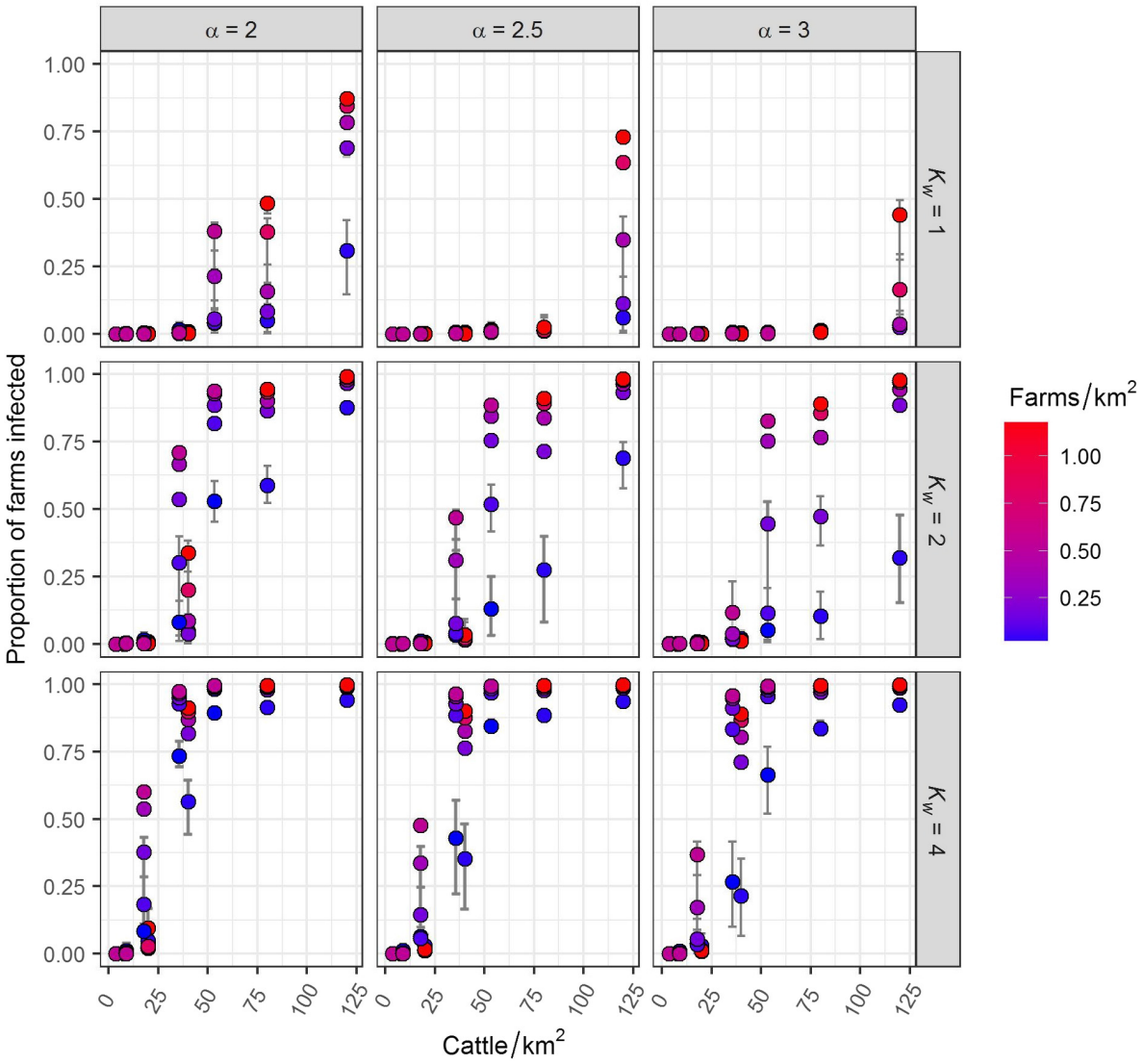

Fig 2. The effect of cattle density (*x*-axis) and farm density (color scale) on foot-and-mouth disease epidemic impact in factorial simulations. Points represent the mean proportion of farms infected. Error bars show the upper 95% and lower 5% tails of epidemic size. Results are shown for representative combinations of kernel width (K_w), and kernel shape (α) parameter values.

density (Appendix S1: Fig. S5). There was also a significant cattle density × farm density interaction in the factorial simulations, but the direction of the effect was positive in the factorial simulations. Increasing the kernel width parameter resulted in larger epidemics (Fig. 3) and decreased the effect of farm density on epidemic size (farm density × K_w; slope = 0.825; SE = 0.108; $P < 0.001$). Increasing the kernel shape parameter (α) value resulted in smaller epidemics (slope = −1.55; SE = 0.447; $P = 0.001$), as would be expected since a higher parameter value results in a thinner kernel tail. The number of cattle infected showed the same qualitative relationships with the predictor variables as the number of farms infected (Appendix S1: Table S2B).

Variable importance analyses.—The importance of cattle density, farm density, the kernel width parameter value, and the kernel shape parameter value did not follow the same pattern as in the factorial simulations. In the US simulations, the

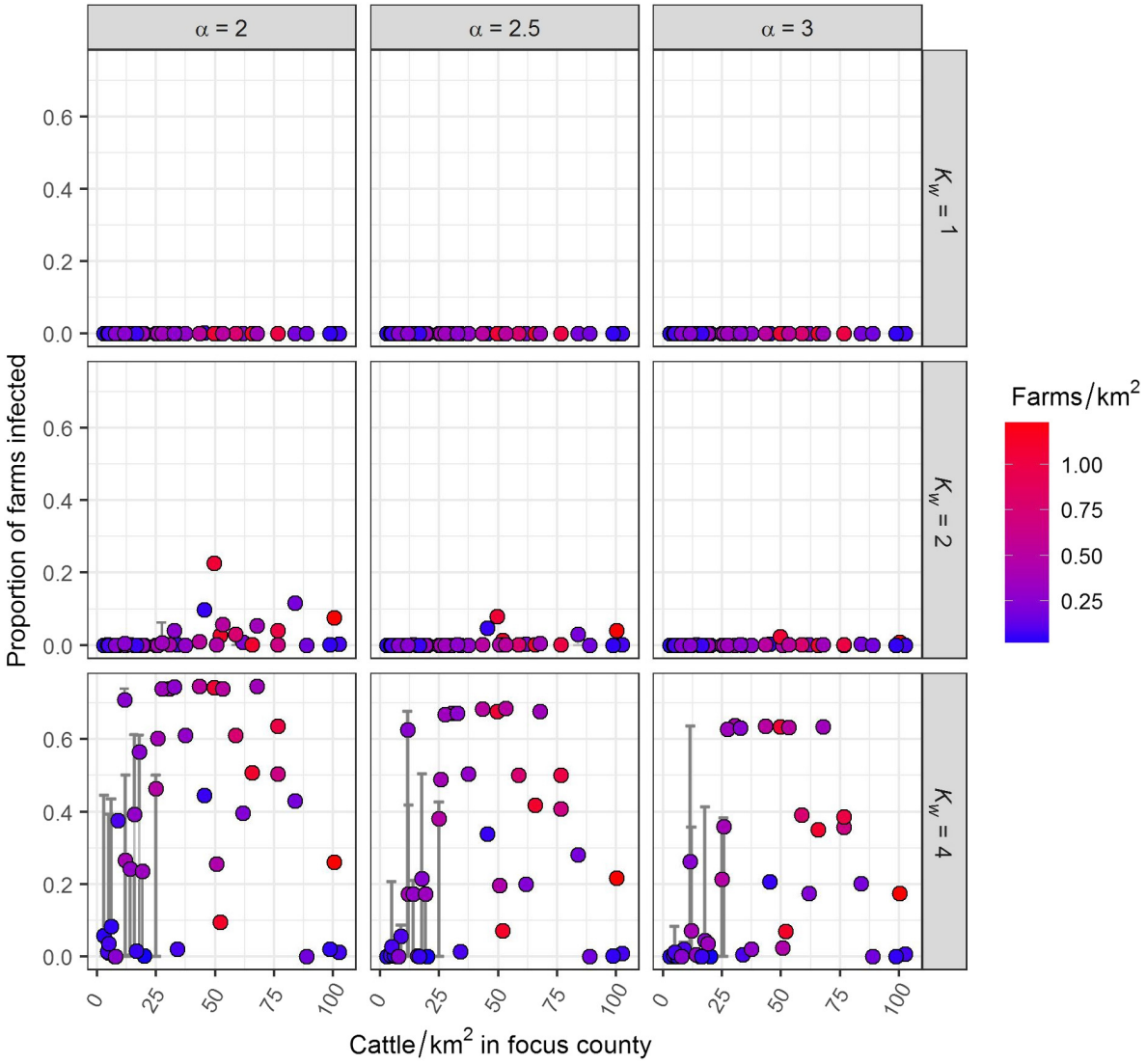

Fig 3. The effect of cattle density (*x*-axis) and farm density (color scale) in the index county on the state-wide epidemic impact in US simulations. Points represent the proportion of farms infected in a state after foot-and-mouth disease outbreaks were initiated in the index counties indicated in Appendix S1: Table S1. Error bars show the upper 95% and lower 5% tails of epidemic size. Results are shown for representative combinations of kernel width (K_w), and kernel shape (α) parameter values. Appendix S1: Fig. S5 shows these proportions as raw numbers.

kernel width parameter was the most important factor influencing epidemic size and cattle density was the least influential variable (Table 2b). Furthermore, the rankings of the remaining variables (cattle density, farm density, and kernel shape) were not consistent within levels of the kernel width parameter (Appendix S1: Table S3B).

Discussion

Knowledge of host density is recognized as a key piece of information for predicting future epidemic risk (Woolhouse 2011). Indeed, previous analyses of livestock epidemics have identified regions of high host density as epidemic hotspots

(Keeling et al. 2001, Boender et al. 2007, Hayama et al. 2015). However, there have not been extensive efforts to distinguish between the influence of livestock and farm density on epidemic risk and severity, possibly because they are tightly associated in many farming systems and regions (e.g., Appendix S1: Fig. S1). However, livestock production is shifting toward fewer, but larger farms and understanding the relative influence of farm vs. livestock density will provide a means to assess how shifting production patterns could influence disease risk. To address this issue, we performed simulations on factorial combinations of county-level farm and cattle population sizes, which resulted in cattle and farm densities representative of many cattle farming regions in the United States (Fig. 1; Appendix S1: Table S1). This approach allowed us to analyze the separate contributions of farm vs. livestock density to epidemic spread because cattle and farm densities were not correlated to the same degree as in the simulations performed on U.S. farm data (Fig. 1).

The results of our simulations suggest that although both aspects of host density are important, livestock density plays an especially important role in mediating the severity of epidemics (Table 2). The factorial simulations clearly revealed a threshold cattle density was necessary before significant epidemics occurred (measured as >10% of farms or cattle infected), regardless of farm density (Fig. 2; Appendix S1: Fig. S4). This threshold value varied depending on the dispersal kernel parameter values but was ~50 cattle/km^2 for parameter values similar to those estimated from the 2001 UK epidemic (K_w = 1 and α = 2). The outcomes of farm and cattle infection in the simulations were qualitatively similar, so we will refer to results regarding farms for the remainder of the discussion. Increasing the cattle population size within levels of farm density acted to increase epidemic severity through increasing mean farm size (Fig. 2). Increasing the farm population size within levels cattle density acted to decrease mean farm size, resulting in a nearly inverse relationship between farm density and epidemic impact for some low and moderate levels of cattle density (Fig. 2). However, when cattle density was sufficiently high (e.g., >50 cattle/km^2 when K_w = 1), increasing farm density within levels of cattle density acted to increase epidemic severity. These results mean that farm densities representative of the most intensive livestock farming counties we examined did not automatically facilitate large FMD epidemics. However, livestock densities representative of these regions did typically facilitate large FMD epidemics, even when combined with farm densities on the lower end of the spectrum. This suggests that the current trend of consolidating livestock on fewer premises has the potential to facilitate larger livestock epidemics. The factorial simulations show these trends clearly but represent a simplified scenario because they were limited to a single county and were not confounded by real-world farm demography patterns.

The results from the U.S. simulations are more difficult to dissect due to the correlation between farm and cattle density in these data and the influence of surrounding county farm demography. There was a tendency for more farms to become infected as cattle density increased (Fig. 3), but cattle density did not rank as high in the variable importance analyses as it did in the factorial analyses (Table 2). Both simulation studies revealed epidemic severity was influenced by a cattle density × farm density interaction, but the U.S. simulations had a negative interaction term and factorial simulations had a positive interaction term. The inconsistencies between the factorial and U.S. simulations could have arisen from the patterns of correlation between farm density and cattle density in U.S. farming systems. In the U.S. farm data, there were no scenarios of high farm density and low cattle density; however, there are cases of high cattle density, but low farm density (Fig. 1), which could explain why the analyses detected that the influence of farm density decreased as cattle density increased and supports the need for factorial simulations to provide representations of the scenarios of high farm, but low cattle density that are lacking in the U.S. farm demography (Fig. 1).

Another notable difference that emerged between the results of the factorial and US simulations was the importance of kernel parameter values on epidemic size and on the relative influence of cattle density vs. farm density. There was a stronger effect of kernel parameters on epidemic size in the U.S. simulations (Table 2) because epidemics were observed over state-level farm landscapes, rather than the isolated counties in the factorial simulations. Increasing the width

parameter allowed local spread to occur over greater distances and acted to connect more farms than in instances where the width parameter was lower (Appendix S1: Fig. S3); in both simulation studies, this resulted in more severe epidemics and lowered the cattle density threshold for significant epidemics (Figs. 2 and 3). However, in the U.S. scenario, higher values of the kernel width parameter increased the chance of spread beyond the index county such that demography in the surrounding county might have obscured the effect of demography in the index county. The largest portion of state-wide farms held by any of these counties is 20% (Washington County, Colorado), but the majority of the counties we examined hold <1% of state-wide farms (Appendix S1: Table S1). Fig. 3 and Appendix S1: Fig. S6 show many scenarios where >25% of farms and cattle in a state become infected when $K_w \geq 2$, indicating spread beyond the focus county. The effect of kernel width on spread beyond the index county is likely why, in the US simulations, cattle density was only more important than farm density when kernel width was low (Table 2). This suggests that livestock density is a better predictor of epidemic impact at smaller spatial scales (i.e., county level), but farm density and the pathogen's dispersal kernel become more important over larger spatial scales.

A principal result of this study was that high farm density had to be met with a threshold cattle density before epidemics occurred, which could have significance for alternative epidemic mitigation strategies. The control measures enacted in previous high-profile livestock epidemics included preemptively depopulating farms considered to be at increased risk of infection (Benard et al. 1999, Keeling et al. 2001, Stegeman et al. 2004). The most severely affected regions in the 2001 UK epidemic enacted culling of susceptible animals within 3 km of infected farms in effort to contain the epidemic (Kao 2002), and simulation studies later confirmed that these rigorous measures were instrumental in containing the epidemic (e.g., Tildesley et al. 2009). This study suggests that instead of completely depopulating at-risk farms, another strategy to consider would be one that aims to bring the livestock density in epidemic foci below a threshold level. For example, instead of completely culling farms within a specified radius of infected farms, alternative strategies might focus on only completely culling infected farms and the highest-risk farms (e.g., dangerous contacts, sensu Keeling et al. 2001) and reducing the population of livestock on other at-risk farms. Smaller farms are less susceptible to infection and might improve the ability of livestock producers to enact strict biosecurity measures. Preemptively reducing the size of farms, as opposed to complete depopulation, might also improve compliance with control measures because livestock producers could spare their most valuable livestock from culling (Kao 2003). Another way that livestock density thresholds could be met would be to completely cull select farms until the target livestock density is met, potentially sparing some farms from being lost to preemptive control. Local policymakers, veterinarians, and epidemiologists could consult on which farms should be prioritized for culling and on the best way to reach the target density for their region, providing an avenue for locally tailored control strategies.

By reducing the correlation between farm and livestock density in factorial simulations, we were able to clearly demonstrate the increase in epidemic size that occurred as farm sizes grew larger (i.e., through increasing county-level cattle populations), across levels of farm density. This trend was robust to variation in kernel and transmission parameter values. Although it is necessary to consider other factors such as the dispersal properties of the pathogen and regional farming practices, we have shown that easily obtainable, aggregated estimates of farm and livestock density provided predictive information regarding the severity of epidemics within the aggregated area. Of course, both aspects of host density interactively influenced the size of FMD epidemics, but variable importance analyses revealed that, at least within county-level spatial scales, cattle density played a stronger role in facilitating large FMD epidemics. This research suggests, especially in the face of changing livestock production patterns, it is important to distinguish between livestock density and farm density and increase understanding of how growing farm sizes may alter epidemic risk and severity.

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