Effects of regional differences and demography in modelling foot-and-mouth disease in cattle at the national scale

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Abstract

Foot and mouth disease (FMD) is a fast-spreading viral infection that can produce large and costly outbreaks in livestock populations. Transmission occurs at multiple spatial scales, as can the actions used to control outbreaks. The U.S. cattle industry is spatially expansive, with heterogeneous distributions of animals and infrastructure. We have developed a model that incorporates the effects of scale for both disease transmission and control actions, applied here in simulating FMD outbreaks in U.S. cattle. We simulated infection initiating in each of the 3049 counties in the contiguous U.S., 100 times per county. Depending on where initial infection was located, specific regions were more likely to produce large outbreaks, driven by infrastructure and other demographic attributes such as premises clustering and number of cattle on premises. Sensitivity analyses suggest these attributes had more impact on outbreak metrics than the ranges of estimated disease parameter values. Additionally, although shipping accounted for a small percentage of overall transmission, areas receiving the most animal shipments tended to have other attributes that increase the probability of large outbreaks. These results demonstrate the importance of accounting for spatial and demographic heterogeneity when modelling potential outbreak trajectories and possible control actions.

Keywords: simulation, geographic scale, sensitivity analysis, vaccination, culling, movement bans

1. Introduction

A fast-spreading disease such as foot-and-mouth disease (FMD) could potentially have significant economic impacts on the United States (U.S.) livestock industry. The FMD outbreak in the United Kingdom in 2001 was estimated to have cost £3.1 billion to agriculture,

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including losses in export value, with similar losses to tourism and business of £2.7 - 3.2 billion [1]. Estimating potential FMD impacts on the U.S. livestock industry requires an estimate of the number of premises impacted and control measures that would be undertaken under different scenarios. An outbreak could predominantly affect one livestock type, as in the 2001 outbreak in Argentina affecting only cattle [2], or multiple livestock types, as in the United Kingdom [3]. Since there has not been an FMD outbreak in the U.S. since the early 1900s [4], we must rely on simulated outbreaks, which can be informed by empirical data from outbreaks in other countries, to estimate the relative impacts of contributing factors and control strategies in an outbreak. Here we address a cattle-only scenario, but this lays the groundwork to include other livestock types as well.

Past outbreaks of FMD in non-endemic countries provide invaluable data for countries that have not had recent outbreaks. Factors at a range of spatial scales can influence the outbreak trajectory [3, 5, 6]. FMD can spread through direct transmission between animals, or indirectly via fomites, both forms of which are more likely to occur over shorter distances. Studies of previous outbreaks suggest that most FMD transmission occurs within localised areas [3, 7]. Additionally, premises spatial distributions can affect predicted outbreak characteristics, including outbreak size [8]. Although most transmission events in an FMD outbreak occur at local scales, larger scale transmission (e.g. via animal shipments) has been important in moving infection to new foci and setting off new chains of local transmission [3, 5]. Simultaneously capturing multiple scales of transmission is therefore an important aspect of FMD simulations.

The most commonly used control actions (culling or vaccination of animals, and shipment restrictions) in FMD outbreaks are applied according to the implemented control policy and the landscape and demographics of the infected area [3, 5, 6, 9]. Vaccination usually occurs on premises not thought to be infected, either in proximity to an infected premises or identified to be at risk and part of a vaccination area. Examples of this type of regional vaccination include vaccinating the hardest hit areas of an outbreak to stem the spread, as was done in Miyazaki, Japan in 2010 [6], or mass vaccination campaigns that target all animals in a country or part of a country, as was done in the 2001 Argentina outbreak [2].

Effective shipment bans can help to contain outbreaks from spreading to uninfected areas of a country and can therefore influence the geographic extent of an outbreak. Countries experiencing outbreaks have also implemented shipment restrictions on or around reported infected premises [2, 6]. Additional restrictions may apply to all livestock shipments in a region or nation [2, 3, 5]. These control actions are inherently affected by the spatial and demographic characteristics of the population to which they are applied.

The U.S. cattle industry has a number of distinguishing attributes compared to cattle industries in countries that have had recent FMD outbreaks. It is larger, both spatially and in animal and premises numbers. Additionally, there are distinct regional concentrations of infrastructure and production practices that vary due to complex economic and resource availability - for example, high concentrations of feedlots and finishing operations near grain production areas [10, 11]. Although these regions may be spread out over large areas, they are also well-connected through networks of animal shipments [10, 12]. Given these characteristics of the U.S. cattle industry, simulations accounting for premises density, spatial relationships, production practices, and shipment patterns will be suited to understand the conditions that increase the probability of large outbreaks in this population.

Our previous [13] FMD simulation incorporated U.S.-specific animal shipment patterns and infrastructure, and the impact of different scales of animal shipment controls. However, due to limited premises location information, the data were aggregated to the county level, and county-to-county transmission was simulated, tracking which counties contained one or more infectious premises. This enhanced version of the U.S. Disease Outbreak Simulation (USDOS) expands on our previous model by increasing the granularity of simulations to the premises level, using a combination of generated premises locations [14] and a shortcut computational technique [15]. We then infer outcomes at larger geographic scales.

USDOS is a tool that can be customised to simulate a variety of scenarios according to available data and parameter information. We simulated cattle-only outbreak scenarios, with and without control options [16], and performed sensitivity analyses to identify the variables that played the strongest roles in driving the model outputs. Understanding what drives outbreak outcomes will be key to efficiently focusing data collection and validation efforts in areas that provide the most information value.

2. Methods

2.1. Model structure

We developed a stochastic disease spread model that included several control options and constraints on control resources. Cattle premises were the most granular unit. Premises attributes included location, production type (dairy or beef) and estimated numbers of cattle on each premises (see Sections 2.3 & S1.1 for details).

Disease spread among premises occurred through two possible routes in this model: shipments of infectious animals and local transmission. Local transmission is distance-dependent and collectively represents multiple factors that may transmit infection from one premises to another, such as wind, or movement of equipment, feed, or other fomites.

Each premises had a disease status and a control status that was tracked throughout each simulation. The disease status reflected the course of infection. The sequence of disease statuses was: "susceptible", "exposed" (pathogen incubation and pre-infectious period), "infectious" (when the pathogen can be transmitted to other premises), and "immune" (no transmission and no further exposure).

The control status reflected what was known about that premises and control actions taken. Each premises began with status "not reported", indicating no reporting or control measures. They could then be identified as either "reported" (from identification of infection until control is implemented) or as a "dangerous contact". Dangerous contacts (DC) are premises which are at higher risk of infection, for example, due to known contact with an infected premises. DC premises could then either become "reported" if infected any time prior to control, or could start the sequence of control application statuses: "implemented" (control applied but not yet effective) and "effective" (transmission reduced according to the effectiveness of control). The disease and control statuses progressed independently, other than a reporting lag time after becoming "exposed" to becoming "reported". We assumed that a DC would be under surveillance and would therefore have a faster reporting time than premises not identified as DC (Table 2). The premises where infection was seeded had its own "index case reporting time". Each of these statuses was assigned a duration until the next status in the sequence (Tables 1 & 2).

All model assumptions and parameter values were informed by published literature, historic outbreak data from other countries, or consultation with subject matter experts.

We simulated combinations of three potential FMD control mechanisms: shipment bans, culls, and vaccination [16]. Culls and vaccination were applied to premises with specific statuses or criteria:

- IP refers to premises that have a disease status of "infectious" and a control status of "reported"
- 3 km ring and 10 km ring refers to premises located within a control zone within a three or ten kilometre radius of a given IP
- DC refers to premises that have been identified as "dangerous contacts" for a given IP.

Each outbreak simulation began with all premises susceptible, except for one randomly selected seed premises designated as exposed. Time steps were modelled as discrete days. Each day, all premises statuses were first updated based on the previous day's events, then all events for disease progression, control actions, and local and shipment-based transmission were determined in that order, going into effect the following day.

Control actions were triggered by new reports of infected premises. Control resource constraints were updated as they were used to ensure resources were not overdrawn. If constraints were limiting, premises were treated as resources allowed, in the order in which they were identified for control.

Simulations continued until one of the following occurred: the outbreak died out (no exposed or infectious premises remained) or 365 simulated days passed, whichever happened earliest.

The code was written in C++11, available in C++ or as an R package on *https://webblabb.github.io/usammusdos/index.html* [17].

2.2. Scenarios simulated

Based on different combinations of the three control actions, we simulated five main control scenarios, each with varying levels of effectiveness (see Section 2.6 and Table 2). These scenarios should not be interpreted as policy, but allowed us to identify patterns in outputs and are based on strategies that have been used in FMD outbreak situations [3, 6, 18, 19]. The scenarios were:

- IP cull scenario: Culling of reported premises and a state-level shipment ban
- IP & DC cull scenario: Culling of both reported premises and dangerous contact premises and a state-level shipment ban
- IP cull & DC vaccination scenario: Culling of reported premises and the vaccination of dangerous contact premises and a state-level shipment ban
- IP cull & 3km ring vaccination scenario: Culling of reported premises and vaccination in a 3km ring around the IP and a state-level shipment ban

- IP cull & 10km ring vaccination scenario: Culling of reported premises and vaccination in a 10km ring around the IP and a state-level shipment ban

Additionally, we had a scenario without control implemented, hereafter referred to as the "base" scenario. We also ran a "no shipments" scenario, with no control and with shipments inactivated, such that the only transmission was from local spread.

2.3. Premises locations and sizes

The precise locations and holdings of livestock premises in the U.S. are not publicly accessible. We therefore used outputs from the Farm Location and Animal Production Simulator (FLAPS) [14], which generates locations for premises based on environmental factors associated with the likelihood of livestock premises location, and numbers of premises per county, as well as livestock populations on each of the premises [20]. We adjusted the FLAPS outputs to generate maximum and minimum population estimates, accounting for calves and the seasonal changes in the U.S. cattle population (details in Section S1.1).

In order to capture the variation inherent in the generated premises locations and population assignments, we used multiple FLAPS realisations of cattle demographics. Preliminary analyses indicated that ten realisations of simulated output sufficiently captured the observed range of variability. For each demographic file and scenario, we seeded infection in each county in the contiguous U.S. at a random premises within the county 10 times for each of the 10 FLAPS realisations, resulting in 100 simulations per seed county or 304,900 total simulations per population estimate (max or min) and scenario.

2.4. Local disease transmission

The probability of transmission from infectious premises i to susceptible premises j is:

$$1 - \exp\left(-a_c h_i b_c h_j D(d_{ij})\right) \tag{1}$$

where h_i and h_j are the herd sizes for the infectious and susceptible premises, respectively, and a_c and b_c are cattle-specific transmissibility and susceptibility parameters, respectively (Table 1). Although animal type-specific parameters can be inputted, in this case we used the same values for all cattle (dairy and beef) based on data availability. D is the distance-dependent component where d is distance between i and j.

The distance-dependent component, $D(d_{i,j})$, is defined as a spatial kernel:

$$D(d_{i,j}) = \frac{k_1}{1 + \left(\frac{d}{k_2}\right)^{k_3}} \tag{2}$$

where d is the shortest linear distance between i and j, k_2 is the scale parameter, and k_3 is the shape parameter. The parameter k_1 is the normalising constant that scales the function so that the following holds true:

$$\int_0^\infty 2\pi r D(r) dr = 1 \tag{3}$$

where r is equivalent to d, the distance between premises, in the spatial kernel equation. The power-law kernel function (Equation 2) we used to capture local transmission dynamics was used previously in the metapopulation version of this USDOS model [13] and has been fit to several FMD outbreak data sets [3, 21]. The transmission rate is high and fairly constant over short distances, and then decays into a longer-distance tail; this shape is consistent with distance-decay of local, density-dependent transmission [3, 13]. Normalising the kernel function distributes the impact of the transmission rate by summing the kernel volume to one (Equation 3).

The transmissibility and kernel function parameters were fit to FMD outbreak data and to published kernel functions using maximum likelihood estimation; the default parameters were estimated by fitting to the UK 2001 FMD outbreak in units of metres (Table 1). The default kernel parameters were validated by running simulations with the Warwick model, an established FMD model that was developed for the UK [3, 18]. With those parameters and 2001 conditions, the Warwick model produced outbreaks with a mean of 1600 IPs (range: 1000-2800) which is approximately 80% (range: 50%-150%) of the total number of IPs observed in the 2001 outbreak.

Table 1: Transmission Parameters

Parameter	**Default Value**	**Range**	**Reference**
Cattle transmission rate (a_c)	10.252	3.6–100	see Section
Cattle susceptibility (b_c)	1	N/A	2.4
Normalising constant (k_1)	$1.46e^{-08}$	$4.07e^{-10}$–$3.91e^{-08}$	
Scale parameter for spatial kernel (k_2)	1686.16	1686.16–5414.72	
Shape parameter for spatial kernel (k_3)	2.267	2.022–3.006	
Latency period	5 days	3–13 days	[13, 22, 23]
Infectiousness period	7 days	5–20 days	[13, 22, 23]

2.5. Disease transmission from animal shipments

Shipment-based disease spread is based on output from the United States Animal Movement Model (USAMM) [12]. Using a validated model is necessary as there is no complete record of cattle shipments available for the U.S. Informed by interstate certificates of veterinary inspection (ICVIs) and current and historic census data, USAMM stochastically simulates production-type specific (beef or dairy) shipments between U.S. counties. Parameters are estimated in a Bayesian Markov chain Monte Carlo (MCMC) framework [12] and describe state-specific distance-dependence and annual number of shipments. Annual probabilities of shipments between counties were divided by 365 to calculate daily probabilities. For each shipment, premises of the appropriate production type and county were chosen randomly as sender and receiver.

In USDOS, shipments for each simulation replicate were predicted based on a random draw from the posterior distribution of USAMM. For computational speed, we only generated shipments originating from exposed or infectious premises and assumed all of these contained exposed or infectious animals, respectively. We assumed that shipments originating from an infectious premises caused the receiver to become infectious on the following

day, bypassing the latency period of the infection. Similarly, receiving exposed shipments meant the receiving premises became infectious at the same time as the sending premises.

2.6. Control action details

2.6.1. Shipments

Shipment bans simulated state-wide restrictions on livestock shipments, which are triggered by the first reported premises in a state. All simulated control scenarios included shipment bans at the state level, meaning once a ban was in effect for a given state, all shipments from premises within that state were reduced to the designated effectiveness level (Table 2).

2.6.2. Culling

We assumed the effectiveness of culls at reducing transmission was 100%. To impose data-based constraints on carcass disposal, we assumed a disposal mechanism at burial sites with the proper facilities and space for handling them. Using the Environmental Protection Agency's (EPA) landfill databases [24] and assumptions about capacity and carcass space requirements (Table 2) we estimated the total burial capacity for each state in the contiguous U.S., ranging from 1.3 to 2.8 billion cattle carcasses nationally. Carcasses could only be disposed of in the same state as the premises. Once that state's landfills were full in a given simulation, no additional animals could be culled in that state.

We also incorporated constraints on carcass transportation into the culling rate, which was estimated (Table 2) based on estimates of truck capacity and loading time. Additional details on calculations for landfill capacity and carcass transportation can be found in the supplement (Section S1.3.1).

2.6.3. Vaccination

We assumed only high-potency outbreak response vaccine with high effectiveness would be used and that only one dose would be given (Table 2). Vaccination rate was based on bovine tuberculosis testing times (Table 2) (see Section S1.3.2 for details). We assumed an estimated 300,000 doses of vaccine would be available 7 days after ordering, then an additional 500,000 doses would be available every 7 days, up to the maximum number of 2.5 million vaccine doses (Table 2) [25].

2.7. Control parameters

Control parameter default values and ranges are detailed in Table 2.

We assumed that reporting always occurred after animals became symptomatic and infectious. Although the disease status of potential dangerous contacts would be unknown at the time of investigation, we assumed there would be different probabilities of identifying actually-exposed versus non-exposed premises as dangerous contacts, implemented as scaling factors for the probability of transmission. This scaled probability, referred to as DC detectability, was evaluated stochastically to determine which premises were identified as dangerous contacts for each reported premises. The values in Table 2 were derived to match observed average numbers of dangerous contacts per reported premises from the 2001 UK FMD outbreak [18, 38].

Table 2: Control Parameters

Parameter	Default Value	Range	Reference
Index case reporting time	15 days	2–31 days	[26]
Non-index reporting time	8 days	5–25 days	UK outbreak data
DC reporting time	2 days	1–5 days	UK outbreak data
Susceptible DC detectability	4	0–6	see text
Exposed DC detectability	5	1.19 –8	
Per carcass space requirements	$1.96m^3$	$1.2 - 2.6m^3$	[27, 28, 29, 30, 31]
Culling rate	240 cattle/prem/day	72-720 cattle/prem/day	see text
Culling effectiveness	100%	N/A	see text
Vaccination rate	6804 cattle/prem/day	600-18000 cattle/prem/day	see text
Vaccine doses per animal	1	N/A	[32, 35]
Time to vaccine protection	11 days	4–14 days	[33, 35, 34, 25]
Vaccine effectiveness	90%	50–95%	[35, 36]
Duration of immunity	183 days	N/A	[35, 37]
Vaccine availability day 1-6	0 doses	N/A	[25]
Vaccine availability day 7-13	300,000 doses	N/A	[25]
Vaccine availability day 14-max doses	500,000 doses/week	N/A	[25]
Max vaccine doses	2.5 million doses	N/A	[25]
Shipment ban effectiveness	90% & 75%	75% –95%	[18]

We used information from non-endemic FMD countries that have had outbreaks to parameterise the range of index case reporting times [26] and the UK 2001 FMD outbreak to parameterise the default index case reporting time and non-index reporting times. The median number of days from when a premises was exposed to when it was reported was 8 days in the UK outbreak and 15 days for the index case. The DC reporting time is also informed by the UK outbreak; however, because DCs were often culled before they were reported, there is less data available on the DC reporting time parameter.

2.8. Sensitivity analyses

Sensitivity analyses were run to quantify the impact of the model inputs on outputs (outbreak metrics), separately for disease transmission and for control-related parameters. To keep computational time manageable, a sample of counties was selected based on premises density, number of in-shipments, number of out-shipments, and premises clustering values (see Section S1.4 for details). For each of these criteria, we ensured that areas across the U.S. were represented. There were 78 counties selected from the stratified random sampling

and eight counties added either (1) to add to the geographic range or (2) from a list of six counties that were used for sensitivity in the county-level model [13]. We include these six counties for comparison and because of their importance in the cattle industry (Figure S1 & Table S1). Both sensitivity analyses used the same subset of counties.

Parameter sets for the sensitivity analyses were determined using Latin Hypercube (LHC) Sampling, selecting 100 values across the ranges of all parameters. The parameters included in the disease transmission sensitivity analysis were: transmission rate (a), kernel parameters (k_2, k_3) and the latency and infectious periods (Table 1). The parameters included in the control sensitivity analysis were: index case reporting time, reporting time, DC reporting time, susceptible DC detectability, exposed DC detectability, culling rate, vaccination rate, time to vaccine protection, vaccine effectiveness, and shipment ban effectiveness (Table 2). Separately from LHC sampling, the lowest, default, and highest carcass space requirement parameter values were used to calculate three possible disposal site capacity data sets. Parameter ranges were chosen based on literature values, credible intervals from our analyses, values from the county-level FMD transmission model [13] for comparability, and standard recommendations for sensitivity analysis when parameter values are unknown.

The transmission sensitivity analysis used only the base scenario, which excluded any effects of control strategies on the results. The control sensitivity analyses used the IP & DC cull scenario and the IP cull & DC vaccination scenario. We selected these to compare a cull-only scenario with a cull-and-vaccinate scenario while maintaining maximum comparability for other variables.

For the transmission parameter sensitivity analysis, each of the 100 parameter sets were used to run 100 simulations (10 replicates of each of the 10 minimum FLAPS files) or 10,000 simulations for each of the 86 selected seed counties, for a total of 860,000 simulations. The control parameter sensitivity analysis required increasing the number of simulations to 30,000 (300 sets of parameters) for each of the 86 seed counties in order to include the three landfill data sets with different capacities. The total number of control parameter sensitivity simulations was 2.58 million per control scenario.

2.9. Output metrics

All results are aggregated to the county level to facilitate interpretation across locations and realisations. All analyses of the simulation outputs were performed using custom code in R version 3.5.0-3.5.3. [39]

Simulation results were quantified using the following outbreak metrics:

- Number of infected premises: the total number (nationally) of infected and reported premises
- Number of cattle infected: the total number (nationally) of cattle on infected and reported premises
- Number of infected counties: the total number of counties infected when infection is seeded in that county, also known as "epidemic extent" [13].
- County risk: the proportion of simulations in which a county is infected, not including the simulations in which infection was seeded in that county.

- Duration: the number of days between the initial seed infection until there are no longer infected premises, or 365 days, whichever happens earlier
- Proportion local transmission: The proportion of non-shipment transmission events at the county-level, relative to all transmission events
- Outbreak take-off (for sensitivity analyses): the probability that >5000 premises will become infected, chosen as a natural breakpoint in the distribution
- Outbreak fade-out (for sensitivity analyses): the probability that >1 and <5000 premises will become infected, and duration will be shorter than 365 days

Each outbreak metric was calculated for both the median and the upper 97.5 percentile for each county over the 304,900 simulations. Because outbreak metrics are bi-modal in that outbreaks either take off or they do not, we used the median to show results for the majority of simulations and the upper 97.5% for outbreaks that do take-off.

For the sensitivity analyses, partial-rank correlation coefficients (PRCC) between the outbreak metrics and the model attributes (both parameters and demographic characteristics) were used to estimate the effect and relative importance of each attribute [40]. Prior to running the PRCC analysis, we checked the relationships between model attributes and outbreak metrics to ensure monotonicity assumptions were met. For disease transmission sensitivity analysis, in addition to the parameters included in the LHC sampling process (Section 2.8), we also the following included demographic attributes: county-level premises density, premises clustering, in-shipment volume, out-shipment volume, and seed premises size. For control sensitivity, we included the same demographic attributes as in the transmission sensitivity analysis and the control parameters described in Section 2.8. The PRCC estimates the effect of individual model attributes on outbreak metrics, but we are also interested in the interactions between attributes [13]. To explore the effect of these interactions, we estimated sensitivities from regression coefficients. We checked the results from regressions without interaction terms to ensure that the regression and the PRCC were giving similar results, since the former includes an assumption of linearity. We then proceeded with the regression analyses that included the interaction terms between model attributes.

In order to determine the drivers of outbreaks that take-off and become large, we used PRCC between outbreak metrics and model attributes on the subset of simulations with large outbreaks. For this analysis, we used the number of infected premises and counties and the outbreak duration as the outbreak metrics and used the same model attributes for the respective sensitivity analyses (disease transmission, culling scenario or vaccination scenario) as we did for the PRCC analyses looking at all outbreaks. Outbreaks were considered large if they were greater than 5,000 premises, reached more than 500 counties and lasted more than 100 days.

3. Results

3.1. Sensitivity analyses

In the PRCC analyses, the attributes that were consistently important across outbreak metrics, in both transmission and control sensitivity analyses, related to the demographics of

where the initial infection was seeded. Of particular importance was the seed premises size (Figures S2-S4). In the disease transmission sensitivity analysis with no mitigation applied, outbreak duration was also driven by infectious and latent periods, predictably. Additionally, transmission rate has a stronger effect on number of premises infected and probability of an outbreak larger than 5,000 premises than for other outbreak metrics (Figure S2). For both the control scenarios for which we performed sensitivity analyses, infrastructure attributes dominated and far fewer parameters impacted the outputs (Figures S3 & S4).

Similarly, in the regression analyses, the attributes with the most impact on model outputs are related to infrastructure and demographics of where initial infection was seeded (Figure 1). With the interactions included, some demographic attributes became more important than they were in the PRCC analysis. In-shipments, premises clustering, premises density, and seed premises size had fairly consistent effects in direction and magnitude on outbreak metrics in the regression analyses (Figures 1 & S5). However, the R^2 values for the regression models are low, so the results from them should be taken with caution (Table S3).

In addition to the infrastructure attributes and model parameters which were important in both PRCC and the regression, some of the interaction terms in the regression had a strong effect on the outbreak metrics. For example, the interaction between in-shipments and premises clustering consistently had one of the largest proportional effect sizes (Figures 1-2, & S5-S7). In both control sensitivity analyses, the few parameters (non-demographic or infrastructure) that impacted the outputs were reporting times for infected premises and detectability of dangerous contacts (Figures 2, S6, & S7). Rates of control application and effectiveness were estimated by both the PRCC and regression to have less impact than these factors under the conditions and ranges we tested.

The results from the PRCC sensitivity analyses on only large outbreaks showed increasing importance of model parameters, while demographic and infrastructure attributes decreased for both disease transmission and control sensitivity (Figures S8-S10). Specifically, for disease transmission sensitivity, latent period duration, transmission rate (a), and kernel shape parameter (k_3) were consistently important for the outbreak metrics. The culling scenario sensitivity was unique because one of the infrastructure attributes, landfills, was by far the most important and this attribute also showed a marked increase from the sensitivity that included all outbreaks. Additionally, reporting time, susceptible DC identification, and cull rate showed an increase in importance. The vaccination sensitivity results also showed reporting time, susceptible DC identification, vaccination rate and delay to effectiveness, and cull rate to be the most important attributes.

3.2. Relationship to county attributes

Given the strong effects of associations with in-shipments and premises clustering, the geographic distributions of these attributes (Figure 3) were consistent with larger numbers of infected premises, counties, and animals, regardless of whether or not mitigation was applied. Where levels of both in-shipments and premises clustering are high, large outbreaks were generated more frequently. Additionally, simulations seeded in counties with many large premises (1000 or more animals) (Figure 3e) were more likely to be seeded in one of these large premises, which strongly affected the probability of large outbreaks where these counties were located, in the western half of the country. Premises density is generally higher, and

with fewer animals on premises, in the eastern half of the country where outbreaks tend to be smaller. However, regions such as central Florida, where both in-shipments and premises density are high tended to have large outbreaks more frequently.

3.3. Shipping vs. local spread

Comparing animal shipments and local transmission across scenarios, local transmission tended to dominate (Figure 4a). As expected, when shipment bans were in effect, the proportion of local transmission increased (Figures 4b, 4c & S11). This was not an absolute increase in local transmission, as is evident when comparing overall outbreak sizes with and without shipments (Figure 5), but only reflects the proportional decrease in shipment-driven transmission, scaling with the effectiveness of the shipment ban. Also as expected, regions with high shipment activity (Figures 3a & 3c) showed the most change in these proportions.

Results from the "no shipment" scenario (no controls, local transmission only) suggest that while shipments increase outbreak sizes (Figures 5 & S12), the lack of shipments is not enough to prevent large outbreaks from occurring (Figure S13b & S13f).

3.4. National scale outbreak sizes

Among the scenarios simulated, not including sensitivity analyses, the vast majority (96%) of the 3.66 million simulations resulted in a total of fewer than ten cattle premises becoming infected. 91% of those simulations (3.24 million) did not spread beyond the single initial index infection (Figure 5).

3.5. Regionally consistent patterns for outbreak metrics

The very largest outbreaks (based on infected premises counts) occurred when the initial infection was located in specific counties, many of which are concentrated in the west, the Great Plains, and central Florida (Figures 6b & S13c-S13f). Even for these counties that more frequently produced large outbreaks, the median simulation result for most was that infection did not spread beyond the single initial index infection (Figures 6a, S13a & S13b).

The regions adjacent to the areas identified above tended to have the next-highest probability of producing large outbreaks (Figures 6 & S13). These regional patterns tended to be fairly consistent across a variety of scenarios, with areas that produced large outbreaks expanding and contracting over the same core regions as conditions varied (Figures 6 & S13). The other outbreak metrics showed similar regional patterns, including number of counties and cattle infected, duration, and county risk (Figures S14, S15, S16, S17).

3.6. Effects of control strategies

Control strategies that targeted uninfected premises (either by DC or proximity), reduced outbreaks across all measured metrics better than IP culling alone (Figures 5 & S12). Strategies targeting dangerous contacts tended to be more efficient than the proximity-based ring strategies at reducing outbreak size metrics (Figures 5 & S12). This pattern was consistent regardless of whether the identified dangerous contacts are culled or vaccinated. However, the outbreak duration metric was similar between DC and ring-based strategies (Figures S12d & S12h).

In scenarios with large outbreaks, over 20 million cattle were targeted for control within a simulation (Figures S12c, S12g). Based on our assumptions about vaccine production,

capped at 2.5 million doses available incrementally over 6 weeks (Table 2), limited resource availability clearly constrained the overall impacts of vaccination scenarios. Although the estimated national total disposal capacity far exceeded this number of animals, the restriction on sending animals to disposal sites only within the same state created regional constraints. These control scenarios showed similar bi-modal behaviour to the base scenarios; some simulations still reached large outbreak sizes, though partially mitigated by control actions. But the majority of the control simulations also tended not to spread beyond ten premises (Figures 5 & S18).

4. Discussion

A previous study from this group that simulated FMD transmission at the county-level [13] identified higher probabilities for large outbreaks in areas that closely coincide with areas of high premises density (Figure 3d). While the county-level model could account for shipments and total premises-per-county density, it could not capture premises clustering without premises locations, so premises were treated as randomly located within each county. Since the original metapopulation study was published, cattle premises locations in the U.S. have been estimated by the FLAPS project [14] enabling the finer scale geographic data used in this study. This higher-resolution premises data is the primary difference between these two studies, and is also the reason for the difference in regions identified as important. The sensitivity analyses showed that infrastructure characteristics consistently had the strongest impacts on simulated outbreaks, and that these attributes, such as clustering and in-shipments identified in the interaction sensitivity analysis, can be used to identify regions of interest.

With shipments factoring significantly in the sensitivity analyses, but playing a small role relative to local transmission (Figure 4), there is a distinct difference between shipments as a transmission mechanism, and as a county-level infrastructure attribute. In terms of mechanism, out-shipments from infected premises did move infectious animals into new areas that then increased outbreak size by local transmission. But as an attribute, the sensitivity analyses indicated that infection starting in counties with many in-shipments was associated with increased outbreak size, and starting in counties with many out-shipments was associated with decreased size, even though out-shipments excluded shipments to slaughter. The strong effect of shipments in the sensitivity analyses are thus not because in-shipment is the explanatory mechanism for spread, but rather indicates infrastructure that promotes the spread of infection.

These patterns of animal shipments driving longer distance transmission events and new disease foci are consistent with the idea of extreme value theory in statistics. In extreme value theory, the extreme tails of a distribution, such as the distance over which transmission occurs, are modelled using different covariates or a different structure than the bulk of the distribution, because the drivers of extreme events are different than those that are normally observed. Here, we take an extreme value perspective by using shipment information to capture extreme transmission events and are able to show that this changes prediction from using only a local spread kernel. Even using local spread kernels that incorporate transmission at longer distances produce different results from using a shorter-distance local spread kernel plus shipments to represent longer distance shipments (unpublished results).

Transmission at long distance is sometimes represented statistically by using an additional fitted term that captures long distance transmission separately [7]. This approach is often successful in capturing many general characteristics of long distance shipments, but can still fail at predicting specific space and time locations of transmission. Using specific information like shipments (or other covariates) that narrow possible space and time locations for extreme events like long-distance transmission generally improve the specificity of predictions as shown in this study.

The vast majority of simulations with this set of parameters and assumptions did not result in large outbreaks. However, other modelling choices we made, not represented in the sensitivity analyses, may affect outbreak frequency and size. The premises used in the simulations only represented cattle operations, not other susceptible livestock or wildlife. While FMD outbreaks only involving cattle have occurred in other countries [2], adding other animal types to the simulations may result in different outbreak frequencies and spatial distributions. By using the same parameters and functional form for non-shipment transmission among dairy and beef cattle, we effectively assumed that distance, herd size, and the parameter values interact in ways that produce the same probability of spread among these cattle types. Control actions may also have different resource availability, effectiveness rates, implementation rates, or other differences from the scenarios we explored. Generating outputs to address most of these changes is simply a matter of specifying the inputs. We suggest the most value lies not in interpreting the outbreak metrics literally, but in comparing relative effects addressed in the sensitivity analyses.

The largest outbreaks tended to be specific to regions concentrated in the western half of the U.S., and the consistent geographic patterns observed at the national level are driven by these regions. Although disease transmission was simulated at the premises-level, these consistent geographic patterns can largely be explained by county-level measures of infrastructure and demographic attributes—many shipments, premises clustering, density, and large premises with over 1,000 head. The sensitivity analyses also indicated the relative importance of these attributes over most parameter values. Premises and county scales in this context are not completely independent; the simulation of shipments to and from premises, as well as the estimated premises locations, are based in part on county-level observations. However, knowing which premises contain over 1,000 head and measuring premises clustering does requires premises-level information.

Comparing the sensitivity between all simulations and just those that take off suggests that a combination of county-level and premises-level attributes were influential in an outbreak taking off. Once take-off occurs, the model parameters further influence outbreak size. Consequently, the accuracy of parameter values may be of less importance for identifying areas that may lead to large outbreaks and there may be more information value in ensuring that county attributes describing shipments and demography are accurately measured.

Control strategy results should not be interpreted as policy recommendations, but tools to identify areas for additional exploration and data collection, and to understand under what conditions resources may become constrained. Under these assumptions and parameters, targeting control actions to only reported premises (IP culling scenario) has less effect than control scenarios that also target uninfected or unreported premises (DC and ring scenarios). This pattern of combining control actions to more effectively reduce outbreak metrics has also been seen in other studies looking at potential FMD outbreaks in other areas [18, 19, 41, 42].

Scenarios that tended to be effective at reducing outbreak size were not necessarily as effective at reducing duration. Specifically, the IP cull & 10km ring vaccination scenario performed as well as, or better than, the DC scenarios at reducing duration. This outcome, in which the strategy that most reduces size may not reduce duration as efficiently, has been seen in previous studies that looked at IP & DC culling and IP culling & ring vaccination in other locations [41, 42].

In large outbreak situations, control strategies did become resource-constrained, illustrating the impact of spatial scales of resource availability. Had the estimated disposal capacities been aggregated as a pooled national scale resource, capacity would have been sufficient for large outbreaks. However, restricting animal disposal to within the same state produced a very different outcome. Because certain regions were impacted much more heavily in large outbreaks, they quickly reached their disposal capacity, at which point culling was no longer possible. Capturing the appropriate spatial scale of control resource availability is therefore critical when anticipating different regional outcomes.

Control scenarios exhibited the same bi-modal behaviours as the base scenario, in which most seeded infections died out before spreading beyond the initially infected premises. This aspect of disease spread was unaffected by reporting and control, because based on the reporting and latency parameters, reporting occurred several days after the premises became infectious. On the other hand, when infection did spread to multiple premises in large outbreaks, the lag in reporting time meant that control targets generally trailed behind disease spread. The limited control resources that were then applied were too little and too late to consistently prevent large outbreaks. Reporting time is therefore another parameter that impacts the outcomes of control actions. Exploring options for reducing this reporting lag could improve the overall effectiveness of any control actions used.

Targeting dangerous contacts rather than non-specifically vaccinating or culling all premises within a given radius takes advantage of any knowledge about which premises may be at higher risk than others, prioritising those premises for limited resources. Of course, the actual benefits of targeting dangerous contacts depends on how accurately they can be identified. Dangerous contacts in previous outbreaks have sometimes been found to be already infected when identified [3, 43], potentially wasting resources for preventing infection. The trade-offs in focusing on identifying dangerous contacts would be better explored using models that more explicitly focus on the mechanisms of identifying dangerous contacts, and the associated costs of control alternatives.

4.1. Conclusions

Ultimately, the predictions that any model produces are highly dependent on the quality of information available for its inputs. While using as much data as possible is the ideal, in reality data availability and collection can be a significant challenge, especially when scaling finer spatial patterns up to larger scales, or when simulating events for which there is no historical record. Additionally, control resource availability and plans can change, which are also inputs to the model. This variability across multiple inputs is where sensitivity analyses provide valuable information in identifying which inputs have the strongest effect on outputs. Our findings suggest that premises-level information is important in the form of premises clustering and size. For county-level information, shipment activity and premises density is most informative. Prioritising limited resources around data quality of these attributes,

and the management of those attributes, if applicable, could provide more value for less effort than prioritising all inputs and parameters equally. Together these results point to the importance of understanding the spatial scales of disease transmission and control, and how these interact with the demographic characteristics of a population. This finding can be used to inform modelling studies in other countries that have not had recent outbreaks, and potentially in other disease systems that occur in spatially heterogeneous populations.

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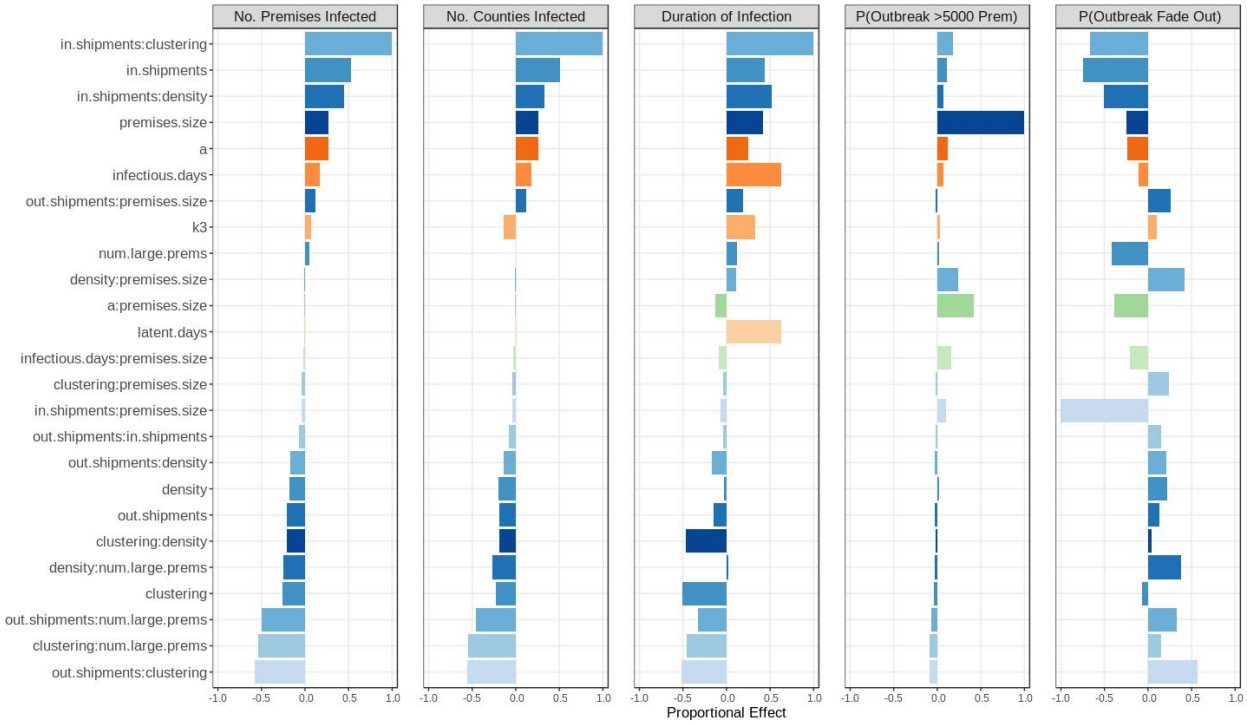
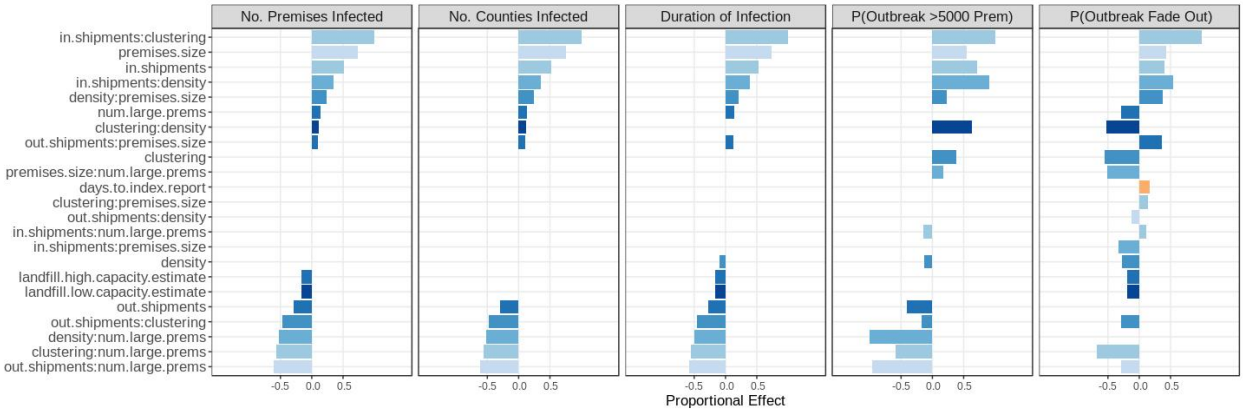


Figure 1: Disease transmission sensitivity analysis of selected parameters and attributes of premises and counties of initial infections with minimum population size estimates (see Figure S5 for results for all parameters and attributes used in sensitivity analysis). The proportional effect (x-axis) were estimated as linear model coefficients for number of infected premises, number of infected counties, and duration and as binomial general linear model coefficients for the probability of outbreak fade-out and take-off. Infrastructure-related attributes are shown in shades of blue, model parameters in shades of orange, and interactions between infrastructure-related attributes and model parameters in shades of green.

(a) IP & DC cull scenario



(b) IP cull & DC vaccination scenario

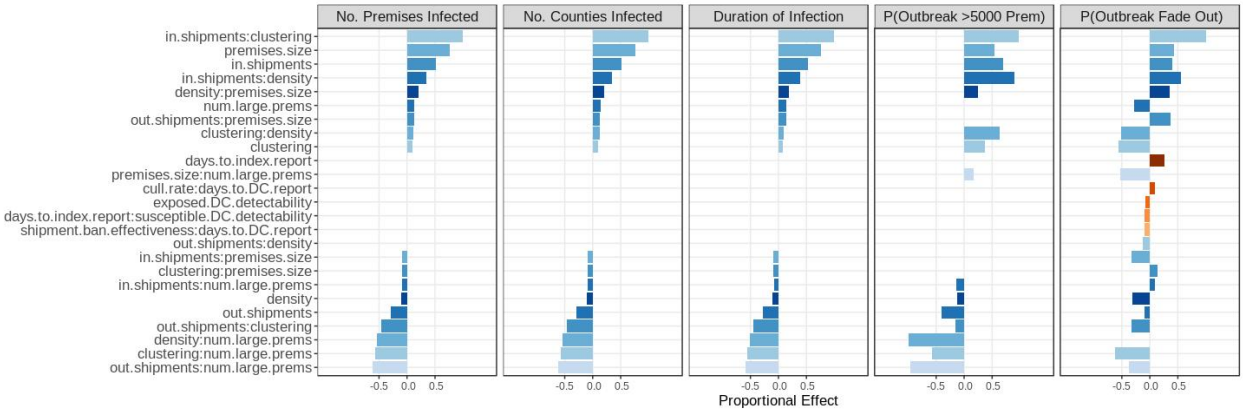
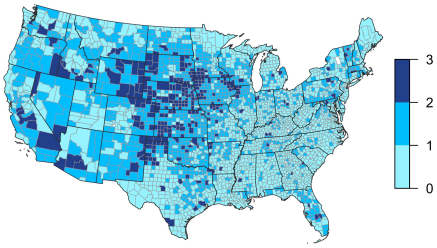
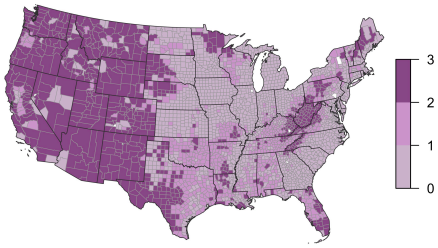


Figure 2: Control sensitivity analysis for (a) IP & DC cull scenario and (b) IP cull & DC vaccination scenario of selected parameters and attributes of premises and counties of initial infections with minimum population size estimates (see Figures S6 & S7 for results for all parameters and attributes used in sensitivity analysis). The proportional effect (x-axis) were estimated as linear model coefficients for number of infected premises, number of infected counties, and duration and as binomial general linear model coefficients for the probability of outbreak fade-out and take-off. Infrastructure-related attributes are shown in shades of blue, and model parameters in shades of orange.

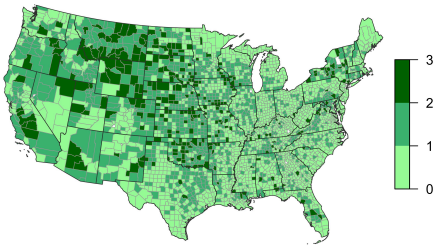
(a) Total annual in-shipments



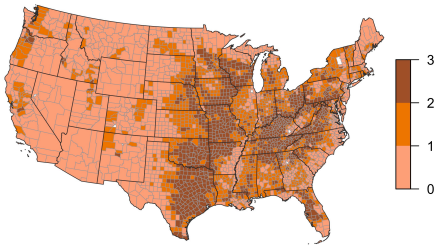
(b) Premises clustering



(c) Total annual out-shipments



(d) Premises density



(e) Count of premises >1000 cattle

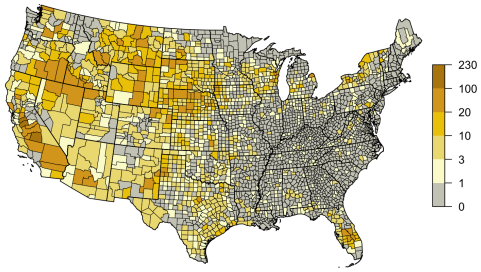
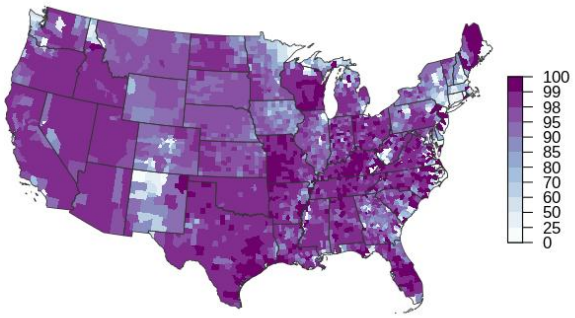
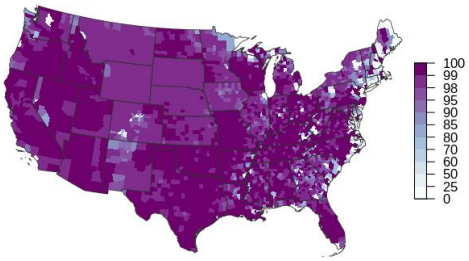


Figure 3: Relative county measures of (a) total annual in-shipments received, (b) degree of premises clustering, (c) total annual out-shipments sent, and (d) degree of premises density, and (e) the count of premises with >1000 animals. Counties are shaded from light to dark representing, low to high bin levels (a-d) or numbers (e) of the attribute. (a-d) Show county attributes and bins used in county selection for the sensitivity analyses.

(a) Base scenario



(b) IP cull scenario



(c) IP cull & 10km vaccination scenario

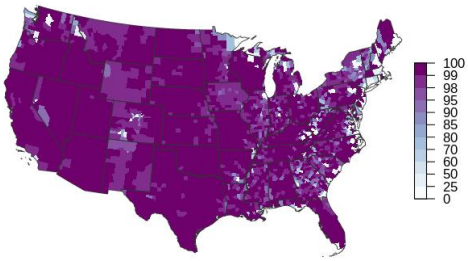


Figure 4: Counties coloured by proportion of transmission due to non-shipment mechanisms for (a) base scenario (b) IP cull scenario with a 75% effective shipment ban, and (c) IP cull and 10km ring vaccination scenario with a 90% effective shipment ban (all with maximum population size)

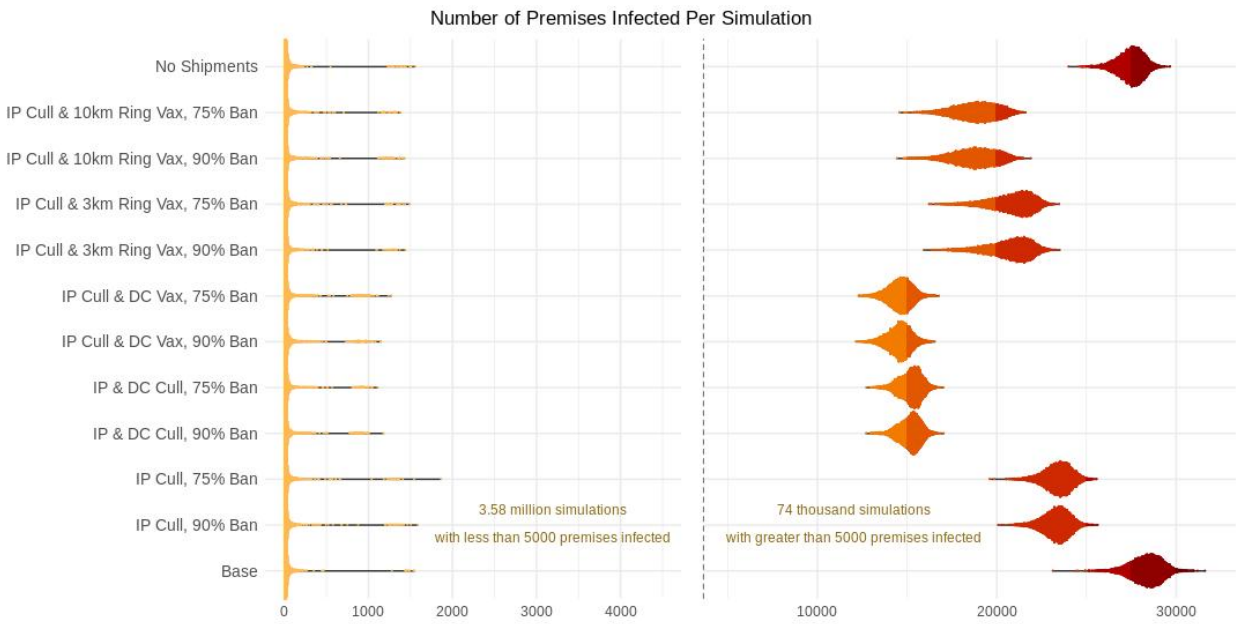
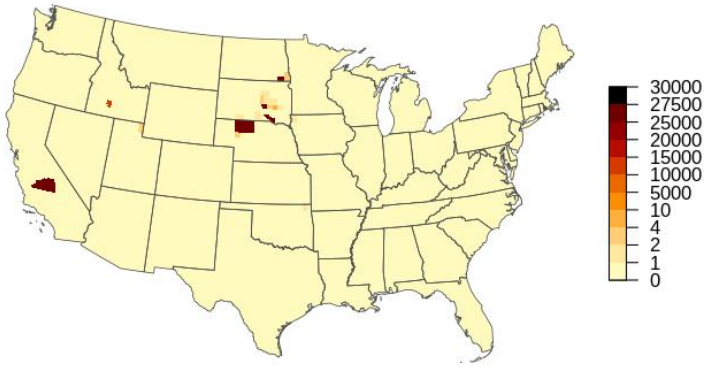


Figure 5: Frequencies of total infected premises per simulation for maximum population size, grouped by scenario conditions. Because the bulk of the frequencies are at 1, the high end of the x-axis is scaled up for visibility. Colours correspond with those in Figure 6 for the base scenario to show associated geographic distributions.

(a) Median total infected premises



(b) Upper 97.5% total infected premises

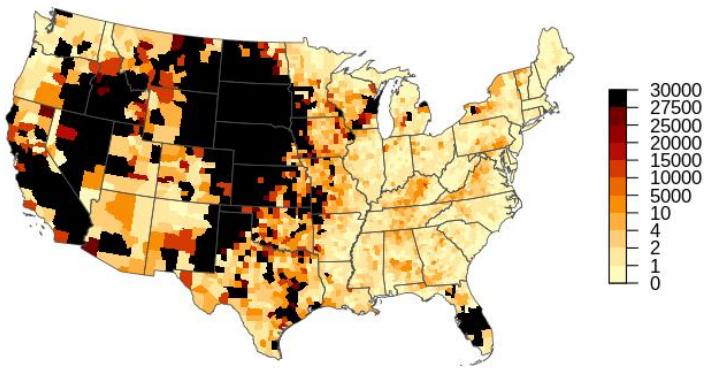


Figure 6: (a) The median and (b) upper 97.5% percentile total infected premises under base scenario with maximum population size. Counties are coloured by the outcomes when infection is seeded in that county.