THESIS

THE IMPACT OF CONTROL ON NATIONAL-SCALE LIVESTOCK DISEASE OUTBREAKS IN THE UNITED STATES

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ABSTRACT

THE IMPACT OF CONTROL ON NATIONAL-SCALE LIVESTOCK DISEASE OUTBREAKS IN THE UNITED STATES

Outbreaks of livestock diseases, like foot-and-mouth disease (FMD) and bovine tuberculosis (bTB), pose a significant economic threat to the United States livestock industry. Significant interest then lies in developing strategies to mitigate the impact of an outbreak should they occur. This thesis explores the effect of control interventions on outbreaks of FMD and bTB in the U.S. In chapter one, I weigh trade-offs associated with delaying the implementation of control on the economic impact of controlling an FMD outbreak in the U.S. This study aimed to understand whether control policies that adopt a conservative initial approach, but may be updated as an outbreak progresses, can reduce socioeconomic harm while achieving desired outbreak outcomes. I find that delaying the implementation of all available control interventions early on in an outbreak does not reduce the cost of small outbreaks and exacerbates the largest outbreaks, suggesting that the potential benefits of this type of adaptive response may be out weighted by the risk of allowing a large outbreak to become worse. Next, I investigate how the culling of infected cattle premises, diagnostic testing, and traceback investigations impact the size of bTB outbreaks. Results from this study show improvements to traceback investigations result in the largest decreases in bTB outbreak size, which suggests that improving the identification of premises via traceback investigations is more important than increasing antemortem diagnostic sensitivity. Although this thesis focuses on the control of livestock disease, we can abstract several broader principles that contribute to ecology and epidemiology's understanding of disease dynamics. Both chapters demonstrate the importance of a population's underlying demography to determining an outbreak's overall trajectory as well as minimizing the time until detection of an infection and the time until control is implemented.

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DEDICATION

I would like to dedicate this thesis to my parents and brother whose curiosity and love for the natural world inspired me to pursue a career in the sciences.

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Chapter 1

Introduction

There are many animal diseases that pose a persistent threat to the United States' (U.S.) livestock population. Some of these diseases, such as foot-and-mouth disease (FMD), are not currently endemic in the U.S., while others, like bovine tuberculosis (bTB), persist at low levels nationwide. FMD is a highly transmissible viral infection that could devastate U.S. livestock production if introduced. FMD transmission typically occurs between nearby premises due to shared equipment, personnel, fence line contact, and aerosols [1, 2]. bTB, however, is a bacterial infection where transmission is primarily driven by shipments of infected animals to susceptible premises and has a lower transmission rate [3–5]. Given this, bTB spreads much slower than FMD. Despite the fact bTB outbreaks are much smaller due to slower transmission dynamics, the management of bTB in the U.S. is quite costly as bTB affected cattle herds must be depopulated and surveillance is expensive [6, 7]. Given the economic consequences of both pathogens, there is a strong interest in developing strategies to control the spread should an outbreak occur. Ultimately, controlling the spread of any pathogen requires blocking the transmission of an infection to susceptible individuals.

In livestock systems, the control of infectious disease can be achieved through depopulating premises that are infected or at-risk of infection, vaccinating animals at risk of infection, and restricting shipments from affected regions. These tools are not always available at the onset of an outbreak or for all pathogens, and political landscapes may discourage the use of some of these tools. For example, the national stockpile of emergency response FMD vaccines in the U.S. is far smaller than what would be required to vaccinate the entire at-risk susceptible livestock population [8] and the U.S. does not currently vaccinate either wildlife or cattle against bTB [6]. Additional uncertainty surrounding whether the World Organisation for Animal Health (WOAH) would allow vaccines to be used to obtain a FMD-free status after an outbreak means that the U.S. would prefer to control an FMD outbreak without the use of a vaccine [8, 9]. These challenges

present managers with difficult decisions surrounding when and where to allocate control-related resources.

Mathematical models were used to inform these type decisions during the 2001 FMD outbreak in the United Kingdom (U.K.) [10]. Models can be used to compare the performance of different control scenarios across many different outbreaks to evaluate how they affect disease spread [11–13]. They can also be used to identify where improvements should be made to control measures, such as surveillance strategies and diagnostic testing [14, 15]. Therefore, they are a powerful tool that can be used to develop strategies to identify and respond out an outbreak to prior to one occurring.

Model-based investigations of infectious disease control strategies have highlighted how delays in control processes negatively impact outbreak outcomes [16–21]. An analysis of the 2010 Japan FMD outbreak attributed the inability of managers to stamp out the disease early-on to the one-month long lag between FMD being introduced and detected [21]. For FMD outbreaks in the U.K., [19] shows that prophylactic vaccination is more effective at reducing the size of FMD outbreaks than reactive vaccination, largely due to the delay between vaccination and immunity. In the case of bTB, longer times to detection were associated with longer outbreaks [15]. Finally, more recently, several studies found that test frequency and turnaround time were more important to containing COVID-19 outbreaks than test sensitivity [16, 18]. Therefore, a key aim of infectious disease controls strategies should be to reduce any delays, whether that be between infection and detection or detection and control.

In the time since the 2001 U.K. FMD outbreak, livestock have been recognized as a strong system for understanding disease dynamics in humans for several reasons. Firstly, although data can be sparse, they are more readily available and less sensitive than data about humans. Additionally, data are easier to collect for domestic livestock than for wildlife because their movements are controlled by humans. Finally, the demographic structure of livestock more closely resembles human population structure than wildlife as they live in close proximity to each other and are transported long distances. For all of these reasons, understanding the transmission dynamics and the effects

of control on disease spread in livestock systems can also advance how we understand the ecology of infectious diseases in humans.

I use a stochastic national-scale model of livestock disease transmission to understand how decision-making delays and bottlenecks in detection processes affect our ability to control infectious disease outbreaks. In two chapters, I simulate the spread of FMD and bTB across the U.S. with and without control. First, I consider how trade-offs associated with a widely adopted strategy for implementing control measures affects FMD outbreaks. I then identify aspects of U.S. bTB eradication campaign that could be improved to achieve smaller outbreaks. Finally, I conclude by drawing connections between the two studies and commenting on how these studies of diseases with very different transmission dynamics contributes to a broader understanding of controlling infectious disease outbreaks.

Chapter 2

Supporting Emergency Disease Management with State-Dependent Control

2.1 Introduction

Controlling infectious disease outbreaks can be achieved by eliminating contact between infectious and susceptible individuals through isolation, reducing the size of the susceptible pool via vaccination or depopulation (in animal systems), or a combination of either option. These control strategies are often limited by logistic and resource constraints that force decisions to be made regarding where resources should be targeted [12, 22–25]. It can be difficult to know where to direct resources at the onset of an outbreak due to little, if any, prior knowledge or experience. Given these uncertainties, it may be beneficial to implement control strategies that can be updated conditionally, depending upon the current state of an outbreak.

So-called state-dependent control strategies have been adopted into pandemic response guidelines for both human and animal pathogens by both nations, such as the United States (U.S.) and United Kindgom (U.K.), as well as international governing bodies, like the World Health Organization (WHO) [9, 26–29]. For example, in the United States (U.S.), if there were an outbreak of the highly transmissible livestock infection, foot and mouth disease (FMD), a state-level livestock shipment ban and the depopulation of infected premises would occur immediately. Then, a vaccination campaign would begin as soon as vaccines become available if the outbreak continued to spread [9]. Similarly, despite not explicitly stating a state-dependent control strategy, the WHO's Pandemic Influenza management plan suggests that countries adopt flexible control strategies that can be targeted and scaled dependent on need [26]. However, many of these state-dependent control policies remain untested during real outbreaks because they were developed as improvements after more fixed control strategies failed to deliver a sufficient response [30–32]. It

is then necessary to understand whether state-dependent control strategies can achieve desired outcomes, especially as the frequency and severity of infectious disease outbreaks increases in both humans and animals [33, 34].

Policy makers and managers may favor state-dependent control strategies over more fixed strategies because they could prevent overreaction and allow for control policies to be improved during the outbreak, thus reducing total socioeconomic harm. By promising to update the control strategy as the outbreak progresses, a state-dependent control strategy can allow for a more conservative initial approach, such that fewer resources are used unnecessarily [35]. Such a response also provides managers more time to gather information regarding the outbreak's trajectory and facilitate a more optimal distribution of resources [35]. Potentially unforeseeable logistical constraints may also change what the optimal distribution of control resources will be, so assuming a more conservative initial approach may allow managers to adjust the control strategy by identifying where the constraints arise once an outbreak has begun [20]. Therefore, state-dependent control not only has the potential save money and resources, but also improve our ability to manage an infectious disease outbreak.

State-dependent control strategies may pose several risks to controlling an outbreak, despite their potential benefits. A recent body of work strongly suggests that minimizing delays during any step of the intervention process, whether that be diagnostic testing, isolating, or contact tracing greatly reduces the number of infected individuals [16, 18, 36, 37]. Incorporating more decision-making opportunities into a control strategy then could exacerbate response delays that are already present and have been shown to allow epidemics to get worse [17]. Further, the benefits of delaying control implementation may not outweigh the risk of allowing an outbreak beyond containment as optimal control strategies can consistently be identified very early on in an outbreak, even if projections of outbreak size are highly uncertain [38, 39].

Although the benefits of state-dependent control strategies have been strongly considered, we still lack a clear understanding of whether these benefits outweigh the potential costs of implementation. FMD outbreaks provide a valuable setting to understand these trade-offs for several

reasons. First, three different control measures are commonly available to managers during an outbreak (movement bans, culling, and vaccination), so decisions must be made surrounding when to use each control measure and what premises should be targeted with them. Second, as outlined earlier, the U.S. officially plans on responding to a FMD outbreak with a state-dependent control strategy [9]. Therefore, we can use the U.S.'s FMD outbreak response strategy as a realistic starting place to evaluate how state-dependent control strategies fare compared to their fixed counterparts.

Here, we consider trade-offs associated with state-dependent control strategies using a validated and highly realistic national-scale model of FMD transmission. Models, like the one used in this paper, are essential to developing control strategies for infectious disease outbreaks because it is impossible to empirically evaluate which control strategies perform best during ongoing outbreaks. They can be used to compare the performance of possible control strategies across many different outbreak scenarios, where otherwise unfeasible or unethical, to decide upon the most effective control strategy [12, 13, 40, 41]. Understanding how state-dependent control intervention strategies impact infectious disease outbreaks is a key axis to improving pandemic planning and response efforts.

2.2 Methods

2.2.1 Overview

We further developed an existing FMD simulation model, the United States Disease Outbreak Simulation (USDOS) [42, 43], to allow control strategies to be state-dependent. We identified several possible control strategies from the literature and conducted cattle-only FMD simulations while applying state-dependent and static versions of these intervention strategies. Finally, we used a global sensitivity analysis to understand how strongly state-dependent control parameters influence FMD outbreak outcomes. The sensitivity analysis also informed whether we needed to explore other possible control strategies.

2.2.2 USDOS Version 2.2.1

The United States Disease Outbreak Simulation (USDOS) is a national scale stochastic simulation model of local and long distance livestock disease spread. Local transmission is determined using a spatial kernel that represents the many modes of transmission between premises, such as fence line contact between animals on two different premises, wind moving aerosols between premises, and the movement of fomites between premises (A.1) [42–44]. Long distance transmission occurs via livestock shipments between premises that are modeled by the United States Animal Movement Model (USAMM) (A.2) [45, 46].

Premises in USDOS may be general beef or dairy farm, feedlots, or markets. Because the exact location and size of premises in the U.S. are not publicly available, USDOS uses 10 unique projections from the Farm Location and Animal Production Simulator (FLAPS) of the number and size of premises in each county. Several realizations of projected premises size and locations were used to capture uncertainty regarding their exact location. Projected premises data are informed by 2012 National Agriculture Statistics Service survey as well as cattle inventory surveys from July 2017 and January 2018 [42, 43, 47, 48] (A.3). All premises are given a disease status at the beginning of each outbreak that is tracked throughout the simulation. We assigned a susceptible status to all premises except for where we seeded an FMD infection to reflect the U.S. livestock population's complete susceptibility to FMD. If transmission occurs between two premises, the susceptible premises is labelled as exposed to reflect pathogen incubation times before being called infectious. After an infection period, or being controlled, the premises is labeled as immune, and is no longer able to be re-infected.

Every premises also has a file and control status that are tracked throughout each simulation. The file status is based upon what is known about a premises' disease status. Premises begin as "not reported" and transition to either "reported" (IP) if they are infected or to "dangerous contact" (DC) if the premises is at-risk of infection due to an epidemiological link to an infectious premises. Both IP and DC premises can be controlled depending upon the strategy being used. Premises may also be controlled in a ring around an IP. Once a premises is identified to be controlled it enters a

waitlist of all premises that have been previously identified for control. Once the entire premises has been controlled it is assigned an "effective" status. All premises are assigned an "implemented" status prior to progressing to an "effective" status, but premises that are culled transition between implemented and effective immediately. There is a lag between vaccinated premises moving from implemented to effective to reflect the time required for vaccination to affect immunity.

2.2.3 Control in USDOSv2.2.1

Control measures in USDOS consist of shipment bans, culling, and vaccination. In USDOSv2.1 the implementation of these control measures was triggered immediately upon the first premises report and left in place for the duration of the outbreak simulation. We updated USDOSv2.1 to include control interventions that could be dynamically applied and removed as the simulation progressed in order to implement state-dependent control policies. In USDOSv2.2.1, vaccination and culling can be turned on by a percent increase in number of newly reported premises between two time steps. Culling and vaccination can also be turned on and off based upon landfill space and vaccine resources. Both control actions can also be stopped depending on the number of days the outbreak has become smaller (Table 2.1). Movement bans are included in our state-dependent control strategies, but they cannot be implemented in response to changes in the outbreak, which means that movement bans remain in place from the time of the first report to the end of the simulation for all strategies.

Turning on control can be further delayed by a decision-making time parameter. This parameter dictates the number of timesteps a percent increase in the number of new premises reports must be observed before control is turned on. Once control is turned on, specific premises must trigger culling or vaccination based upon their infection status, risk of infection, or proximity to an IP. Given this, culling and vaccination can be turned on, but no culling or vaccination of premises will occur until premises become reported. Premises may trigger control by becoming reported if a control strategy targets DCs or premises within a given radius of an IP, in addition to the IP (Table 2.1).

After triggering a control action, premises enter a waitlist prior to being controlled. The order of this waitlist is determined by a prioritization parameter, such that premises may be controlled in the order that they entered the waitlist, their size, or their proximity to the infection (only if that premises is a DC or ring culling/vaccination is on). If control is stopped due to a lack of resources or declining number of reports, premises on the waitlist will remain on the waitlist until they are controlled. The ability to prioritize the control of premises based on their size and proximity is new to USDOSv2.2.1. All state-dependent control policies in USDOS must include switch, threshold, control action, target, prioritization, and decision-making time parameters, all of which are summarized in Table 2.1 with default parameter values and ranges.

We note that previous versions of USDOS included several control-related parameters not addressed here. There are no updates to these parameters in USDOSv2.2.1, but some are included in the sensitivity analysis described below and all are used during simulations. USDOSv2.1 had the ability to control the lag between an infection or DC being identified and that premises being reported with reporting time parameters (Table 2.2). Additionally, USDOS includes resource constraint and control efficacy parameters. All simulations assume shipment bans are 75% effective, culling is 100% effective, and vaccines are 90% effective at blocking transmission. Please see A.5, [43], and [42] for more specifics about control efficacy and resource constraints in USDOSv2.2.1.

2.2.4 Simulated scenarios

We simulated the spread of FMD across the United States while applying five different control policies. We simulated outbreaks with each control strategy twice, one time as state-dependent and again as static. Every control strategy had five components: the metric that should trigger a control, the threshold at which a new control will be triggered, the control that should be applied, the premises that this new control will target, and the priority in which these premises will be controlled (Table 2.1). The five strategies were:

- IP cull, DC vaccination, state-level shipment ban

- IP cull, DC cull, state-level shipment ban
- IP cull, three kilometer ring vaccination, state-level shipment ban
- IP cull, 10 kilometer ring vaccination, state-level shipment ban
- IP cull, three kilometer cull, 10 kilometer ring vaccination, state-level shipment ban

Each control strategy was simulated 304,900 times because every county in the contiguous United States received 100 randomly seeded premises-level exposures. Every simulation ran until there were zero exposed or infected premises or until 365 days passed [43].

After simulating these outbreak scenarios, we conducted three additional outbreak simulations while implementing an IP cull, DC vaccination, and state-level shipment ban control strategy. We chose this strategy because it is the official USDA FMD response strategy [9] and was one of the two best performing control strategies. For these simulations we varied the decision-making time parameter (Table 2.1) from 0 – 3 days to understand how decision-making time impacts outbreak outcomes.

2.2.5 Outbreak metrics

We considered how state-dependent and static control strategies impacted FMD outbreak outcomes using the following commonly used metrics [42, 43]:

1. Number of infected premises
2. Outbreak duration
3. Number of affected counties

These outbreak metrics are highly bimodal, so we calculated all metrics for the median and top 2.5% of the outbreaks. We aggregated simulation results to the county level to evaluate the number of infected premises, outbreak duration, and the number of infected counties. We also consider the proportion of FMD spread attributed to local vs. shipment-based transmission. This metric should

indicate whether state-dependent control policies alter national-scale patterns of disease spread, and is calculated by dividing the number of new infections due to local transmission by the total number of transmission events during a simulation.

Next, we estimated the cost of each outbreak to evaluate whether delaying the implementation of control measures offered any economic benefit. We modified a previously developed cost function to estimate the cost of each outbreak under three different control scenarios [35, 49]:

$$Cost_{ij} = 255.5 \times C_{ij} + 6 \times V_{ij} + 2160000 \times D_{ij} \tag{2.1}$$

$$Cost_{ij} = 255.5 \times I_{ij} + 6 \times V_{ij} + 2160000 \times D_{ij} \tag{2.2}$$

$$Cost_{ij} = 255.5 \times I_{ij} + 255.5 \times V_{ij} + 6 \times V_{ij} + 2160000 \times D_{ij} \tag{2.3}$$

Equation 2.1 represents the cost of an outbreak for which culling only occurs during an outbreak, such that previously infected but recovered animals are not culled. Equation 2.2 is the cost of an outbreak where all infected animals are culled. Equation 2.3 calculates the cost of an outbreak where all infected and vaccinated animals are culled. All cost calculations are strongly driven by the duration of the outbreaks because of the high cost of trade restrictions [50, 51]. Cost is in U.S. dollars (USD), and is estimated for the i^{th} replicated outbreak for the j^{th} FLAPS file. C is the number of cattle culled, V is the number of cattle vaccinated, D is the duration (in days), and I is the number of infected animals for the i^{th} outbreak of the j^{th} FLAPS file (farm location and size realization). We modified the equation to estimate cost in USD instead of Pound Sterling and added a duration coefficient to account for lost agricultural sales both nationally and internationally as a function of the outbreak's duration [50]. Cost of culling includes the cost of the act of culling as well as indemnification [50]. We only estimated cost for outbreaks that ended prior to 365 days because our simulations end, regardless of outbreak size, when an outbreak reaches 365 days to manage computation time. Therefore, by excluding these outbreaks, we avoid underesti-

mating their cost as they were ongoing outbreaks. We note that these equations do not account for the number of days after the outbreak is over before trade restrictions are lifted, which means the costs presented should not be taken for exact outbreak cost estimates and are instead meant to be relative metrics by which we can compare state-dependent and static control strategies.

To understand what could be driving cost differences between state-dependent and static controls strategies we evaluated the probability that a control sequence completes and the probability that that an outbreak fades out for each control strategy. We define outbreak fade-out to be when an outbreak that spreads beyond the index infection subsides prior to reaching 5000 infected premises and 365 days. We used a generalized linear model with a binomial distribution and logit link to predict both probabilities. In both models, we regressed dummy variables indicating whether or not the control sequence had completed by the number of days required for decision-making and duration of the outbreak. We allowed both predicting covariates to interact, which allowed us to also assess how decision-making time impacted both probabilities.

2.2.6 Sensitivity analysis

We conducted a global sensitivity analysis to determine the impact of state-dependent control parameters on outbreak outcomes. We also used the results from these analyses to explore alternative state-dependent control policies as they indicate how the specific parameter values influence an outbreak. We used Latin Hypercube Sampling (LHC) to generate 123 state-dependent control parameter sets. Each parameter set included a shipment ban, culling, and vaccination as control measures as well as their associated parameters (Table 2.1). Our sampling protocol also included reporting times for index, non-index, and DC cases to determine how strongly interactions between reporting time and decision-making time influence outbreak outcomes. We did not include any disease or resource related parameters in our sensitivity analysis as their impact on outbreak metrics has been previously evaluated [42,43]. Values and ranges of parameters used in LHC sampling are listed in Tables 2.1 & 2.2.

Thresholds for the three different control switches (percent increase in number of reports between two time steps for three days, landfill capacity or vaccine availability, and number of days with decreasing number of reports, Table 2.1) cannot be compared to each other. To address this, we conducted a preliminary sensitivity analysis where we systematically held control switch and control action type constant across all parameter sets and varied the remaining control parameters using the LHC sampling protocol described. This preliminary analysis revealed that outbreak metrics were very weakly influenced by control switch type. Given those preliminary results, we only considered the percent increase switch from thereafter to reduce the dimensionality of our sensitivity analysis and facilitate interpretation.

We generated more than 100 parameter sets to gain enough replicates to get robust sensitivity estimates for all state-dependent control parameters. We used a subset of 78 counties that were selected using stratified random sampling of county characteristics to seed initial infections and maintain reasonable computation time. See [43] for a complete explanation about how these counties were selected. County characteristics that we considered include premises density, number of in- and out-shipments, and premises clustering values. We added eight additional counties to this sample to expand geographic reach and include counties known to be important to the cattle industry [42–44]. We seeded infections in each of the 86 counties 100 times for each of the 123 parameter sets, for a total of 123,000 simulations.

We used linear regression to quantify the effect of each parameter set on outbreak metrics. We prefer the use of regression over other tools commonly used for sensitivity analyses because it provides greater accuracy [52] and allows us to estimate interaction coefficients. However, the relationship between these parameters and outbreak metrics are highly bimodal and often non-linear. Regression assumes that the relationship between the average outbreak metric and control parameters is strictly linear, but is quite robust against this assumption. We evaluated whether violating regression's linearity assumption produced expected results by comparing results of a partial-rank correlation coefficients (PRCC) and regression analysis without interaction terms. PRCC is a useful tool for this comparison because it is used for sensitivity analyses and has the less strict assump-

tion that there is a monotonic relationship between covariates and response variables [53]. Upon confirming a monotonic relationship was present in our data, and once we were confident that the results of the PRCC and regression analyses matched, we decided to proceed with using regression to estimate the relative effect of parameters on outbreak metrics for the rest of the sensitivity analysis (Figure B.2) [42–44].

2.3 Results

2.3.1 Effects of control on outbreak metrics

All outbreak scenarios, regardless of control policy, exhibited bi-modal behavior for all outbreak metrics (Figure 2.1). The vast majority of outbreaks (89%) did not spread beyond the initial index infection or remained very small (96% below 10 infected premises). Outbreak duration and the number of counties infected both followed similar patterns, where 91% of outbreaks lasted less than 30 days and infected premises in only one county.

The effect of control policies on outbreak duration, number of infected counties, and number of infected premises varied very little for 97.5% of outbreaks, regardless of whether the policy was implemented as state-dependent or static (Figure 2.1). Control strategies that targeted dangerous contacts for control performed better than policies that targeted premises by proximity, regardless of whether control measures were implemented as state-dependent or static (Figure 2.1). IP and DC culling performed the best across all outbreak metrics for both state-dependent and static control strategies, closely followed by IP culling and DC vaccination. We will only consider an IP cull and DC vaccination from hereafter because it was one of the top two performing control strategies and it is the USDA's official FMD response policy [9].

2.3.2 Static vs. state-dependent control strategies

State-dependent control performed similarly to static control policies for 97.5% of outbreaks (Figure 2.1). For the most extreme outbreaks, state-dependent control policies resulted in longer outbreaks as well as more infected premises and counties than static control policies (Figure 2.1).

More simulations reached the 365 day cut-off when state-dependent control was applied to the outbreak, which means the infection never faded out (Figure 2.1, Table B.3).

There was no difference between strategies when we varied the number of days required for decision-making, including when no control was applied, for 97.5% of the outbreaks (Figure 2.2). Static control resulted in fewest number of infected premises, even when only one day was required to implement the next control measure in state-dependent control during the largest outbreaks (Figure 2.2, Figure B.1). For these large outbreaks, both static and state-dependent control strategies resulted in fewer infected premises than the no control strategy. There was no difference between control strategies that required two and three days to make a decision, but both resulted in more infected premises than the state-dependent control strategy that only required one day for decision-making (Figure 2.2).

There are no significant differences between the geographic distribution of outbreaks when static and state-dependent control strategies were applied (Figure B.3). The largest outbreaks emerged when the index infection was seeded in the USDA Basin and Range region, Great Plains, or Central Florida. These regions generally have the most clustered and largest number of premises with greater than 1,000 animals, as well as the most incoming and outgoing animal shipments [43]. Despite producing the most severe outbreaks, outbreak metrics for these regions are still highly bimodal, such that the median number of infected premises for most counties in those regions is one across all outbreak scenarios (Figure B.3). Number of infected counties and outbreak duration exhibited similar spatial patterns. Similarly, the geographic distribution of the proportion of infections attributable to local transmission was not noticeably different between outbreaks with state-dependent and static control strategies for the vast majority of the U.S. A few counties in the eastern U.S. experienced more local transmission with state-dependent control (Figure B.4).

2.3.3 Cost analysis

Consistent with other outbreak metrics, static and state-dependent control policies cost the same for 97.5% of outbreaks (Figure 2.3a). For the worst 2.5% of outbreaks that faded out prior to

reaching 365 days, the cost of the outbreak was dependent upon whether all infected animals were culled after the outbreak had subsided and whether animals were vaccinated-to-kill or not (Figure 2.3). If infected animals were not culled after the outbreak ended, state-dependent control cost less than the static control strategy (Figure 2.3a). However, if infected animals were incorporated into the cost calculation, static control strategies cost less (Figures 2.3b & c).

The probability that state-dependent control strategy sequences would complete during an outbreak did not reach one until 150 – 300 days had passed, whereas the probability reached one for a static control strategy by the 50th day (Figure 2.4). The variation around the probability a given control strategy is completed increases with the number of days required for decision-making (Figure 2.4). The static control strategy exhibited very little to no variation (Table B.1).

This analysis considered the vast majority of outbreaks despite only considering outbreaks that did not 365 days. Between 97.7% and 99.9% of all outbreaks, regardless of control policy, ended prior to becoming 365 days (Table B.3). 99.9% of outbreaks with static control policies ended prior to reaching 365 days while outbreaks with state-dependent control policies ended between 98.0% and 98.8% of the time. Over ninety-seven percent of outbreaks faded out when no control was applied (Table B.3).

2.3.4 Sensitivity analysis

The results of this sensitivity analysis revealed how sensitive our outbreak metrics were to model parameters. Specifically, we evaluated the effect of state-dependent control policy parameters and seed county demographic attributes on outbreak metrics. Both our PRCC and regression with no interaction analyses revealed that outbreak metrics were more sensitive to seed county demography than control policy parameters (Figure B.2).

When we included pairwise interaction terms between all combinations of covariates in our regression model, county characteristics became much less important predictors of outbreak metrics (Figure 2.5). However, outbreak metrics were much more sensitive to control policy parameters when we ran the regression model with interaction terms only on outbreaks that grew beyond 5,000

infected premises (Figure 2.5). Effect sizes varied significantly between outbreaks that faded-out and took-off for the same covariate. Control parameters that dictated the prioritization of premises sent to be culled or vaccinated had the largest, non-significant effects. Seed county demography and interactions with decision-making and reporting time had smaller but significant effects on outbreak metrics (Figure 2.5). Control policies that prioritized premises control based off of premises size or when a premises was identified to be controlled resulted in larger outbreaks than control policies that used distance to prioritize control (Figure 2.5). Conversely, outbreak metrics were much more sensitive to county demography for outbreaks that faded out prior to reaching 5,000 infected premises and the end of the simulation (Figure 2.5).

2.4 Discussion

There is a strong interest in developing optimal control policies for any given infectious disease outbreak. Given that it is computationally unfeasible to enumerate all possible future outbreak scenarios, and thus generate optimal control strategies for any given outbreak, recent work has highlighted the potential importance of adjusting control measures during an active outbreak based on the outbreak's current trajectory [13, 30, 35, 38, 54]. Although both nations and international health organizations having adopted state-dependent approaches to controlling infectious disease outbreaks in humans and animals [9, 26–29], few studies have weighed the impact of state-dependent control policies on outbreak outcomes against static control policies. Allowing control measures to be dynamically added and removed from a control policy and incorporating decision-making time into this process allowed us to more realistically model the process of responding to an infectious disease outbreak.

We find that for the vast majority of outbreaks there is no difference between static and state-dependent control strategies, regardless of decision-making time and when control is implemented. This result can be attributed to reporting time and the bi-modal behavior of the outbreak simulations. Outbreaks either die out before spreading beyond the initially infected premises or grow extremely large when they spread to multiple premises. Control policies do not have the opportu-

nity to alter the trajectory of these small outbreak because the infected premises is reported long after it has become infectious. Instead, seed premises size, and other county attributes like the number of large premises and degree of premises clustering are stronger drivers of whether or not an outbreak will remain small. All of these attributes have been shown the be strong drivers of outbreak outcomes and risk of infection in both the U.S. and the U.K. [17, 42, 43, 50].

Differences between control strategies are only apparent for the very largest outbreaks that spread to multiple premises. A previous study by this group that compared several static control policies suggested that the largest outbreaks are uncontrollable due to control trailing outbreak spread due to the reporting lag [43]. When state-dependent control is applied, delays associated with decision-making only exacerbate the time between becoming infectious and targeting that premises for control, explaining why state-dependent control policies result in worse large outbreaks. Analyses of the 2001 FMD outbreak in the United Kindgom (U.K.) demonstrated that increased demand for resources, by identifying a very large infected premises or identifying many infected premises all at once, causes additional delays that exacerbate already limiting resource constraints [17, 25]. Therefore, delaying the onset of an entire control strategy may not only mean that control further lags behind the spread of an infection, but it could harm the operational capacity of an outbreak response later on. This means that if a state-dependent control policy is adopted, a special emphasis should be placed on reducing reporting and decision-making delays to reduce the chance of making a large outbreak worse.

Our sensitivity analysis suggested that seed county demography was the strongest driver of whether an outbreak took-off or not. Given this result and relatively low variation between the top performing control policies, reducing the time between infection and identification by targeting regions susceptible to seeding large outbreaks for surveillance may be more effective at reducing the impact of an outbreak than developing an optimal control strategy. Interestingly, for these outbreaks that take-off, our sensitivity analysis suggests that it may be more effective to control largest premises first, rather than the order in which they are identified or by their proximity to an IP. These results are consistent with recent work that showed FMD infectiousness scales up with

premises size [55] and that large premises can drive onward transmission [56], thereby highlighting the importance of controlling large premises first. Although these results are not consistent with [12] who find that vaccinating premises closest to a reported infection is the best prioritization of vaccine administration, results from both studies recommend a risk-based approach to control prioritization.

One of the primary motivations for implementing a more conservative control strategy early on in an outbreak are the potential economic benefits. Our analysis suggests that these theoretical benefits may be outweighed by the substantial additional cost accrued by state-dependent control policies during the most severe outbreaks. This is especially true because state-dependent control strategies did not cost less than their static control counterparts even for the smallest outbreaks where we would expect to see the largest economic benefit of state-dependent control. In fact, state-dependent control strategies were only less costly when only short term costs were considered, but became more expensive when the cost of culling the remainder of previously infected animals was incorporated into the calculation (Figure 2.3b). Incorporating the vaccinate-to-kill control into our cost estimate increased the static control strategy cost more than the state-dependent control cost (Figure 2.3c), which indicates that state-dependent control results in fewer animals being culled or vaccinated, as expected (Figure 2.4). Although our cost analysis was coarse and does not consider many additional costs [50, 51], we show that even in the event of a best-case scenario, where the World Organization for Animal Health (WOAH) does not require all vaccinated animals to be culled after an outbreak ends, (Figure 2.3b), state-dependent control still costs more money [9,57]. We also do not consider the arguably most costly element of an FMD outbreak, which is the amount of time required to complete culling premises that were targeted for control prior to simulations ending. Given that more state-dependent control simulations hit the 365 day cutoff we would only expect that the cost difference between static and state-dependent control to grow if this cost were incorporated.

Ultimately, the goal of a state-dependent control policy would be to maximize a manager's ability to control an outbreak while minimizing socioeconomic harm. One way to achieve this is to

treat the control of an infectious disease as an optimization problem, where the cost and benefit of each control action could be considered repeatedly throughout the simulation. Such an approach may be able to achieve a more successful and less costly state-dependent control policy, but would likely require realism be compromised for computational tractability, as seen in [58]. Because we only explore the most standard control policies that can be found in previous publications and official response policies, this may have limited our ability to find a more optimal state-dependent control strategy. Additionally, although we consider several delays as they relate to controlling and decision-making, we do not consider how delays and uncertainty associated with diagnostic tests impact outbreaks. These additional delays are known to affect outbreak outcomes in a variety of disease systems [16, 59–61]. Finally, we consider cattle-only outbreak scenarios, which ignores large populations of susceptible animals that, if considered, could alter a county's demographic landscape, and therefore potentially impact transmission dynamics [62]. Other susceptible animals, such as sheep, goats, and pigs, transmit FMD at different rates, which may change the optimal prioritization in which to control premises in multi-species outbreak scenarios [63, 64].

We have systematically compared the performance of several plausible state-dependent and static control policies to understand the potential benefits and challenges associated with minimizing economic harm while controlling an infectious disease outbreak. We warn against using our results as policy recommendations as the optimal disease control policy is likely highly dependent upon the state of an ongoing outbreak, particularly current resource constraints [12]. Instead, this work demonstrates that any additional delays in implementing control measures contribute to producing larger and longer foot-and-mouth disease outbreaks. These findings highlight the importance of pandemic scenario modeling efforts and developing outbreak response strategies *a priori* to minimize the time required to respond to a novel outbreak. While FMD specific, these results may provide some insight into how state-dependent control policies for other highly transmissible viral infections in livestock, such as African swine fever or highly pathogenic avian influenza, might fare during an epidemic [65, 66]. Alternatively, state-dependent control policies may be more suitable for less transmissible infections, like bovine Tuberculosis (bTB). In the bTB case,

however, it may be less necessary to have a rapid response plan outlined as the infection will not move rapidly enough to cause a major outbreak in just a few days.

Table 2.1: State-dependent control parameters.

Parameter	**Definition**	**Default Strategy (control 1 → control 2 → control 3)**	**Range/Values**	**Reference**
Switch	Type of threshold used to turn control actions on and off	n.a. → percent increase → percent increase	percent increase, resource availability, and number of days with no new or decreasing number of reports	Expert opinion
Threshold	Number used to turn on a control action	n.a. → 0% → 10%	0 – 25% (percent increase switch), 0 – 10 days (resource availability or days decreasing switch)	[9], Expert opinion
Action	Type of control applied to premises identified to be controlled	movement ban → cull → vaccinate	cull, vaccinate, movement ban	[9, 42, 43]
Target	Type of premises to be targeted for control	state-level ban → IP → DC	IP, DC, 3km Cull/Vax, 10km Cull/Vax	see text
Priority	Order in which premises are controlled	n.a. → earliest → earliest	earliest, smallest, largest, closest, farthest	[9, 43], Expert opinion
Decision-making time	The number of days where the threshold value must be observed before turning on the next control action	n.a. → 3 days → 3 days	0 – 10 days	[9], Expert opinion

Table 2.2: Control parameters. Range is only listed if the parameter was included in sensitivity analysis.

Parameter	Default Value	Range	Reference
Index case reporting time	15 days	2–31 days	[43]
Non-index reporting time	8 days	5–25	[43]
DC reporting time	2 days	1–5	[43]
Susceptible DC detectability (scaling parameter)	4	n.a.	[43]
Exposed DC detectability (scaling parameter)	5	n.a.	[43]
Carcass space requirements (per animal)	1.96m^3	n.a.	[43]
Culling rate	240 animals/premises/day	n.a.	[43]
Culling effectiveness	100%	n.a.	[43]
Vaccination rate	6,804 animals/premises/day	n.a.	[43]
Vaccine doses per animal	1	n.a.	[43]
Vaccine time to protection	11 days	n.a.	[43]
Vaccination effectiveness	90%	n.a.	[43]
Duration of immunity	183 days	n.a.	[43]
Day 1 – day 5 vaccine dose availability	0 doses	n.a.	[43]
Day 6 – day 13 vaccine dose availability	300,000 doses	n.a.	[43]
Day 14 – max vaccine dose availability	500,000 doses/week	n.a.	[43]
Vaccine dose maximum	2.5 million	n.a.	[43]
Shipment ban effectiveness	75%	n.a.	[43]

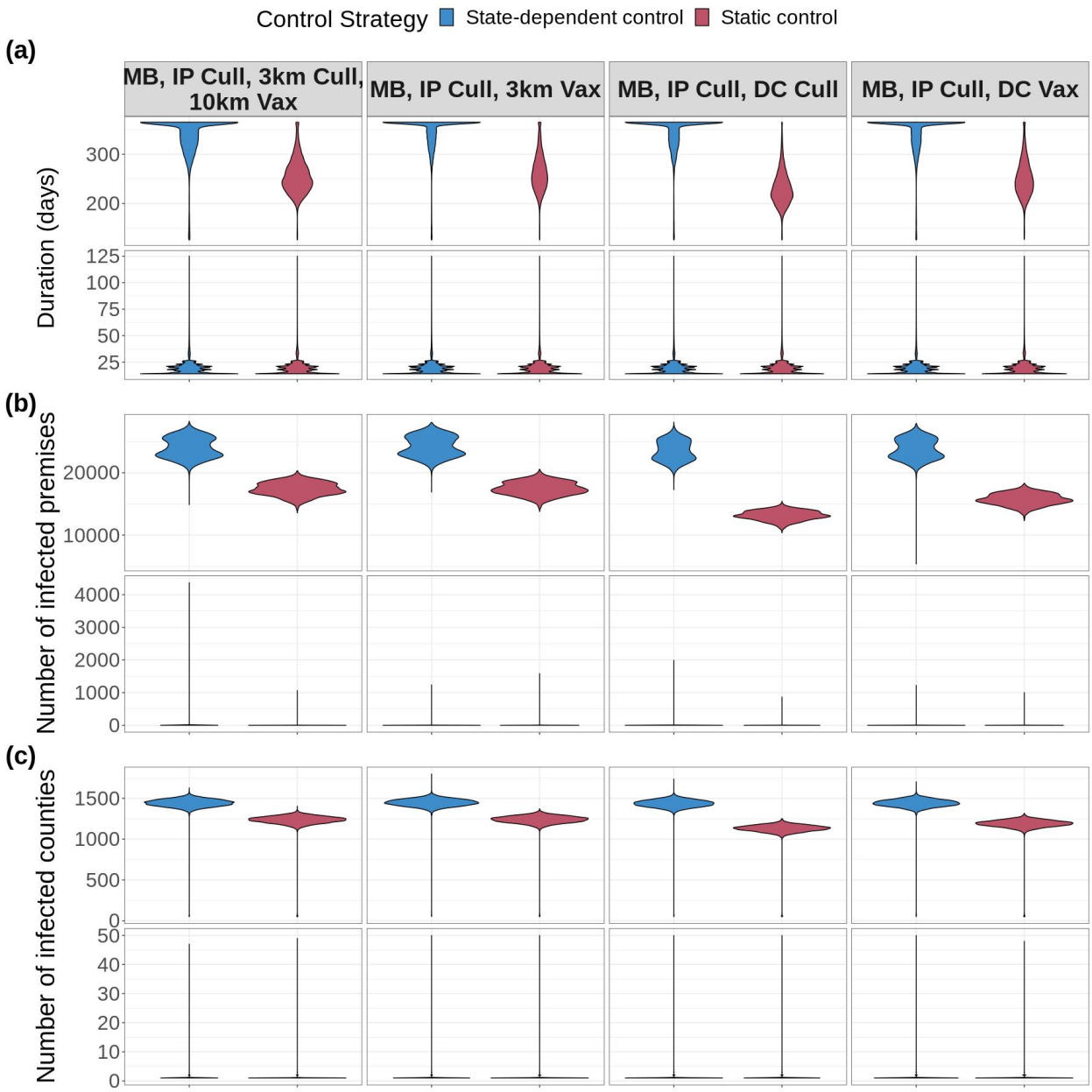

Figure 2.1: Outbreak outcomes are similar between state-dependent and static control policies for 97.5% of outbreaks. Duration, number of infected counties, and number of infected premises simulations with four different control policies implemented either statically or state-dependent. Each strategy includes a movement ban (MB), culling, and vaccination. For state-dependent control, movement bans are triggered upon the first reported premises and culling begins the following day, while 10% increase in new premises reports for three days triggers vaccination. All control is triggered immediately upon the first premises report for static control strategies. The targets of these control actions vary for each control strategy, and may be one of the following: infected premises (IPs), dangerous contacts (DCs), and or all premises within a three or 10 kilometer radius (3km/10km) from an IP.

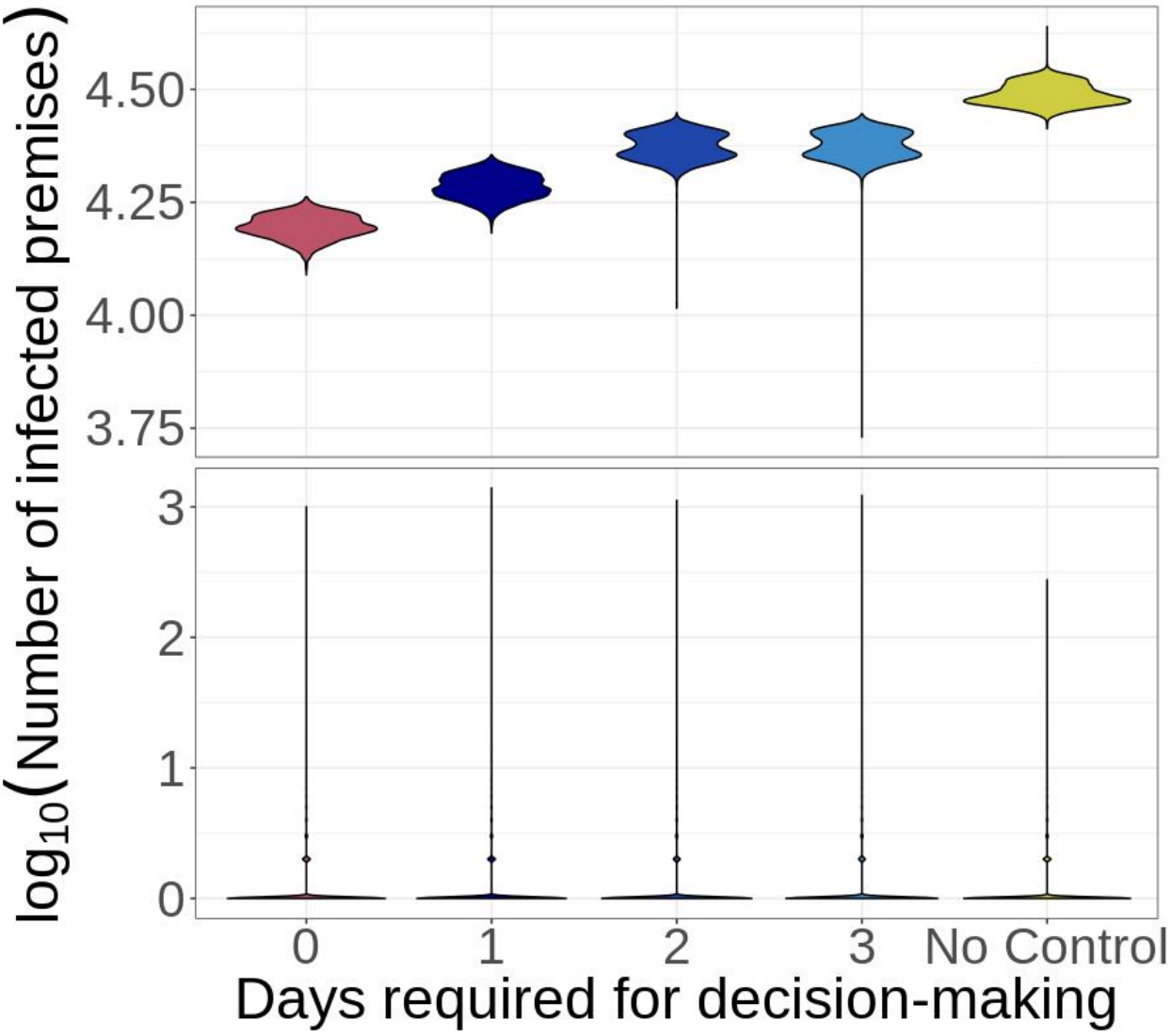

Figure 2.2: Delays associated with decision-making exacerbate differences between MB, IP Cull, and DC vaccination control strategies. Days required for decision-making is the number of days that a 10% increase in the number of new premises reports must be observed to trigger vaccination. Static control policies are in red, state-dependent control policies in blue, and no control in yellow. Vertical axes are faceted by outbreak size, such that 97.5% of outbreaks are in bottom panel for each outbreak metric and the largest 2.5% of outbreaks are the top facet for each metric. Vertical axis is $log_{10}(\text{Number of infected premises})$.

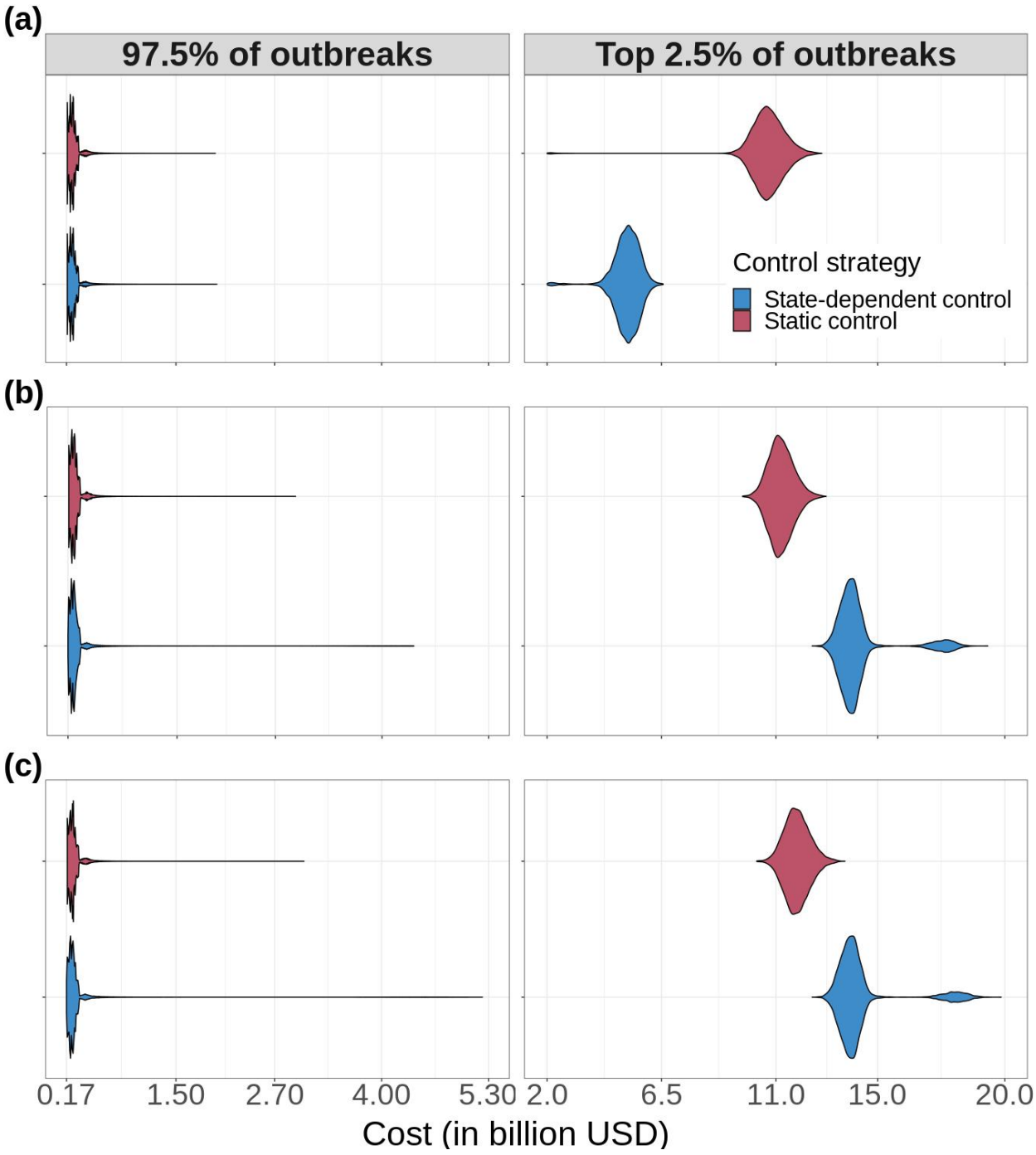

Figure 2.3: Cost of FMD outbreaks when static and state-dependent MB, IP cull, and DC vaccination control strategies are used. (a) is the cost when the outbreak ends and does not include the cost of culling animals that were infected, but not culled during the outbreak (Equation 2.1). (b) assumes every infected animal will be culled, but vaccinated animals are not culled (vaccinate-to-live, Equation 2.2). (c) includes the cost of culling both infected and vaccinated animals (vaccinate-to-kill, Equation 2.3). Static and state dependent control policies cost the same for 97.5% of outbreaks, but differences between types of control strategies arise for the largest 2.5% of outbreaks that fade out prior to reaching 365 days.

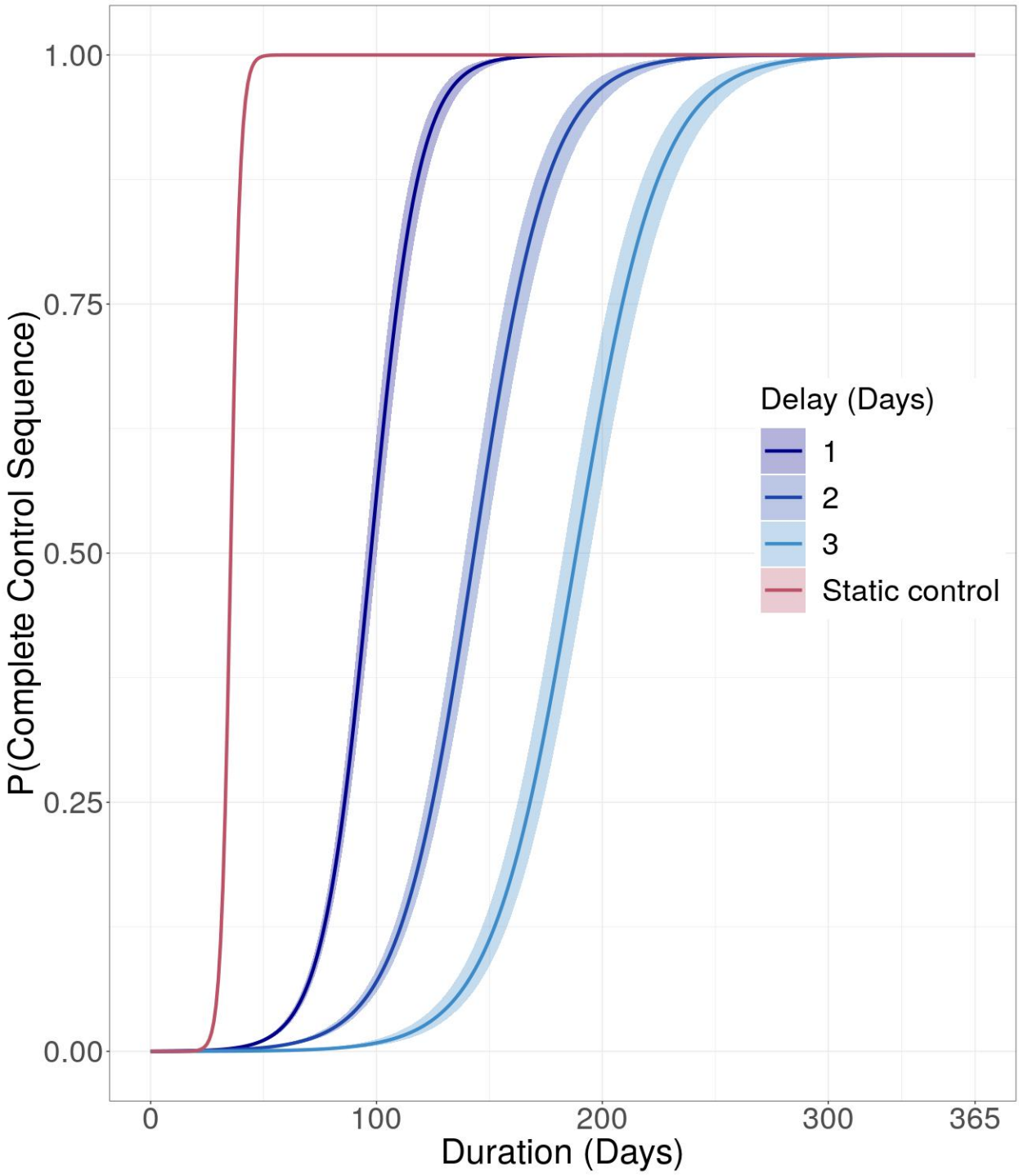

Figure 2.4: Static control strategy sequences are more likely to complete and result in an outbreak fading out than state-dependent control strategies if FMD spreads beyond the initial index infection. (a) The predicted probability that static and state-dependent control sequences complete during an outbreak based upon the duration of an outbreak. State-dependent control strategies are blue and static control is in red. Lighter bands represent 95% confidence intervals. Probabilities are derived from logistic regression.

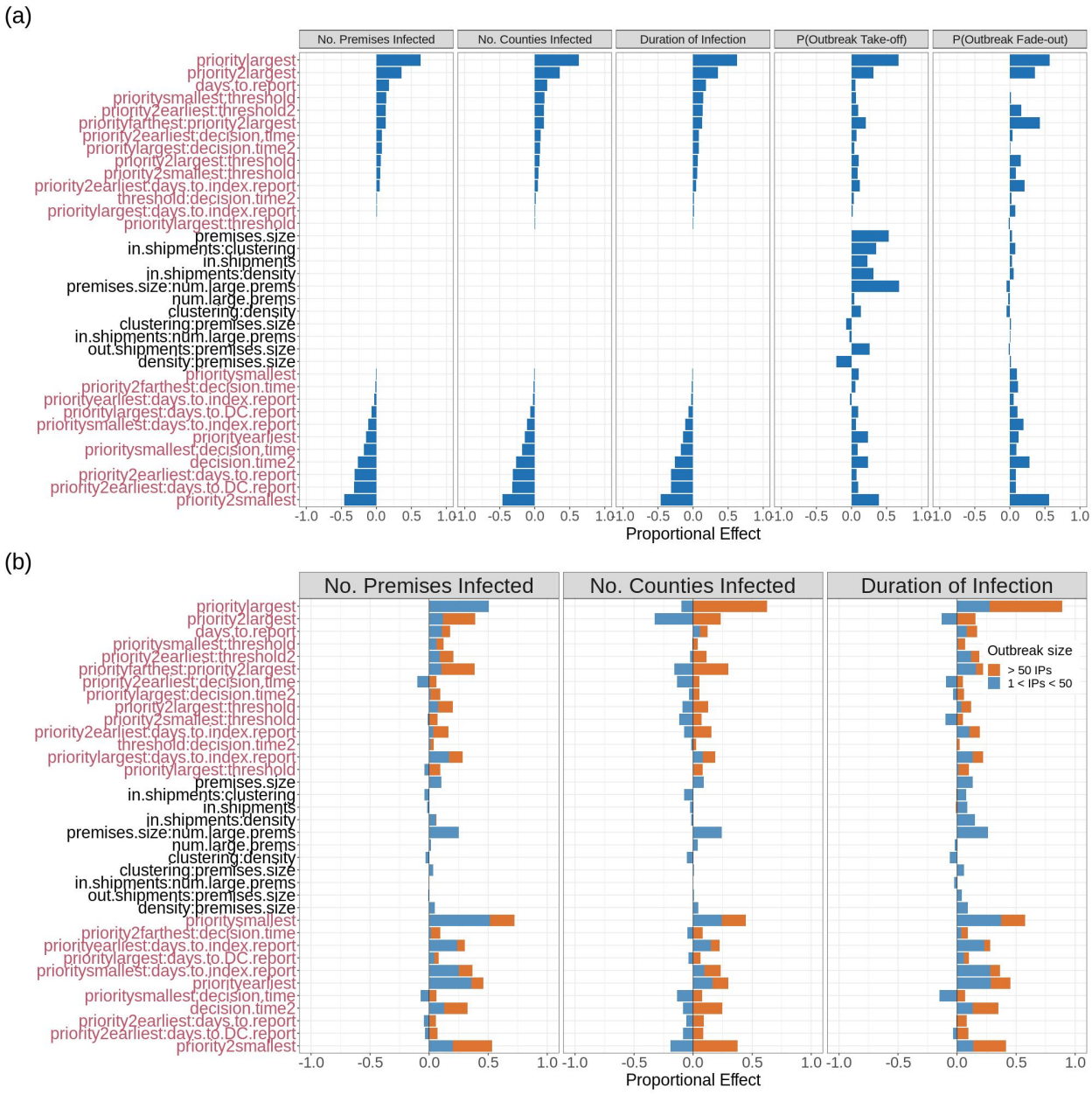

Figure 2.5: Sensitivity analysis showing the scaled effect of county demography and state-dependent control policy parameters on disease outbreak metrics. State-dependent control policy parameters shown in red and county demography in black. Outbreaks that take off are in orange and outbreaks that fade out are in blue. Results only show parameters with a highly significant on outbreak metrics ($p < 0.001$). The number two (2) following a parameter name indicates that parameter controlled the second step of the control policy. State-dependent control parameter descriptions can be found in Table 2.1. Parameters with scaled effect sizes < 0.001 are excluded from the figure for clarity.

Chapter 3

Evaluating the impact of diagnostic testing and trace investigations on the management of bovine tuberculosis outbreaks in the United States

3.1 Introduction

Bovine tuberculosis (bTB), caused by *Mycobacterium bovis*, is a zoonotic pathogen that continues to threaten both human and animal health worldwide [57, 67]. Despite international eradication efforts, bTB is endemic in much of the world, and Australia is the only major beef and dairy producer to have successfully eradicated the disease [68]. In the United States (U.S.), over 100 years of eradication efforts have struggled to prevent small, sporadic bTB outbreaks [69, 70]. bTB prevalence in the U.S. ranges from 0.0002% in beef herds and 0.0001–0.0019% in dairy herds [70], and endemic infection only exists in 11 counties in the state of Michigan's Lower Penninsula [71–73]. Although spillback from wildlife reservoirs, such as white-tailed deer, and proximity to a previously infected premises is thought to be the primary risk for bTB emergence in Michigan [72, 74, 75], the movement of infected animals likely plays a stronger role in driving between farm transmission in areas where more sporadic infection is observed [3, 4, 76, 77].

The primary challenge to eradicating bTB both nationally and internationally has been identifying infected cattle [71, 78]. The problem of identifying infected premises is twofold and is especially complicated when disease prevalence is low. Detecting an infection is the first challenge, and the primary mechanism for doing so in the U.S. is through post-mortem inspections for lesions in slaughterhouses [69, 78]. Slaughter surveillance efforts may only detect between 28 – 50% of infections, leaving up to two thirds of all infections unidentified [7, 70]. If an infection is detected, the challenge then becomes identifying the premises where that infection originated through a successful traceback investigation. If the origin is identified, a series of antemortem diagnostic tests is

triggered. This series of tests includes first administering the caudal fold tuberculin test (CFT). If the CFT is positive, the comparative cervical tuberculin (CCT) test or gamma interferon (GI) assay is administered as a confirmatory test, depending on the confidence the infection originated at the premises [6]. The sensitivity of these tests currently range from 37 – 100% [79, 80], and have been identified as an important area that could improve the U.S. bTB eradication campaign [69].

Improvements to the sensitivity of antemortem diagnostic tests and the slaughterhouse surveillance campaign could aid the U.S.' goal of bTB eradication. Increasing the sensitivities of antemortem diagnostic testing and slaughterhouse surveillance would potentially help identify infected cattle that would otherwise go undetected. The ability to detect infections through slaughter surveillance is inherently limited by the number of cattle being sent to slaughter, the low prevalence of bTB, and uneven sampling of both beef and dairy herds because of the industry's structure [7]. Improving slaughter surveillance's capacity to detect infected cattle is then unfeasible as it is unlikely that managers could change the number of cattle being sent to slaughter. This leaves increasing the sensitivity of antemortem testing as the only avenue for improving managers' ability to detect infections. Although recent work has improved antemortem test sensitivity [81, 82], further advancement has been hindered by animals that remain unreactive to tests despite being infected. These challenges mean that other aspects of bTB control efforts must be improved in order to reduce bTB incidence below current levels.

Given the challenges facing improving our ability to detect infections, traceback investigations are another tool that could be improved to identify more potential infections. Currently traceback investigations from slaughter houses identify anywhere between 13 – 85% of origin premises, depending on the type of origin premises, which leaves significant improvement possible [78]. Epidemiological traceback investigations have also occurred in the U.S. that aim to identify premises with an epidemiological link to an infected premises. Epidemiological links for these non-slaughter related trace investigations may include premises that received shipments of animals from an infected premises or premises located near previously infected premises. The movement of infected animals between premises is known to be a particularly common source of new bTB infections

in other countries, especially in low prevalence areas like the majority of the U.S. [3, 4, 68, 83]. Therefore, tracing shipments to and from premises identified as infected could provide a potentially less costly and more effective means of identifying premises to test for bTB [14, 84]. These trace investigations were a key element to Australia's bTB eradication campaign and have been relatively successful in the U.S., identifying up to 39% of all known infected premises between 2000–2019 [68, 78] (USDA, Ruminant Health). However, it remains unclear how many affected premises go undetected despite these investigations, and therefore what the actual impact of trace investigations is on detection and control of bTB outbreaks.

Historically, mathematical models have been essential to understanding the unobservable processes and patterns of disease transmission and spread. Models can therefore reveal the impact of surveillance and control on disease spread. Although models have been used to inform bTB management strategies in other countries [14, 85–88], there are only a few cases in which they have been used to evaluate the impact of control on disease outcomes in the U.S. [15,84,89]. [15] present the only national-scale model that has been developed, while other bTB models only model disease dynamics up to the state level. While these models consider how the size of an initially infected herd and various control measures affect disease spread, they do not explicitly consider how the U.S. cattle industry's structure and the external force of infection from wildlife affect bTB spread. These gaps have prevented a complete national-scale understanding of the impact of diagnostic sensitivity and trace investigations on unobserved disease prevalence and spread. To address this gap, we present an updated version of the United States Disease Outbreak Simulation (USDOS) that simulates the national-scale spread of bTB, conducts slaughter surveillance, diagnostic testing, and trace investigations [42,43]. A key feature of USDOS that presents a novel opportunity to understand the effects of control and surveillance on U.S. bTB dynamics is the complete national-scale shipment network, generated by the United States Animal Movement Model (USAMM) that drives long-distance transmission [46].

We used the new version of the United States Disease Outbreak Simulation (USDOS) to understand the national-scale effects of slaughter surveillance, diagnostic testing, trace investigations,

and control strategies on bTB outbreaks in the United States. We simulated cattle-only outbreak scenarios of bTB with and without control measures, diagnostic testing, and trace investigations. Finally, we used sensitivity analyses to determine which parameters are the strongest drivers of outbreak outcomes. Results from these simulations should reveal the most critical features of bTB outbreak control efforts and their effect on unobserved prevalence. Our findings suggest that although increasing diagnostic test sensitivity can improve bTB outbreak outcomes, improving slaughterhouse traceback investigation success and decreasing diagnostic test variance are also essential to reducing the size of bTB outbreaks.

3.2 Methods

3.2.1 USDOS Version 3.0

USDOS is a national-scale stochastic livestock disease spread model that was originally developed to simulate fast-spreading infections, like foot-and-mouth disease (FMD) [42, 43]. Here, we present USDOSv3.0, an updated version of USDOSv2.2 that can simulate the spread of bTB, detect infections through slaughterhouse surveillance, diagnostic testing [90], and conduct trace investigations to identify where infected animals were shipped to and from.

Premises in USDOS were general beef or dairy, feedlots, or markets. The size and locations of beef and dairy premises were predicted by the Farm Location and Agricultural Production Simulator (FLAPS) because premises-level data are not publicly available [47]. The premises locations and sizes estimated by FLAPS are based on totals in the National Agriculture Statistical Survey (NASS) 2012 census data for the “Cattle Cows Beef," “Cattle Cows Milk," and “Cattle on Feed - Inventory" categories, which do not include calves [47, 91]. The size of the U.S. cattle population changes by about ten percent during the course of a year due to the birth of new animals and the removal of animals through the slaughter system [92, 93]. To account for the number of calves in the population and the seasonal changes in the size of the U.S. beef population, we estimated quarterly U.S. cattle population sizes using Excel models (based on NASS data) that capture the annual dynamics of the U.S. beef and dairy cattle industry (USDA, personal communication). The

cattle numbers for the minimum population (quarter 1) were estimated by assigning calves to the original 2012 FLAPS estimates, increasing the population on premises proportionally by the original size of the premises to reach a national population size of 94.4 million cattle. The maximum population size (quarter 3) was estimated by proportionally adding calves to the beef premises only, again based on original premises size until the national cattle population reached 103 million cattle. The intermediate population size estimates (quarters 2 & 4) were assigned population sizes based on the Excel model described above and our understanding of U.S. cattle population dynamics (USDA, personal communication). The total population size numbers were based on the NASS cattle inventory surveys from January 2018, June 2018, and January 2019 [93–95].

Market size and location data were available, but incomplete. To generate a complete dataset, we updated a list of all cattle market locations originally compiled by [96], and used available market-level volume data to inform a spatial model that we then used to predict county-level market volumes where market-level volume data were unavailable [97]. We validated the model fit by predicting known market volumes and compared them to our model's predictions. Finally, we divided county-level market volume estimates by the number of markets in each county to obtain market-level volumes. More information regarding the sources for these data and about the model can be found in [42, 46, 96, 97].

Disease spread in USDOS occurred via both local and shipment-based long-distance transmission. The movement of infected animals between premises via shipments was the main route of between premises bTB transmission and the only mode of long-distance transmission. All shipments were modeled by the United States Animal Movement Model (USAMM) [42,43,46]. Local spread of bTB also occurred from cattle to cattle, wildlife to cattle, or fomite contact. The probability of bTB infection spreading from infected premises i in county ω to another premises j each time step (month) is given by the kernel function and the prevalence of infectious animals present at i,

$$P(i \text{ infects } j) = \frac{I_i}{N_i} C(d_{ij}, w_\omega), \tag{3.1}$$

where I_i is the number of infectious animals on premises i and N_i is total number of animals on premises i. C is the mixed local-wildlife transmission kernel where d_{ij} is the distance between premises i and j and w_ω is the normalized white-tailed deer density of county ω to which premises i belongs. Therefore, the probability that i infects j is a function of the distance between the two premises, the county's white-tailed deer population, and the total number of infectious animals present on premises i increases. The local spread component (Equation C.1) is a distance-dependent spatial kernel that represents the many possible modes of local transmission such as aerosols, fence line contact, or fomite spread. The wildlife component (Equation C.2) only changes the shape of the kernel, but not the total infection pressure. See C.3 for individual descriptions of the local spread and wildlife kernels and their parameters referenced here. It is important to note that the kernel shape and parameters discussed in C.3 are estimated for bTB outbreaks in Uruguay because no kernel has been fit to U.S. outbreak data yet [14]. If Equation C.2 determined that a local spread event occurred, one susceptible animal on premises j was moved to the *exposed 1* class. Transmission was not restricted to only susceptible premises – any premises with susceptible animals were at risk of becoming infected.

At the beginning of every simulation, premises were assigned disease, control, diagnostic, and file statuses that were tracked throughout the simulation. All status sequences in USDOSv3.0 remained the same as they were in previous versions of USDOS, with the exception of the disease status. Therefore, we will only present how the disease status has changed, and an overview of the other statuses can be found in [42, 43] and C.1. Figure 3.1 provides a visual depiction of how these statuses interact. In USDOSv3.0, the disease status tracked the course of infection from "susceptible" to "infected" as done in older versions of USDOS, but the sequence of these statuses has changed to reflect biological differences between the foot-and-mouth disease and bTB course of infection.

Once a premises became infected, the course of infection was modeled by a within-herd model that determined the number of animals transitioning between four infection classes. These infection classes included "susceptible", "exposed 1", "exposed 2", and "infectious". Animals in the

“exposed 1" class were exposed, but lacked an immune response, while animals in the “exposed 2" class were exposed and exhibited an immune response. Within a premises, new exposures occurred when susceptible animals contacted infectious animals. The rate at which each susceptible animal on a premises transitioned from “susceptible" to “exposed 1" was a function of the base transmission rate of the disease as well as the rate of contact between animals and the number of infectious animals present.

USDOSv3.0 allowed for open population dynamics, such that infected animals were slowly replaced by new susceptible animals. New susceptible animals were introduced to the premises via three processes. The first was through new births based on a birth rate that varies between beef and dairy premises. The second was via the implicit modeling of incoming shipments from uninfected premises via an import rate (distinct from USAMM’s import rate). These two internal processes only introduced new susceptible animals, and the balance between them controls how the within premises prevalence of bTB in the different infection classes evolves over time. The third process of replacement was not strictly a part of the within-herd model, but occurs via explicitly modeled shipments from premises with infected animals. These shipments were modeled with USAMMv3.0 and the number of infected animals present on the shipment is determined by the shipment size and the prevalence in the different infection classes of the sending premises. More specifics about how animals were replaced on premises can be found in C.2

3.2.2 Interventions in USDOSv3.0

USDOSv3.0 included several possible interventions, including slaughterhouse surveillance, diagnostic testing, trace investigations, and culling.

Slaughterhouse surveillance

The initial trigger for on-farm bTB diagnostics – for premises not triggered by being a DC or neighbor of a reported premises – was detection at slaughter of an infected animal, followed by a successful traceback to the farm of origin. The probability of a premises being triggered for bTB diagnostics as a result of slaughter surveillance was estimated by

$$
\begin{aligned}
P(\text{detect.any.premises.A}) &= 1 - P(\text{not.detect.any}) \\
&= 1 - \prod_{i=1}^{n} P(\text{not.detect.animal}_i) \\
&= 1 - \prod_{i=1}^{n} (1 - P(\text{detect.animal}_i)) \\
&= 1 - (1 - P(\text{detect.animal}))^n
\end{aligned}
\tag{3.2}
$$

where *i* is animal and *n* is the total number of infected animals. The probability of detecting one or more infected animals from premises A (thus triggering A for on-farm diagnostics) is one minus the probability of not detecting any infected animals. The probability of not detecting any animals is the product of the probability of not detecting each animal (animal$_i$, *i* in 1,...,n) sent to slaughter. The probability of not detecting animal$_i$ is one minus the probability of detecting it, and this is applied for all animals sent to slaughter. The probability of detecting one or more infected animals at slaughter is therefore a joint probability that accounts for the probability of detecting any given animal and the number of infected animals sent to slaughter. If premises A was identified as having infected animals, a traceback investigation occurred to find the origin farm. We treated identifying the origin farm as a Bernoulli process with probability p of successfully locating the origin farm. Following the detection of an infected animal and successful traceback investigations, premises are classified as “suspected", which triggers on-farm diagnostic testing.

On-farm diagnostic testing

Once a premises was identified through the slaughter surveillance joint probability as “suspected", that premises then triggered on-farm diagnostic tests to identify whether there were additional infected animals in the herd. To model detection of exposed herds in USDOS, we used a combined sensitivity value representing a diagnostic test series consisting of CFT, CCT, and culture (see Table 3.1). These tests can all be completed within one month, and are not currently resource-limited. Two different diagnostic tests may be used in the same simulation provided that they have different targets. For example, we simulated outbreaks while testing suspected premises

with a test sensitivity of one and DC premises with a lower test sensitivity (see Section 3.2.3, Simulation Scenarios). Parameters control the sensitivity of the implemented test type (see below), resource constraints, and time it takes to complete the test once started.

The outcome of a diagnostic test on a premises (whether tested positive or negative) was determined once a premises entered the started diagnostic status. We only modeled the diagnostic test sensitivity because we assumed that the required confirmatory tests would mean that false positives would not occur at the herd level. The probability of a herd testing positive for infection is

$$Prob.Herd.Positive = 1 - (1 - sensitivity)^n \tag{3.3}$$

where, n is the number of infected animals on a premises and $sensitivity$ is given by the following beta distribution with test specific parameters (α_{sens} & β_{sens})

$$sensitivity = Beta(\alpha_{sens}, \beta_{sens}). \tag{3.4}$$

The number of infected animals influenced the probability that the premises tests positive, such that more infected animals increased the probability that a herd tested positive (Equation 3.3). A premises is assigned a “reported" file status upon testing positive. More specifics about how diagnostics are implemented in USDOS or how they reflect real on-farm processes can be found in [90] and C.4.

Trace investigations

For bTB simulations in USDOSv3.0, USAMM generated all possible shipments from premises, whether or not they were infected. Shipment trace investigations identified premises that have shipped animals to where an infection had been reported (back tracing) as well as the premises that the reported premises had shipped animals to (forward tracing). Trace investigations were triggered

by a positive diagnostic test results on suspected premises. As soon as the positive test result was received, a trace investigation identified all shipments sent and received from the positive premises that occurred within a specified time frame of the premises receiving the positive test. Once all shipments were identified, a Bernoulli trial with probability p of success determined whether the trace investigation was successful. We assigned the same probability of success to both forward and backward trace investigations as to our knowledge there are no data to support doing otherwise. Parameters controlled both the age of shipments available to be traced as well as the probability that an individual shipment was successfully traced (Table 3.2).

Culling

Culling in USDOS was triggered after a positive bTB test result (Table 3.1) and a premises was classified as reported. Culling simulates the depopulation of premises to reduce the number of infectious animals and was subject to resource constraints [43]. However, premises could be re-populated with animals after culling had occurred due to USDOSv3.0's open population dynamics (C.2). This means that once culling was completed, a premises would return to a susceptible disease status as soon as new animals emerged on the premises. Further details about culling can be found in [43].

3.2.3 Simulation Scenarios

We ran simulations with either suspect premises (SP) diagnostics alone or in combination with Dangerous Contact premises (DC) diagnostics. We ran each diagnostic test scenario with and without tracing. The diagnostic test scenarios we ran were:

- **Base:** No control measures implemented (no tracing implemented)
- **SP-Current:** Suspected premises (SP) identified based on slaughter surveillance and tested on farm with current diagnostic test sensitivity and specificity
- **SP-Ideal:** SPs identified based on slaughter surveillance and tested on farm with ideal diagnostic test sensitivity and specificity

- **SP-DC, Ideal-Current:** SPs identified based on slaughter surveillance and tested on farm with ideal diagnostic test sensitivity and specificity. Dangerous contacts (DCs) tested on farm with current test sensitivity and specificity. (DCs are premises with an epidemiologic link to an infected premises, for example due to a known exposure)

To explore the impact of trace investigations on three different diagnostic test sensitivity scenarios, we ran the SP diagnostics-only scenario using two different assumptions about diagnostic test sensitivity with and without trace investigations. These different assumptions are denoted as the current and ideal test sensitivity, respectively. Both the current and the ideal sensitivity tests have a test start-to-complete lag of one month (Table 3.1). The current sensitivity scenario uses the current sensitivity of the on-farm diagnostic series, whereas the ideal sensitivity scenario uses an idealized sensitivity of one. The expected values of the beta distributions that dictate the diagnostic test sensitivities (e.g. E(sensitivity)) were 0.608 and 1, respectively. For the SP & DC diagnostics scenario we assumed the suspect premises (SP) would be tested with the more sensitive test and therefore we ran these simulations with the ideal sensitivity test for SP and current sensitivity test for DC premises. The following tracing scenarios were run with each diagnostic scenario:

- **Trace: 60,70%:** 70% of traceback investigations are successful and they can trace shipments from the previous 60 months.
- **Trace: 60,90%:** 90% of traceback investigations are successful and shipments from the previous 60 months are available to be traced.
- **Trace: 300,70%:** 70% of traceback investigations are successful and shipments from the previous 300 months are available to be traced.
- **Trace: 300,90%:** 90% of traceback investigations are successful and shipments from the previous 300 months are available to be traced.
- **Slaughter traceback: 100%, Shipment trace: 60,70%:** 100% of slaughterhouse traceback investigations are successful, 70% of shipment traceback investigations are successful,

and shipments from the previous 60 months are available to be traced during shipment investigations.

All scenarios assumed that slaughterhouse traceback success was 50% except for the last scenario because [78] estimated that slaughterhouse traceback investigations successfully identify origin premises between 13 – 83% of the time. By systematically improving one feature of traceback investigations we were able to use the current tracing scenario (Trace: 60,70%) as a baseline to conduct a structural sensitivity analysis to understand how improvements to each feature of traceback investigations impact bTB outbreaks.

The simulations were seeded with one index premises selected randomly from the farm population (excluding feedlots and markets) of one county. We seeded infection in 86 selected counties that we have used in previous USDOS work [43]. These counties represent a range of cattle-industry demographic characteristics that are present in the U.S. (C.7). Seeding was done ten times for each selected county for each of the ten FLAPS realizations [47] meaning that each county was seeded in 100 separate replicates. Each time an index case was seeded, 10% of its entire herd (rounded up to nearest integer) was assigned to be in the *exposed 1* class of the within-herd model.

3.2.4 Outbreak Metrics and Statistical Analyses

All outbreak results are aggregated by scenario to facilitate interpretation across the scenarios and the two diagnostic test types. Analyses of the simulation outputs were performed using custom code in R version 3.5.0-3.5.3 [98].

Simulation results were quantified using the following outbreak metrics:

- Number of infected premises: the total number (nationally) of infected premises (includes both unreported and reported premises)
- Number of reported premises: the total number (nationally) of reported premises
- Number of infected counties: the total number of counties infected when infection is seeded in that county, also known as “epidemic extent" [42–44]

- Duration: the number of months between the initial seed infection until there are no longer infected premises, or 120 months (10 years), whichever happens earlier

- Proportion of local transmission: the proportion of transmission events that are due to non-shipment based transmission of bTB (e.g. $\frac{\text{No. local tranmission events}}{\text{Total no. transmission events}}$).

Each outbreak metric was calculated for both the full distribution and the upper part of the distribution, which includes large outbreaks only, over the 86,000 simulations. Large outbreaks were defined as having more than 50 infected premises, which is a natural break-point in the outbreak size distribution. Because outbreak metrics are bi-modal in that outbreaks either take off or they do not, we used the full distribution to show results for the majority of simulations and the upper part distribution for outbreaks that do take-off.

We used a hierarchical cluster analysis to understand how each improvement to control done for the structural sensitivity analysis impacted bTB outbreaks across all outbreak metrics. Cluster analysis is a class of unsupervised learning that groups similar observations into n number of clusters. Therefore, in this context cluster analysis groups simulation scenarios by their outbreak metrics, thus revealing multivariate relationships that may otherwise be difficult to observe. We prefer this analysis to other multivariate analysis tools as it does not assume collinearity or other relationships between measured variables and assigns groups without prior knowledge of group membership. This means that the resulting clusters are due to naturally occurring similarities between outbreak metrics. We only considered outbreaks that grew beyond one reported premises as this is the only time that shipment tracing occurs, which meant the data were no longer bimodal. We also did not include proportion of local transmission in this analysis. Given the omission of these data, the analysis assigned groups to simulation scenarios based upon the median number of infected premises, counties, duration, and reported premises for outbreaks that grew beyond one reported premises. After determining that the results of this analysis were robust to the number of clusters, distance matrix, agglomeration algorithm used to build the clusters, our final analysis used three clusters, a euclidean distance matrix and the complete agglomeration algorithm in the “hclust" function from R package “stats" [99].

3.2.5 Sensitivity Analysis

Sensitivity analysis was performed on a selection of the bTB diagnostics and control parameters for default values of bTB transmission parameters (indicated with a range in Tables 3.1, 3.2 & C.1). Latin hypercube sampling was used to select 100 sets of parameter values and each set of sampled parameters was used to seed the subset of counties 10 times with each of the ten FLAPS realizations, giving 8,600 separate replicates simulated for each of the parameter sets, for a total of 86,000 replicates used in the sensitivity analysis. The same counties were used in the sensitivity analysis as the simulation scenarios described above.

We used linear regression to estimate the relative importance of each parameter on the number of infected premises, number of infected counties, duration, and probability of outbreak take-off and fade-out [42, 43]. However, because our data are bi-modal and often nonlinear, we first used a partial rank correlation coefficient (PRCC) analysis to estimate effect sizes for each parameter because it maintains the less strict assumption of monotinicity between outbreak metrics and parameters [53]. We then used regression without interactions between all parameters to estimate proportional effect sizes for each parameter. After verifying that the results of our no-interaction regression model were similar to our PRCC analysis (Figure D.1), we proceeded with estimating proportional effect sizes for all possible combinations of parameters. Ultimately, we use regression as it allows us to estimate interactions between covariates and provides greater accuracy than PRCC [52]. Generalized linear models were used to estimate the effect of parameters on the probability that an outbreak takes-off ($P(\text{Take-Off})$) and fades-out ($P(\text{Fade-Out})$). We defined take-off as an outbreak exceeding 50 infected premises and fade-out as an outbreak ending in under 300 months while infecting between two and 50 premises.

3.3 Results

3.3.1 County demography drives outbreak trajectory

Our sensitivity analysis revealed that the demographics of the seed county are the strongest drivers of the probability that an outbreak takes-off or fades-out (Figure 3.2a,b). As expected,

of all of the county attributes, number of large premises, premises size, and out shipments were strongly positively correlated with outbreak metrics. Density had a strong negative effect without any interactions. Despite premises size having a strong positive effect on number of infected premises, counties, and duration, the interaction between premises size and density had a strong negative effect on all outbreak metrics (Figure 3.2a). The interaction between out shipments and number of large premises as well as density with no interaction had the strongest effects on the probability an outbreak took-off or faded-out (Figure 3.2a).

The only diagnostic and control parameters with strong effects on outbreak metrics without interaction terms were diagnostic test lag and shipment traceback success probability (Figure 3.2a). These two parameters had the smallest proportional effect of all parameters. Mean diagnostic test lag was positively correlated with all outbreak metrics, but had a small effect on the probability an outbreak took-off. Larger premises and longer diagnostic test lags had a positive, but small effect on outbreak metrics. Shipment trace success probability had a negative effect across all metrics (Figure 3.2a). Both slaughter and shipment traceback success probabilities showed a negative effect on outbreak metrics when they interacted with premises size. Neither interaction had a strong effect on the probability an outbreak took-off or faded out (Figure 3.2a).

When only considering outbreaks that faded-out, only a smaller subset of the parameters that drove outbreak metrics for the full sensitivity analysis had an effect on these outbreaks (Figure 3.2b). The parameters with a significant effect on outbreaks that faded-out included density, premises size, diagnostic test lag, clustering, and slaughter trace success probability. All diagnostic and control parameters exhibited a smaller effect on outbreak metrics than county attributes during these outbreaks(Fig 3.2b). County attributes had the strongest effect on outbreak metrics for outbreaks that faded-out. Density had the largest negative effect on outbreak metrics, while premises size had the strongest positive effect on outbreak metrics (Figure 3.2b). No parameters had a significant effect on outbreak metrics for outbreaks that took-off.

3.3.2 Diagnostics and control reduce bTB outbreak size and alter transmission dynamics

Ninety-three percent of all simulated outbreak scenarios infected less than five premises, and 85% of these scenarios did not spread beyond the initial index infection (Tables 3.3, D.3 & D.2, Figure 3.3). When the infection spread beyond the index premises, the median number of IPs across all outbreak scenarios jumped from one to four IPs (Table 3.3). These outbreaks spread to a median of three counties and lasted 32 months. Less than three percent of all outbreak scenarios infected more than 20 premises and lasted between five and 300 months.

All diagnostic scenarios reduced the size of the largest outbreaks (Figure 3.3a,c,e). There was very little effect of improving diagnostic test sensitivity on the number of IPs and affected counties (Table 3.3). Improving test sensitivity did significantly reduce the duration of the largest outbreaks (Table 3.3). Improving test sensitivity had a larger effect on reducing the duration of outbreaks than targeting both SPs and DCs (Table 3.3).

Ninety-nine percent of all transmission occurred due to the shipment of infected animals across all scenarios (Table 3.4). The proportion of local transmission increased when diagnostics and control were applied. This increase is due to a decrease in the total number of transmission events and not an increase in local transmission events. Therefore, this increase reflects a proportional decrease in shipment-driven transmission (Table 3.4).

3.3.3 Shipment trace investigations aid the identification of infected premises

Shipment trace investigations only occurred if more than one premises was reported. Therefore, we will limit the reporting of the impact of shipment trace investigations to outbreaks with more than one reported premises. Only 2.5% of the 137,600 simulations resulted in more than one premises being reported. Of these simulations, tracing reduced outbreak size across all metrics (Figure 3.3, Table 3.3). Trace investigations had the largest impact on reducing the duration of the outbreak, followed by the number of counties affected.

Outbreaks where tracing occurred culled a larger proportion of IPs than when tracing was not used (Figures 3.4 & D.3). All reported premises were culled if the simulation ended prior to the 300 day cutoff. Tracing identified 50% of all reported premises for these outbreaks. Both improving diagnostic test sensitivity and the percentage of shipments that are successfully traced resulted in a larger percentage of IPs being reported (Figures 3.4 & D.3, Table 3.5).

3.3.4 Increasing slaughter traceback success improves the identification of infected premises

The largest number of additional reported premises occurred when the slaughter traceback success rate was improved to 100% (Figure 3.5c). Increasing the amount of time that shipments are allowed to be traced resulted in the second largest increase in number of reports, followed by improving the success rate of shipment trace investigations (Figure 3.5a,b). The hierarchical cluster analysis grouped simulation scenarios by shipment tracing parameters over diagnostic test sensitivity (Figure 3.5d). Most notably, perfect slaughter traceback investigation scenario (Slaughter: 100%, Trace: 60 months, 70%) was grouped with the best performing tracing scenarios (Trace: 300 months, 90%) (Figure 3.5d). These results are consistent with our analysis of local spread that show a current diagnostic and tracing scenario combined with perfect slaughter traceback investigations results in the fewest transmission events and second highest percentage of local transmission (Table 3.4).

3.4 Discussion

A previous analysis of bTB outbreaks in the state of Minnesota estimated that on average one – 1.5 premises would be infected with bTB and an outbreak would last between 20 – 30 months given a bTB outbreak on a beef or dairy premises [84]. In our study, the median number of infected premises was one and the median duration of an outbreak was 18 months across all outbreak scenarios with diagnostics and control (Table 3.3). The median size of our largest outbreaks for scenarios with diagnostics and control was 13, which is consistent with [74]'s analysis of bTB

outbreaks in Michigan between 1975 and 2017. These outbreaks never infected more than 15 premises [74]. Our median outbreak size estimates are smaller than the values reported in those studies. This could be due to the stochasticity of USDOS or because we only report our summary statistics as medians due to bTB outbreaks being highly bi-modal in USDOS. Another reason our estimates may not exactly match ones from these studies is that we simulate outbreaks in U.S. counties that are representative of Michigan and Minnesota counties in terms of their cattle industry structure, but most of these counties are not in Michigan or Minnesota. This means that we may observe outbreaks that are larger and smaller than the outbreaks in these two studies simply because we are seeding outbreaks in counties outside of those states. Finally, the only other national-scale study of bTB outbreaks in the U.S. predicted many small outbreaks that fade-out naturally, which is what we also observed. Despite distinct differences between model structures and scales, we highlight the similarities between outbreak sizes in these three studies and ours using USDOS to emphasize that our simulated outbreaks capture both the frequently small and more sporadic larger bTB outbreaks that occur in the U.S.

To our knowledge, this is the first national-scale and model-based investigation of bTB transmission and control in the U.S. that explicitly models the shipments of infected animals. Given that new foci of bTB infection are believed to arise from the shipment of infected animals [3,4,68], USDOS' complete shipment network, generated by USAMM, provides a novel context from which to understand national-scale bTB dynamics. This new version of USDOS also includes key aspects of bTB disease dynamics, such as within-herd infection processes and an external force of infection from wildlife reservoirs. The results from this study offer insight into how several features of control and eradication efforts affect bTB outbreaks in the U.S.

We focused on understanding how different aspects of diagnostics and control impact bTB outbreaks. We find that culling infected premises upon the discovery of infected animals resulted in dramatically smaller outbreaks. The addition of shipment trace investigations decreased the size of outbreaks due to more infected premises being culled than in scenarios without trace investigations. This result supports the notion that the principle challenge with controlling bTB outbreaks in the

U.S. is detecting infections, and that shipment trace investigations provide a valuable avenue for doing so [68, 71, 78].

Our sensitivity analysis suggests that the probability of an outbreak taking-off is largely due to the demography of the county that it was seeded in, such as the number of shipments in and out of a county as well as the degree of premises clustering and premises size. This is likely because if an outbreak is seeded in a county where there are many outgoing shipments, without a shipment ban and prior to detecting an infection, there is no way to prevent infected animals from leaving that county or bringing more susceptible animals onto a premises. Bringing more susceptible animals onto an infected premises would increase the duration that a premises is infectious because of the within-herd infection process, and thereby increase the chance that it ships infected animals out. More active and targeted surveillance in counties at higher risk of large outbreaks in combination with shipment restrictions are potential improvements that may help further reduce the probability that a bTB outbreak takes-off [100–102].

Although no intervention scenario completely mitigated the risk of an outbreak taking off, improving various features of diagnostics and control resulted in smaller outbreaks. Perfect diagnostic sensitivity and improved shipment trace investigations resulted in the smallest outbreaks. On the other hand, under current diagnostic and trace investigation parameters, improving the success rate of traceback investigations from slaughterhouses resulted in the largest decrease in outbreak size. The decrease in outbreak size is likely because the only way to trigger shipment trace investigations is after a premises has tested positive for bTB. This finding suggests that slaughterhouse surveillance is the largest bottleneck in the bTB detection process, and highlights the importance of decreasing the time to detection as a key axis to bTB control efforts. There are challenges to improving slaughterhouse surveillance sensitivity due to animal husbandry practices, but these results suggest that investing in increasing slaughter traceback success could help substantially decrease bTB incidence without addressing the sensitivity of any tests [7, 78].

Interestingly, premises size, which otherwise had a strong positive effect on outbreak metrics, displayed a strong negative effect on these same metrics when it interacted with shipment

and slaughter traceback success probability. This could be because slaughterhouse surveillance is more likely to detect infections from premises that ship larger volumes of animals to slaughter. Therefore, slaughterhouse surveillance sensitivity can naturally vary such that if an infection is seeded in at a large premises, the probability of detecting an infection would increase relative to an outbreak seeded at a smaller premises because more infected animals would be sent to slaughter. A higher slaughterhouse sensitivity due to premises-level demography would result in more traceback investigations, thereby increasing the importance of the slaughter traceback success probability. Shipment trace investigation success would also become more important in counties with large premises as it would be the next largest bottleneck in detecting infected premises. Larger premises are then not only a risk factor, but an opportunity to potentially detect more infected animals. These results suggest that in the absence of being able to increase slaughterhouse surveillance sensitivity for all premises and counties, the targeted surveillance of smaller premises that possess other risk factors could help increase the number of infections detected if traceback success can be improved substantially. However, if there are many large premises in a county, the increased premises-level slaughter surveillance sensitivity may be less beneficial due to large premises' role in driving bTB persistence [87].

All modeling requires making assumptions where data are not available or to manage the complexity of the model. We made several assumptions here that may affect our model predictions. Uncertainty surrounding the livestock shipment network generated by USAMM could potentially affect our predictions of bTB spread. This uncertainty is especially important to consider here because bTB transmission is primarily driven by the movement of infected animals, but previous studies with USDOS suggest that model predictions are robust to uncertainty in shipment patterns [42]. We also do not consider the effect of shipment bans on bTB outbreaks because USDOS is only capable of shipment bans down to the county-level. Restrictions on shipments would likely occur at the premises-level if a premises were to be tested for bTB infection is confirmed. Because shipments are not restricted from a premises until it has received a positive test result, we would not suspect a premises-level shipment ban to affect our results because control occurs in the

same time step that a premises is reported. Therefore, no reported infections remain uncontrolled. However, if shipments were restricted from suspected premises in the process of being tested, then a premises-level shipment ban may block the shipment of infected animals for the time step that premises is being tested. Despite USDOS lacking a shipment ban, control scenarios resulted in a proportional decrease in number of shipment-based transmission events, suggesting that merely controlling an outbreak by reducing the size of the infectious pool helps reduce the number of infected animals shipped. Finally, we used a kernel shape and parameters that were estimated for bTB outbreaks in Uruguay. It is reasonable to speculate that a kernel estimated for outbreaks elsewhere may not reflect bTB dynamics in the U.S. However, local spread is such a small proportion of bTB transmission that its effect on overall bTB dynamics in the U.S. is likely minimal.

By simulating bTB outbreaks in counties that are not necessarily affected by bTB, we sampled how a range of cattle industry covariates affect bTB outbreak sizes. Seeding outbreaks in these counties allowed us to show that county demography is the strongest driver of an outbreak's overall trajectory. We have also highlighted how of several features of the U.S.' bTB control campaign impact bTB outbreak dynamics. The results from this study suggest that prioritizing the improvement of slaughter and shipment traceback investigations over the sensitivity of antemortem diagnostic tests could disproportionately improve bTB control efforts. We also find that county-level variation in premises size can change the impact of both shipment and slaughter traceback investigations on the size of an outbreak. Given that slaughterhouse surveillance sensitivity would be difficult to improve due to the inherent structure of the U.S. cattle industry, we emphasize the importance of additional surveillance in counties at risk of generating large outbreaks as well as the counties that send very few animals to slaughter. Ultimately, the findings of this study highlight the difficulty of detecting infections where prevalence is low, and offers several feasible avenues for improving bTB surveillance.

Table 3.1: bTB On-Farm Diagnostic Parameters. Sensitivities are reported for the current and ideal on-farm diagnostic series. The current series is a combination of three tests, sensitivities of which are also presented. The parameters α_{sens} and β_{sens} are the parameters that USDOSv3.0 uses to set diagnostic sensitivity. These parameters give the number of positive tests plus one and negative tests plus one that correspond to the test sensitivity. Parameters for diagnostic testing lag and constraints, which apply to both tests, are also included. The sources for the parameter values are described in Section C.4.

Parameter	**Default Value**	**Reference**
Diagnostic Type: Current series		
α_{sens}	7.6	C.4
β_{sens}	4.9	
Series components		
CFT		
α_{sens}	13.9749	[80]
β_{sens}	3.4714	
CCT		
α_{sens}	5.2957	[80]
β_{sens}	1.2986	
Culture		
α_{sens}	35	[103]
β_{sens}	2	
Diagnostic Type: Ideal Series		
α_{sens}	10000	C.4
β_{sens}	0.1	
Test start to complete lag:	One Month	C.4 & [90]
Monthly constraint	No limit	C.4 & [90]

Table 3.2: Tracing parameters for both slaughter and shipment traceback investigations. t_{max} is the maximum number of timesteps since a shipment occurred that it can be traced.

Parameter	Default Value	Range	Reference
Slaughterhouse traceback investigations			
$p_{success}$	0.5	0.1 – 0.99	[78]
Shipment traceback investigations			
$p_{success}$	0.7	0.1 – 0.99	USDA Ruminant Health
t_{max}	60	12 – 300	[84]

Table 3.3: Summary statistics for select outbreak scenarios. Upper refers to the 97.5th percentile of runs. The IP 'Median (excl 1)' column shows the median number of IPs across runs when excluding runs with only 1 IP. Slaughter:100 represents 100% slaughterhouse traceback success, and the two numbers following trace (e.g. "Trace:") are the number of months post shipment that it is available to be traced as well as the tracing success rate. See section 3.2.3 for further explanation of the nomenclature.

	Duration		IPs			RPs		Epidemic Extent	
Scenario	**Median**	**Upper**	**Median**	**Median Excl 1**	**Upper**	**Median**	**Upper**	**Median**	**Upper**
Base	65.5	300	1	1	553	0	0	1	274
SP:Current	18	140	1	1	12	1	1	1	10
SP:Current-Slaughter:100	18	128	1	1	11	1	1	1	8
SP:Current-Slaughter:100-Trace:60-70	18	108	1	1	10	1	2	1	8
SP:Current-Trace:300-70	18	110	1	1	10	1	2	1	8
SP:Current-Trace:300-90	18	102	1	1	11	1	2	1	8
SP:Current-Trace:60-70	18	131	1	1	13	1	2	1	9
SP:Current-Trace:60-90	18	119	1	1	11	1	2	1	9
SP:Ideal	18	79	1	1	12	1	1	1	10
SPDC:IdealCurrent	18	159	1	1	13	1	1	1	10

Table 3.4: The impact of tracing on the proportion of transmission events attributed to local vs. shipment-based transmission. Proportion local transmission is the number of local transmission events divided by the total number of transmission events.

Scenario	**Local**	**Shipment**	**Events**	% **Local**
Base	3649	648706	652355	0.56
SP:Current	158	14356	14514	1.09
SP:Current-Trace:60-70	172	10084	10256	1.68
SP:Current-Trace:60-90	299	9245	9544	3.13
SP:Current-SlaughterTrace:100	431	10402	10833	3.98
SP:Current-Trace:300-70	606	10374	10980	5.52
SP:Current-Trace:60-70-SlaughterTrace:100	564	8168	8732	6.46
SP:Current-Trace:300-90	924	10205	11129	8.3

Table 3.5: The impact of tracing on identifying and reporting infected premises. All metrics are medians for outbreaks that grew beyond one report because tracing can only be conducted after an initial premises is reported. The last two columns are the percent of infected and reported premises that were identified by tracing.

Scenario	**RPs**	**IPs**	**Add. RPs**	% **IP Trace-ID**	% **RP Trace-ID**
SP:Current-Slaughter:100-Trace:60-70	2	7	1	0.32	0.5
SP:Current-Trace:300-70	2	8	1	0.35	0.5
SP:Current-Trace:300-90	2	7	2	0.45	0.67
SP:Current-Trace:60-70	2	9	1	0.31	0.5
SP:Current-Trace:60-90	2	8	2	0.4	0.78

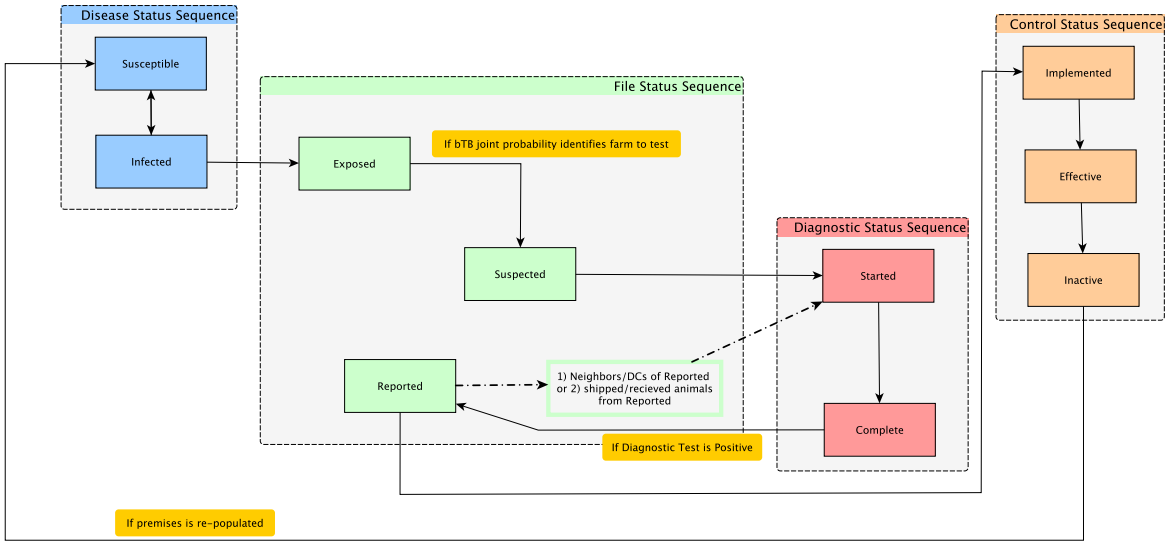

Figure 3.1: USDOSv3.0 status sequence: The box colors represent the different types of statuses that premises in USDOSv3.0 may be assigned. Blue boxes show the disease status sequence, which occurs regardless of the other statuses. The green boxes show the file status, and represent what is known about a premises' disease status at a given time during the simulation, and is only activated when either diagnostics or control is turned on. The red boxes and orange boxes show the diagnostic sequence and the control sequence, respectively. The different arrow types in the file status sequence show the various options that are available. If diagnostic testing for neighbors or dangerous contacts is on, then these will be triggered by a reported premises and follow the dot-dash lines. If shipment trace investigations are on, they occur after a premises has been reported. Farms which test positive will be reported and move into the control sequence if applicable.

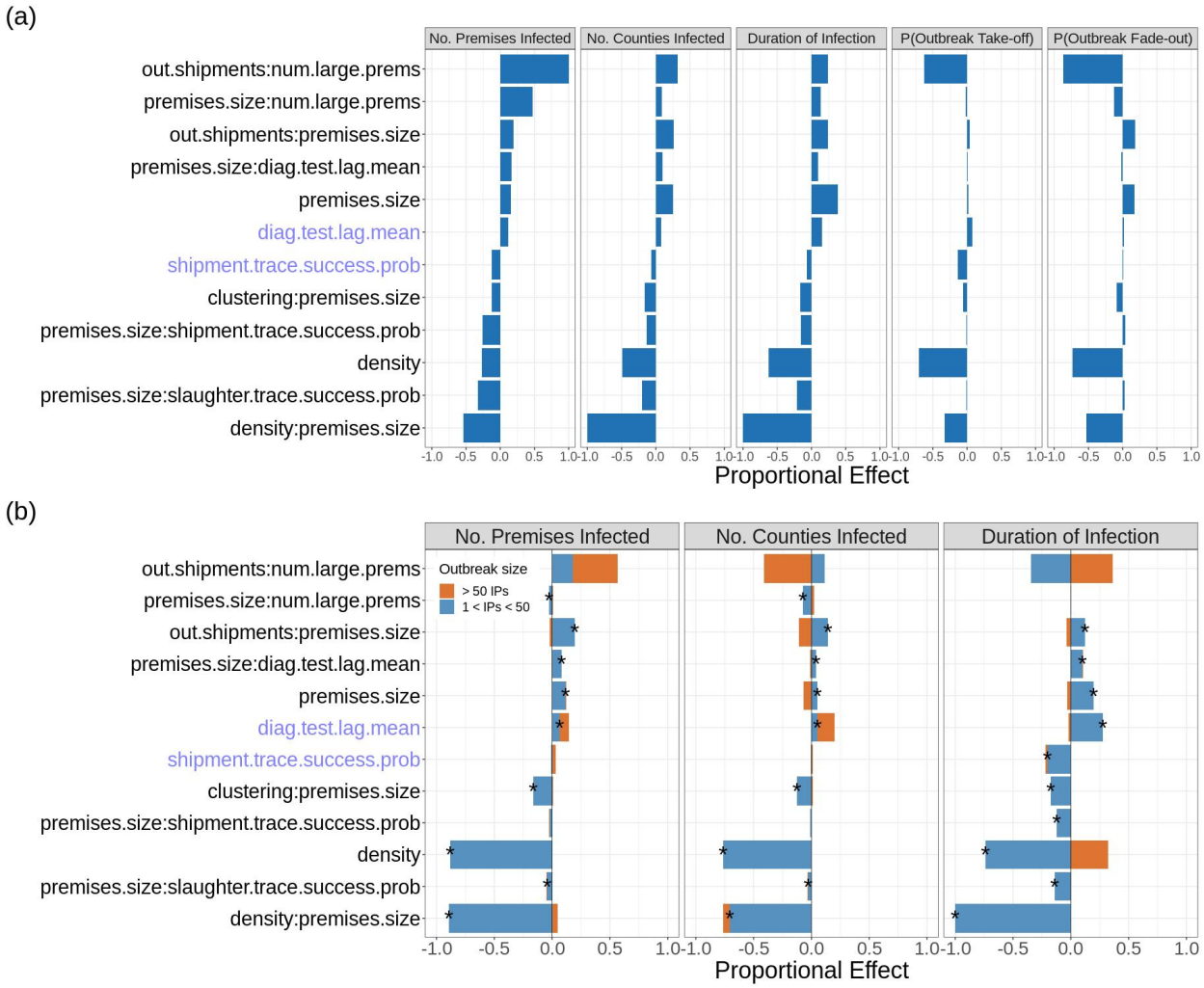

Figure 3.2: Sensitivity analysis of diagnostics and control parameters. Labels for parameters related to county demography are in black and control and diagnostic parameters are in blue. (a) Proportional effect of parameters on outbreak metrics across all outbreaks, including those that take-off and fade-out. All parameters except for premises size is significant ($p < 0.05$) across all five outbreak metrics. (b) Proportional effect sizes of parameters for outbreaks that fade-out (blue) and take-off (orange). Stars indicate parameter has a significant effect on outbreaks that fade-out ($p < 0.05$). No parameter has a significant effect on outbreaks that take-off. Outbreaks that fade-out infect between two and 50 premises and last less than 300 months. Outbreaks that take-off infect more than 50 premises.

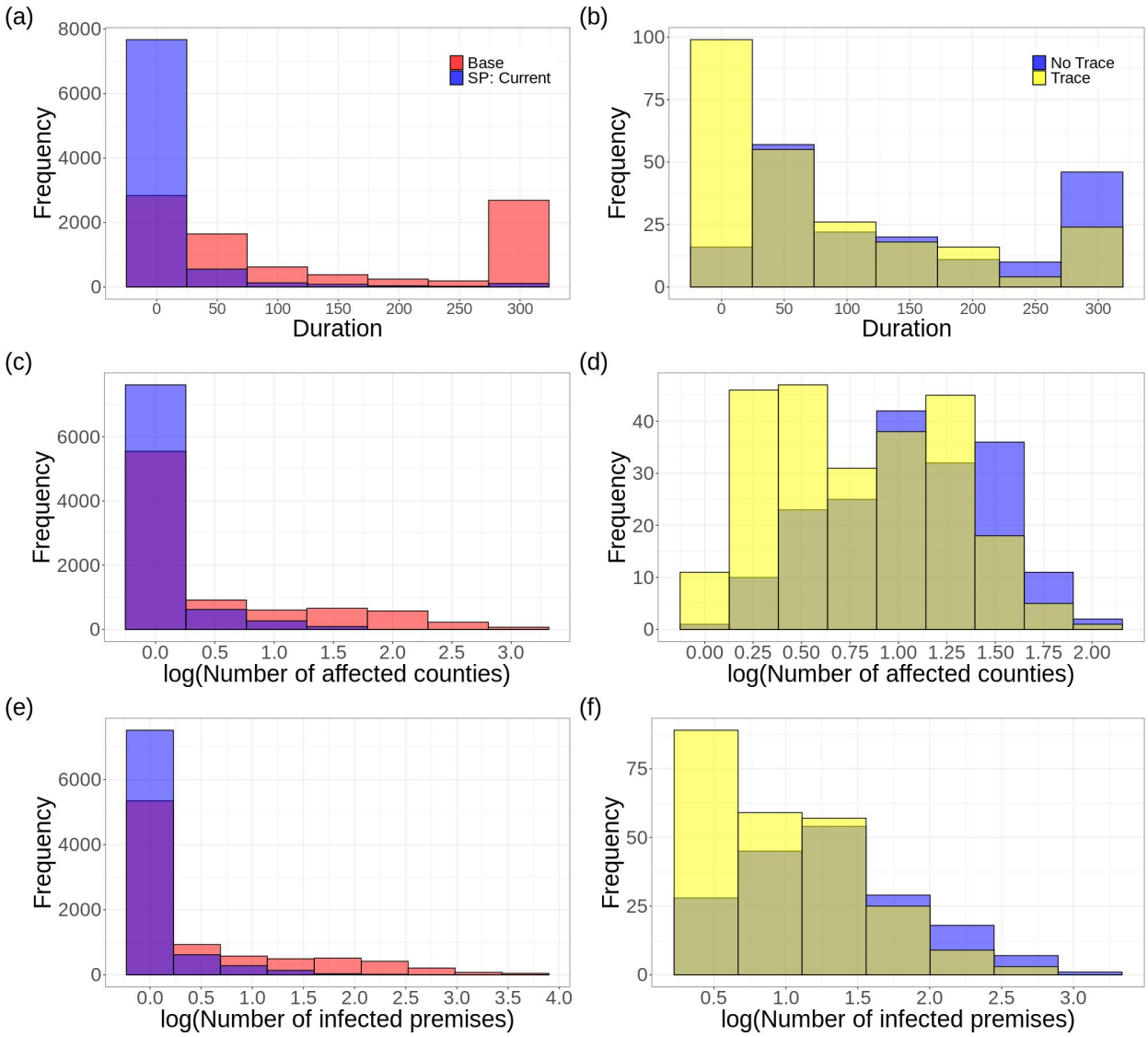

Figure 3.3: Diagnostic testing, culling, and trace investigations result in smaller bTB outbreaks. (a) & (b) Outbreak duration. (a) No control vs. IP culling, and current diagnostic scenario. (b) Current diagnostic testing scenario and IP culling with and without tracing. The same scenarios are using in the panels below. (c) & (d) Number of affected counties. (e) & (f) Number of infected premises. Panels with tracing (b,d,f) only include outbreaks where more than one premises is reported.

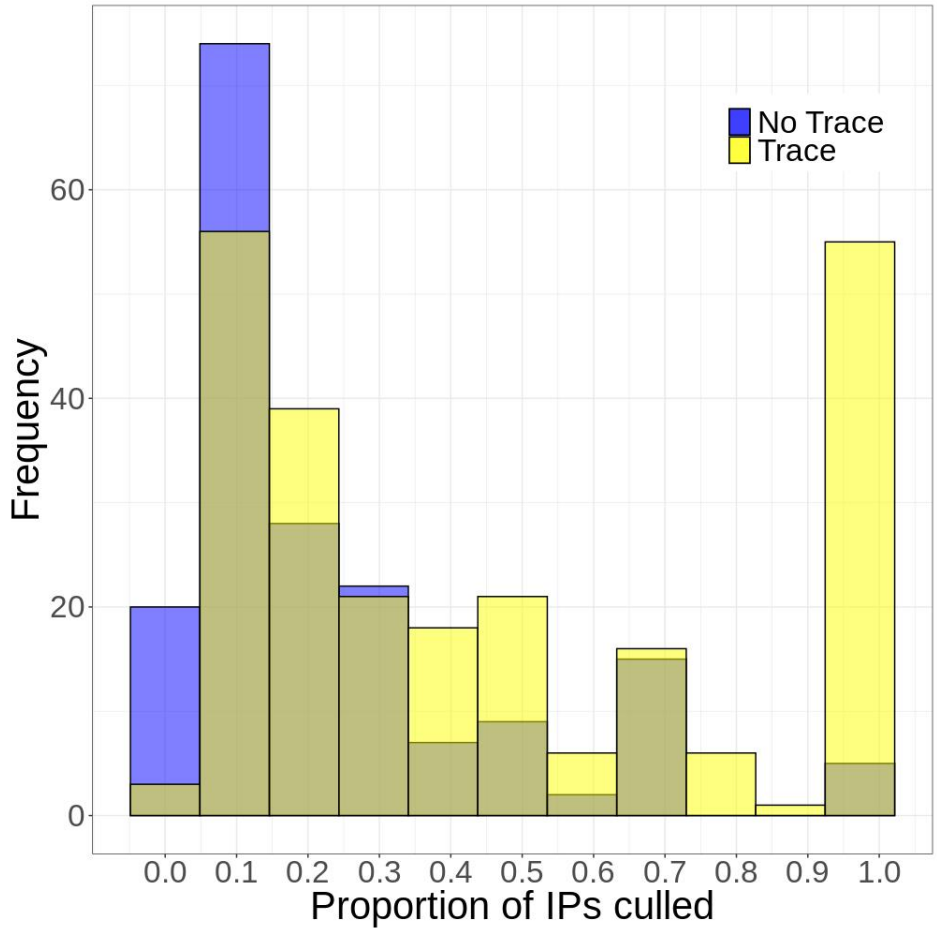

Figure 3.4: Histogram of the proportion of infected premises culled with and without tracing for a SP: Current diagnostic and Trace: 60, 70% scenario in blue and current diagnostics-only scenario in yellow.

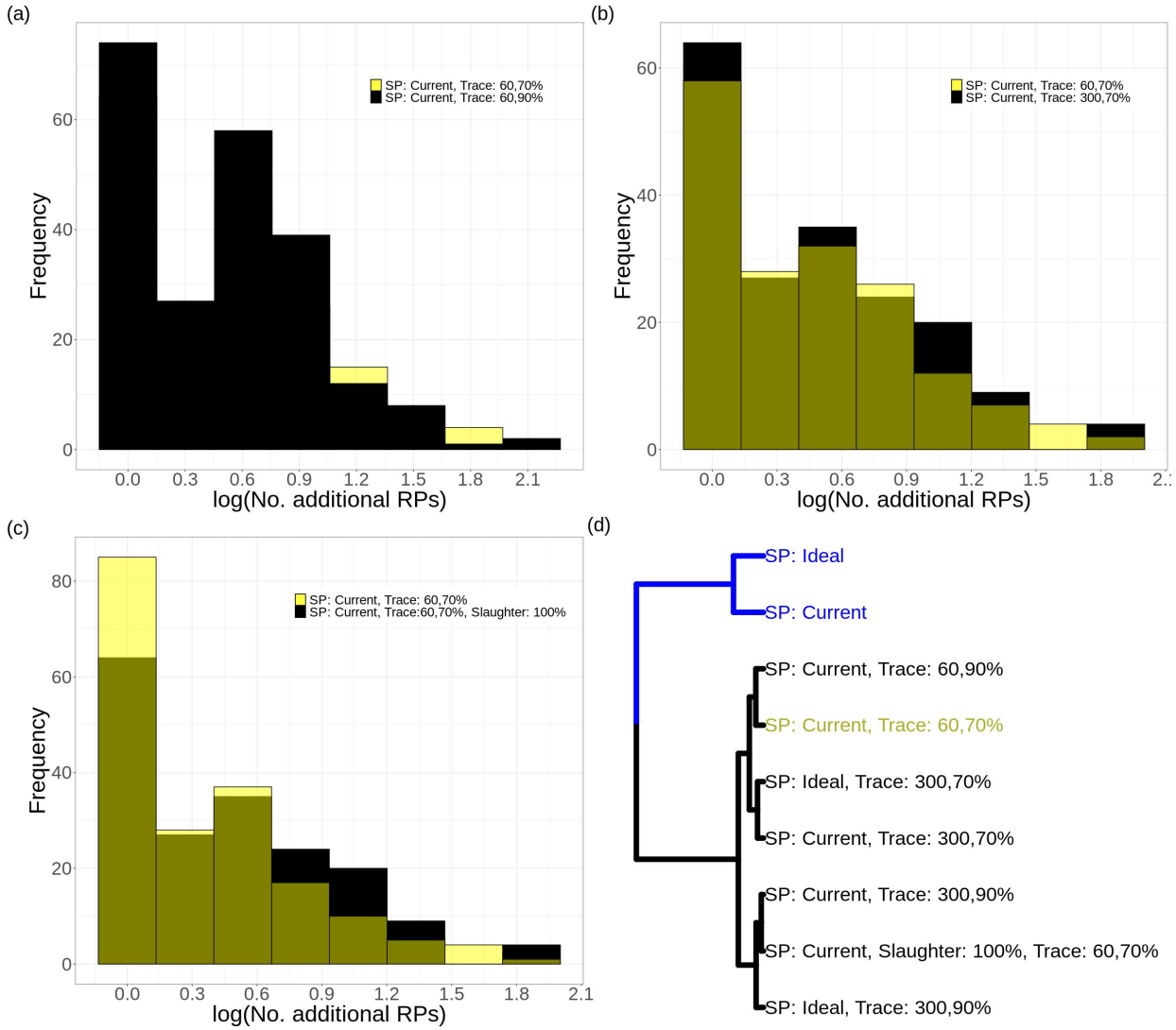

Figure 3.5: Improvements to several features of bTB surveillance can increase the number of infected premises identified. Yellow colors indicate a current diagnostic test scenario with tracing that can investigate shipments from the past 60 months and are 70% successful. Black colors are the improved tracing scenario. Blue colors on the dendrogram are diagnostics scenarios without tracing. (a) The number of reported premises when shipment trace investigations are improved such that a higher percentage of infected origin and destination premises are identified (Trace: 60,90%). (b) The number of reported premises when managers can use shipment records from the past 25 years (the maximum outbreak duration) instead of only the past five years to identify origin and destination premises (Trace: 300,70%). (c) The number of reported premises when slaughter traceback investigations become perfect (Trace: 60,90% with perfect traceback success from slaughterhouses). (d) Dendrogram from a hierarchical cluster analysis using euclidean distance and a complete linkage agglomeration method.

Chapter 4

Conclusions and future directions

I have illustrated how various aspects of control impact both national-scale FMD and bTB outbreaks in the U.S. USDOS provides a novel context for understanding the questions posed in the chapters above for several reasons. Although studies have investigated how control strategies that change conditionally on the state of the outbreak interact with resource constraints [35,38,58], none have evaluated the effect of these strategies in a setting as realistic as USDOS. I also presented the first model-based national-scale study of bTB outbreaks that explicitly models the shipment of infected animals between premises in addition to within-herd dynamics. USODS predictions of bTB outbreaks matched expected bTB outbreaks sizes, and therefore offer a realistic picture of how diagnostics and control changes bTB outbreak dynamics.

Despite different transmission modes and timescales, results from both of these studies share similarities that speak to fundamental principles of infectious disease outbreaks. Outbreak sizes were highly bimodal for both FMD and bTB, where the vast majority of seeded outbreaks did not spread beyond the initial index infection, and most infected fewer than 10 premises. In these cases, differences between control strategies had a negligible effect on outbreak size, likely because reporting and detection delays meant the outbreak subsided by the time control was able to be implemented. However, differences became apparent for the outbreaks that grew very large.

Control drastically reduced magnitude of the largest outbreaks and the frequency with which they occur. However, the underlying demography of the population that an infection is seeded in ultimately dictates the overall trajectory of an outbreak. The sensitivity analyses in both studies showed that county attributes related to husbandry practices are the strongest drivers of the probability that an outbreak grows very large or eventually fades-out. Given relatively little variation between the best performing control strategies in both systems, identifying the best possible control strategy may be secondary to improving our ability to respond quickly to an outbreak.

In both studies, I showed that decreasing the time decide on implementing the next control measure and detecting infection helps reduce the size of these larger outbreaks. My results are consistent with the understanding that slaughterhouse surveillance is the largest bottle-neck in the bTB detection process. I observed the largest decrease in outbreak size when I allowed slaughter surveillance traceback operations to become 100% successful, suggesting that supporting the identification of the first infected premises was critical to managing the size of bTB outbreaks. In the FMD study, delays associated with decision-making exacerbated the worst outbreaks. Results from both of these studies emphasize the importance of early detection and early action.

There are a few key differences between the FMD and bTB systems should be highlighted and provide important context for understanding these findings. Compared to the bTB system, control is highly resource limited during large FMD outbreaks, which often means that there are large lags between when a premises is identified for control and when the premises is controlled. Therefore, prioritizing where resources are used is much more critical, whereas the primary challenge is detecting infections before new infection foci are established in the bTB context. On the other hand, the FMD study does not investigate bottlenecks in the FMD detection process as animals develop visible lesions, unlike bTb where animals can be cryptically infected. Therefore, the landscape on which the control of bTB takes place looks very different than that of FMD.

These studies offer several possible future directions to improve our understanding of the impact of decision-making and control on infectious disease outbreaks. In the FMD study, decision-making processes are represented linearly when in reality decision-making processes are not linear. In addition, while control measures can be switched on and off in response to changes to an outbreak's trajectory, the overall control strategy (e.g. the interventions being used and when they are implemented) cannot be changed during simulated outbreaks. It would then be interesting to allow for the overall control strategy to be updated based on how it has performed in previous time steps and simulations, which would more accurately reflect the cyclical nature of decision-making processes. This type of study would reveal whether real-time feedback from ongoing outbreaks can help improve a control policy and highlight which control strategies are most frequently suc-

cessful. A similar study to this suggestion has been done, but on a highly simplified landscape that did not consider the full range of available control measures, and therefore cannot be used for recommending policy [58]. It would also be interesting to evaluate whether state-dependent control would be useful for addressing outbreaks of less transmissible infections, like bTB. However, given the vastly different timescale on which bTB outbreaks are detected and controlled, a state-dependent control strategy may provide no economic benefit because managers are already afforded the time to consider an outbreak's trajectory prior to implementing control.

Finally, perhaps the most important future study that could be drawn from the results of this thesis is one that evaluates the impact of targeted surveillance strategies on counties susceptible to producing large bTB and FMD outbreaks. Here, seed counties with many large premises and lots of shipments entering and leaving them consistently produced the worst FMD and bTB outbreaks. Given this, targeted surveillance and control in these counties may help reduce the size of an outbreak should one occur. It would also be useful to understand if actively targeting different types of premises, like dairy farms or feed lots, for surveillance would aid in detecting outbreaks before they become uncontrollable. These additional studies about decision-making and the targeted response efforts could help further clarify the role of control in mitigating both FMD and bTB outbreaks.

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Appendix A

Chapter 2: Supplemental Methods

A.1 Local disease transmission

We briefly review the kernel that dictates the probability of transmission here, but see [43] for a full description of local transmission in USDOS. Local disease spread in USDOS is dictated by a distance-dependent spatial transmission kernel. This kernel represents all modes of transmission that are not shipments with infected animals. We model the probability of disease transmission from infectious premises i to susceptible premises j as

$$1 - \exp(-a_c h_i b_c h_j K(d_{i,j})), \tag{A.1}$$

where a_c is the transmission parameter for infectious herd, h_i, and b_c is susceptibility parameter for susceptible herd, h_j. Distance-dependent kernel function, K, is defined as

$$K(d_{i,j}) = \frac{k_1}{1 + (\frac{d_{i,j}}{k_2})^{k_3}}, \tag{A.2}$$

where $d_{i,j}$ is the shortest distance between between premises i and premises j. k_2 is the scale parameter, k_3 is the shape parameter, and k_1 is a normalizing constant that scales the function such that

$$\int_0^\infty 2\pi r K(r) dr = 1, \tag{A.3}$$

where r stands for $d_{i,j}$.

A.2 Shipment-based long range disease transmission

Long-distance disease transmission in USDOS is driven by livestock movements within the continental United States. USDOS uses random draws from the United States Animal Movement Model (USAMM) posterior distribution to predict the probability that a shipment between two premises occurs. A model is necessary to inform animal movements in USDOS because the U.S. lacks a national database of all cattle shipments between premises due to individual states being largely responsible for tracking shipments that enter and leave their borders.

USAMMv3.0 is a heirarchical Bayesian model that determines the probability of observing an intrastate cattle shipment between two premises given a 10% sample of 2009 ICVI data. The probability and number of animals in a shipment depends upon the size (head of cattle) and type of premises (dairy, beef, feedlot, or market). The size of each shipment is modeled as either a gamma-Poisson or beta-binomial random variable depending on the type and size of the origin and destination premises. Because ICVI data cannot directly connect premises, USAMM assigns origin and destination premises based upon county characteristics and premises demography. Receiving premises become infectious the day after a shipment with infectious animals arrives. If a premises receives a shipment from an exposed premises then the receiving premises becomes infectious at the same timestep as the sending premises. See [46] for a complete description of USAMMv3.

A.3 Premises demography

Premises in USDOS may be general beef or dairy premises, feedlots, or markets. The number and size of premises in each county are from the 2012 and 2017 National Agriculture Statistics Service (NASS) results [48]. Because the NASS does not provide U.S. cattle premises locations and these data are not publicly available elsewhere, except for markets, USDOS premises size and locations are predicted by the Farm Location and Agricultural Production Simulator (FLAPS) [47]. FLAPS projections are based upon environmental covariates that are important for livestock production [47]. We used 10 different FLAPS realizations during simulations to capture uncertainty about premises locations and sizes [43].

Market locations and sales data are publicly-available, but not for all markets in the United States. To generate market sizes we used a previously compiled list of markets to generate a data set of all markets in the U.S. and their annual sales [96]. We verified market locations and volumes from [96] and completed the list using information from USDA APHIS Federally Approved Market List, USDA 89 GIPSA, USDA Agricultural Marketing Service (AMS), and Livestock Market Association 90 (LMA). We fit a spatial model to existing market volume estimates to predict volumes for markets that did not have publicly available sales data [97]. County-level market volume estimates were divided by the number of markets in a given county to produce premises-level market volume estimates. These estimates were then combined with each of the 10 FLAPS realizations. Access information and a full description of how these data were generated can be found in [97].

A.4 Partial transition of disease states

In addition to classifying all premises as susceptible, exposed, infectious, or immune, USDOS considers within-herd dynamics to determine the infectiousness of premises at time t. Therefore, the rate at which infectious premises i infects susceptible premises j depends upon the number of infected animals on premises j at time t and is modeled as

$$\begin{aligned} rate_{(i,j)} =&([N_{(beef,j)}^{p_{beef}}]S_{beef} + [N_{(dairy,j)}^{p_{dairy}}]S_{dairy}) \times ([I(t)_{(beef,i)}^{q_{beef}}]T_{beef} \\ &+ [I(t)_{(dairy,i)}^{q_{dairy}}]T_{dairy}) \times K(d_{ij}) \end{aligned} \tag{A.4}$$

where $N_{(beef,j)}$ is the number of beef cows on premises j and $N_{(dairy,j)}$ is the number of dairy cows on premises j. $I(t)$ is the number of infectious animals at time t at any given beef or dairy farm. Power law parameters, p_b and q_b, force a non-linear increase in susceptibility and transmissibility as the number of animals on a premises increases. Infection spreads between premises via the transmission kernel K according to $d_{(i,j)}$, the distance between premises i and j. S_b and T_b are the

susceptibility and transmissibility measures for premises of type b. A complete description of the partial transmission process can be found in [42].

A.5 Control

A.5.1 Movement bans

Shipment bans simulate state and county-level restrictions on moving animals between premises. They are triggered with the first newly reported infection in a region. Every outbreak simulation included state-wide shipment bans that remained in place for the duration of the outbreak.

A.5.2 Culling

Culling is the depopulation of premises to reduce the number of infectious animals. We assumed culling to be 100% effective at eliminating transmission between infectious and susceptible animals. We assumed that animal carcasses could only be disposed of in the state in which they were culled via burial in solid waste landfills that are capable of handling them. We determined the location and size of landfills capable of handling carcasses from the Environmental Protection Agency's Envirofacts database [104]. We allowed 5% of every capable landfill to be used for carcasses. Therefore, the total number of animals that can be culled is constrained at the state-level based on the number and size of landfills in a state (Table 2.2). Culling was also constrained daily by a processing time parameter to account for the time and resources needed to remove animals and transport them to landfills (Table 2.2).

A.5.3 Vaccination

Vaccines only become available on the sixth day of an outbreak to reflect the time required to develop a high-potency vaccine (Table 2.2). After the 14th day of an outbreak, 500,000 vaccines are available per week until 2.5 million vaccines are administered. Vaccines are no longer available after 2.5 million doses are administered (Table 2.2). We assume that only one vaccine must be

administered per animal. We also constrain the number of animals that can be vaccinated per day based on bovine tuberculosis testing times (table 2.2).

We assumed that vaccines were 90% effective at preventing premises-level infection after an exposure. Premises-level vaccine efficacy was modeled by treating every animal as a Bernoulli trail where p = vaccine effectiveness such that the effective herd size after the vaccination of an entire premises is a binomial random variable with n = herd size and p = 1 – vaccine effectiveness. This means that, on average, 10% of the herd will remain susceptible after the premises is vaccinated. After vaccination, only the susceptible animals were involved in exposure or infection calculations. All other control parameters used in simulations are included in table 2.2.

Table A.1: USDOSv2 Transmission Parameters

Parameter	**Default Value**	**Range**	**Reference**
Cattle transmission rate (a_c)	10.252	3.6– 100	[43]
Cattle susceptibility (b_c)	1	n.a.	[43]
Normalising constant (k_1)	$1.46e^{-08}$	$4.07e^{-10}$– $3.91e^{-08}$	[43]
Scale parameter for spatial kernel (k_2)	1686.16	1686.16– 5414.72	[43]
Shape parameter for spatial kernel (k_3)	2.267	2.022– 3.006	[43]
Latency period	5 days	3–13 days	[43]

Table A.2: FMD partial transition parameters.

Parameter	**Description**	**Value**	**Reference**
t_σ	Final day on which there are only susceptible or exposed animals	0 days	[42]
$t_{S=0}$	Time at which all animals are infectious	4 days	[42]
γ	Recovery rate of animals per day	0.44	[42]
r	Rate of increase of number of infecteds	r_0 = 0.05, r_1 =0.006	[42]

Appendix B

Chapter 2: Supplemental Results

Table B.1: Generalized linear model results for P(Complete Control Sequence) analysis.

Term	**Estimate**	**Standard error**	**Statistic**	**P-value**
(Intercept)	-16.5328325	0.2386872	-69.26569	0.0e+00
factor(delay)1	7.3356800	0.3189447	22.99985	4.7e-117
factor(delay)2	7.9597017	0.3198233	24.88781	1.0e-136
factor(delay)3	6.3903172	0.4185321	15.26840	1.2e-52
Duration	0.4661387	0.0068342	68.20656	0.0e+00
factor(delay)1:Duration	-0.3718220	0.0074770	-49.72873	0.0e+00
factor(delay)2:Duration	-0.4062640	0.0071286	-56.99099	0.0e+00
factor(delay)3:Duration	-0.4123055	0.0071129	-57.96621	0.0e+00

Table B.2: Generalized linear model results for P(Fade-Out) analysis.

Term	**Estimate**	**Standard error**	**Statistic**	**P-value**
(Intercept)	-2.7193971	0.0081651	-333.0494725	0.0e+00
factor(delay)1	0.0416724	0.0114426	3.6418575	2.7e-04
factor(delay)2	0.0076817	0.0115076	0.6675355	5.0e-01
factor(delay)3	0.0219512	0.0114777	1.9125131	5.6e-02
Duration	0.0056098	0.0001182	47.4513418	0.0e+00
factor(delay)1:Duration	-0.0017551	0.0001596	-10.9958426	4.0e-28
factor(delay)2:Duration	-0.0032881	0.0001490	-22.0711532	6.0e-108
factor(delay)3:Duration	-0.0033467	0.0001486	-22.5166190	2.9e-112

Table B.3: Proportion of outbreaks that faded out prior to reaching 365 days. Each control policy received a total of 304,900 simulations.

Control policy	**Control policy type**	**Delay**	**No. $<$ max duration**	**% $<$ max duration**
MB, IP Cull, 10km Cull	Static control	0	304842	0.9998098
MB, IP Cull, 3km Cull, 10km Cull	State-dependent control	3	301418	0.9885799
MB, IP Cull, 3km Cull, 10km Vax	Static control	0	304818	0.9997311
	State-dependent control	3	300370	0.9851427
MB, IP Cull, 3km Vax	Static control	0	295628	0.9994793
	State-dependent control	3	299119	0.9810397
MB, IP Cull, DC Cull	Static control	0	304880	0.9999344
	State-dependent control	3	299278	0.9815612
MB, IP Cull, DC Vax	Static control	0	304803	0.9996819
	State-dependent control	1	304445	0.9985077
		2	298960	0.9805182
		3	299131	0.9810790
No control	No control	No control	297978	0.9772975

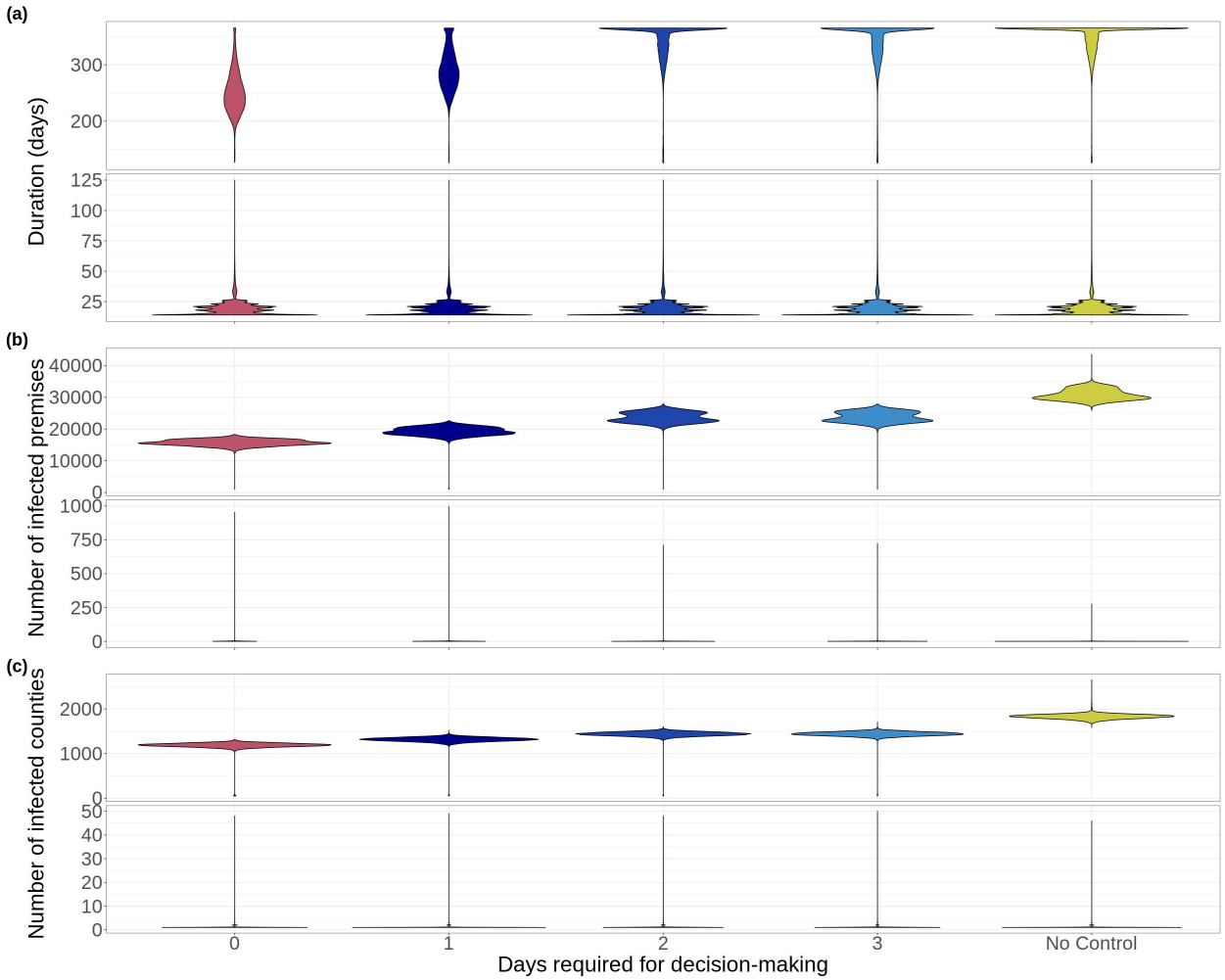


Figure B.1: Delays associated with decision-making exacerbate differences between control strategies. Static control policies are in red, state-dependent control policies in blue, and no control in yellow. Vertical axes are faceted by outbreak size, such that 97.5% of outbreaks are in bottom panel for each outbreak metric and the largest 2.5% of outbreaks are the top facet for each metric

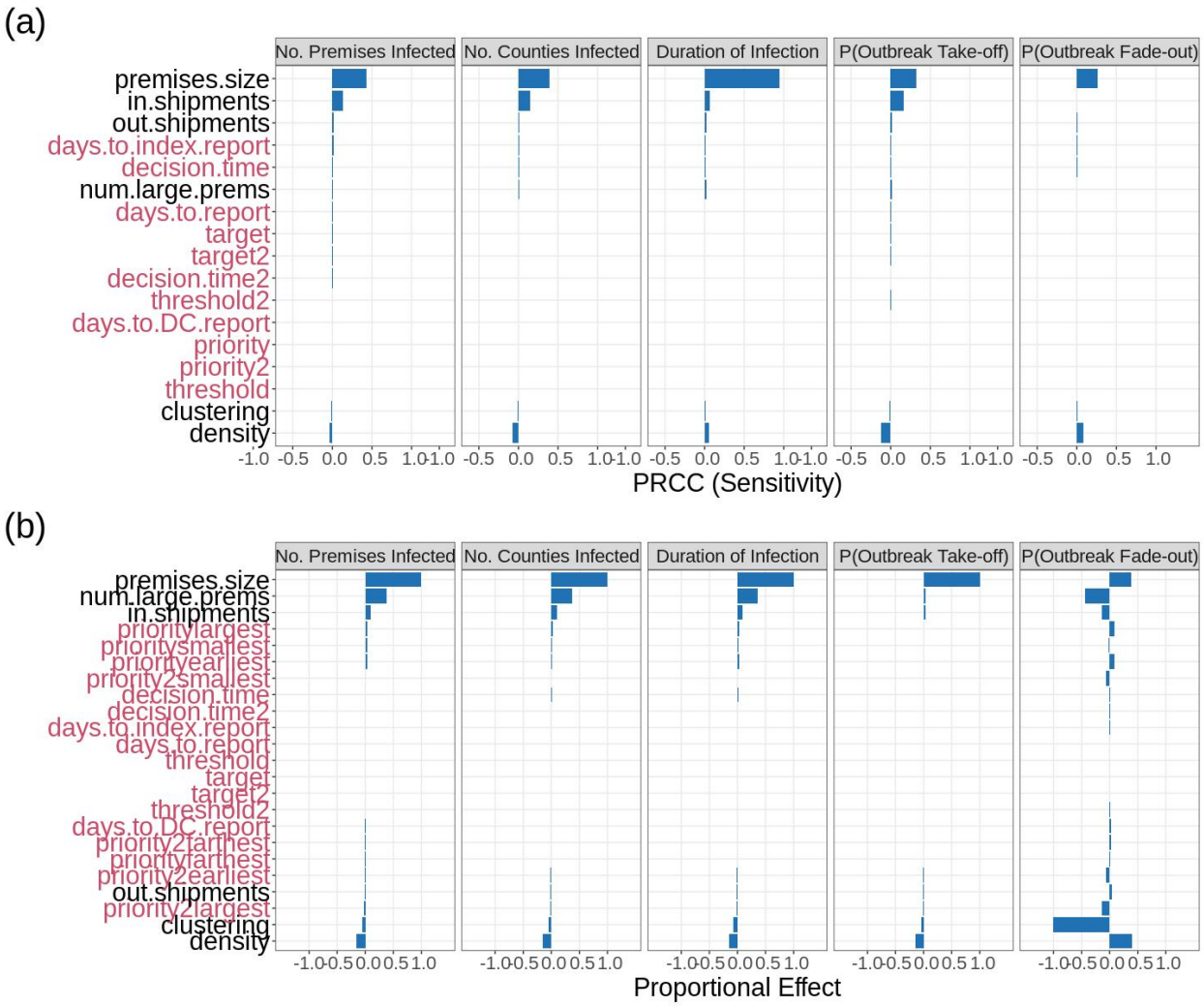
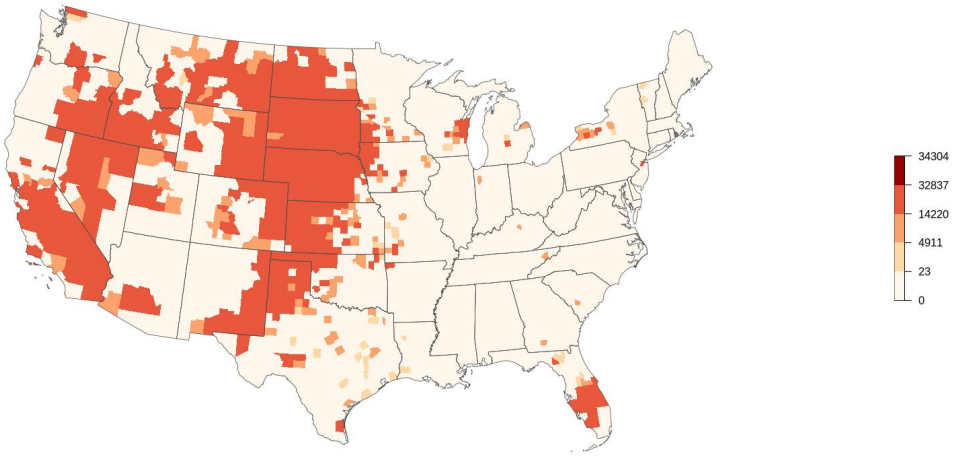
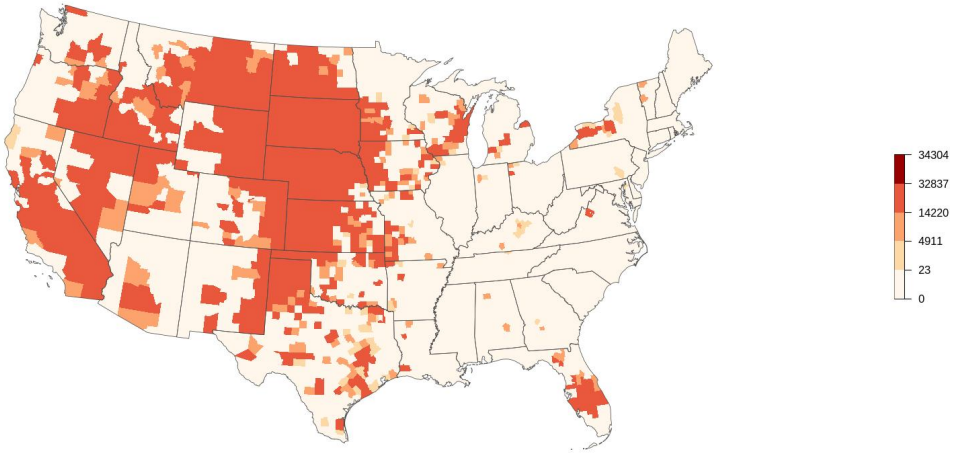


Figure B.2: Sensitivity analysis Partial Rank Correlation Coefficient (a) and linear model (b) results.



(a)



(b)

Figure B.3: The spatial distribution of where large outbreaks are seeded is similar for (a) static control and (b) state-dependent control. State-dependent control policy included a three day decision-making delay. The number of infected premises for upper 97.5% when an outbreak is seeded in a given county.

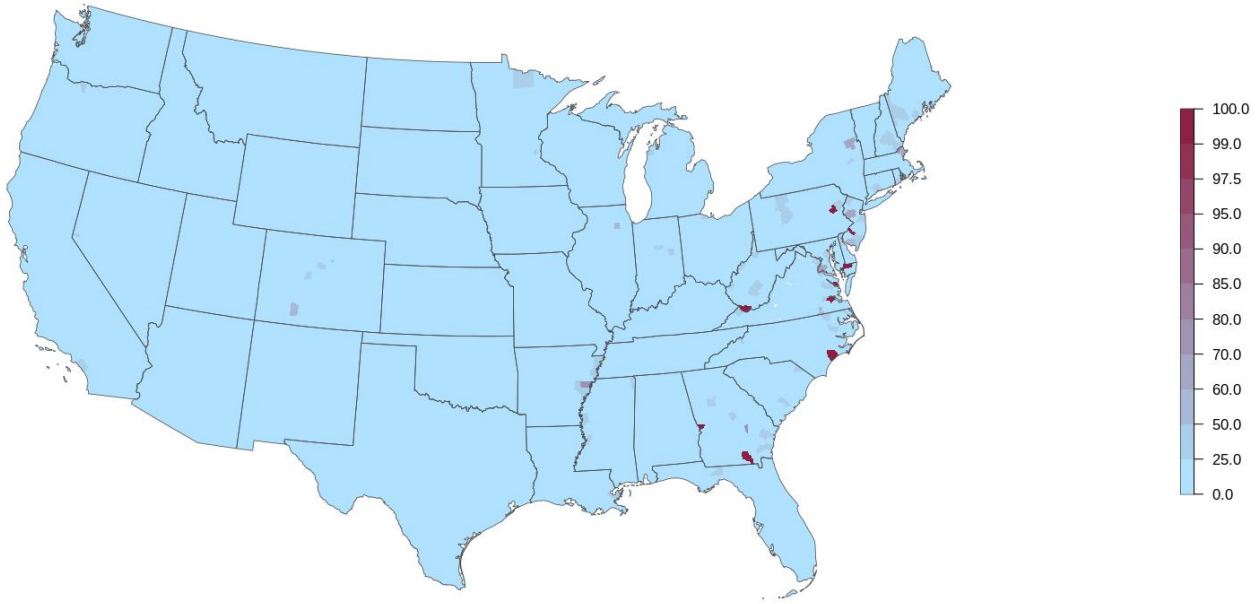


Figure B.4: Difference between the proportion of infections attributed to local vs. shipment-based transmission when state-dependent and static control are implemented. State-dependent control policy included a three day decision delay. Higher numbers mean more local transmission occurred when state-dependent control was applied.

Appendix C

Chapter 3: Supplemental Methods

C.1 Statuses

The file status of a premises reflects what is known about the disease or risk status of a premises. File statuses are used to trigger diagnostic or control sequences to begin. File statuses include, suspected (premises thought to be infected but not confirmed by diagnostic test), reported (confirmed infected premises), or Dangerous Contact (DC). DCs are premises that are known to have a higher risk of infection because of any epidemiological link (not limited to direct contacts). Premises are first assigned an Exposed status when they move into the infected disease status. Premises that are file status Exposed, can then move to file status suspected if they are identified through slaughter surveillance (Equation 3.2). Premises that are file status suspected trigger the diagnostics sequence. If premises test positive they move to file status reported.

Diagnostic and control statuses reflect what is known about a premises and the diagnostic or control actions that have been applied. The diagnostic status sequence is: Started (diagnostic testing has begun but is not finished), and Complete (diagnostic testing has finished, and the test result has been determined). The time that it takes to complete a diagnostic test, called the test started to complete lag, can be changed by USDOS parameters (Table C.2) [90]. The control status sequence in USDOSv3.0 is the same as it was in USDOSv2.2 and is as follows: Implemented (control action has been applied), Effective (control action is in effect and transmission is reduced or stopped depending on the effectiveness of the applied control), and Inactive (an optional status, which can be used to increase transmission on a controlled premises if the applied control action becomes less effective after a period of time). Similar to the diagnostic test lag time, the time that it takes to move through the different control statuses is parameter based. The disease, diagnostics, and control statuses progress independently of each other.

C.2 Open Population Dynamics

The replacement of animals on a premises via shipments was a stochastic process, so an infected premises could send a shipment with only susceptible animals. The prevalence on the shipment was determined by treating the number of animals in the different classes on the shipment as a hypergoemetric random variable (which is similar to a multinomial one, but without replacement), which meant animals were effectively picked at random from the infection classes on the sending premises.

Each new animal added to the receiving premises' herd was assumed to replace one animal that was already present, regardless of the infection state of either animal. Each such substitution event was also modeled as a multivariate hypergeometric random variable similarly to the prevalence of shipments. First, the number of animals to be removed were sampled from the classes, and after they had been removed, the new animals were added to the class they belong to.

Lastly, shipments to slaughter from infected premises were also modeled explicitly. Each premises had a monthly slaughter shipment rate according to which slaughter shipments arise (Equation 3.2). When that happened, the number of animals that were shipped were sampled from the sending premises, once again as a hypergeometric random variable, and were replaced by susceptible animals.

By always replacing any animal that is removed, the herd sizes were kept constant throughout time and only the prevalence of infection changes. One exception is that we allowed premises to change the total herd size in the bTB model once every quarter of the year, while keeping the prevalence fixed. This reflects seasonal changes in premises' sizes that are thought to play a role in the population dynamics underlying the transmission patterns of bTB [105].

C.3 Local Spread Kernel

Although the main route of transmission of bTB between premises is via shipments of infected animals, there is still a possibility of local spread which was modeled using a local spread kernel for bTB. The kernel models the probability of infection as a function of the distance between an

infected premises and any other susceptible premises. As there has not been such a kernel fit to U.S. bTB outbreak data, we used the kernel shape and parameters estimated by [14] for bTB outbreaks in Uruguay,

$$P(\text{farm } i \text{ infects farm } j) = \frac{I_i}{N_i}\phi \exp\left(-\gamma d_{ij}\right). \tag{C.1}$$

Here I_i is the number of infectious animals on premises i, N_i is the total herd size of i; ϕ and γ are kernel parameters and $d_{i,j}$ is the distance in kilometers between i and j. The kernel parameters were estimated in [14] to be $\phi = 0.05$ and $\gamma = 1.46$ and we have used these values as default, dividing γ by 1000 to translate the kernel to the scale of meters, which is what USDOSv3.0 uses internally.

The kernel from [14] does not include any transmission via wildlife and therefore we combined the local spread kernel with a wildlife component in order to construct a mixed local-wildlife transmission kernel, C. The wildlife component is a normal distribution fit to white-tailed deer movements, describing the probability of a premises being visited by white-tailed deer each month. It does not provide any information about wildlife transmission and therefore we scaled the combined kernel to have the same volume under the function as the original kernel from [14], which allows the wildlife component to affect the shape of the kernel, but not the total infection pressure,

$$C(d_{ij}, w_\omega) = V_L\left(xw_\omega \frac{W(d_{ij}, \mu_q, \sigma_q)}{V_{W,q}} + (1-x)\frac{L(d_{ij}, \phi, \gamma)}{V_L}\right), \tag{C.2}$$

where W is the normal distribution pdf, with seasonal (q) white deer movement parameters μ_q and σ_q fit to data from a deer collar study; L is the local spread kernel and V_L and V_W are constants which normalize the respective function to have the volume 1.0. The parameter $x \in [0, 1]$ gives the relative weight that should be given to the wildlife component, i.e. if $x = 1.0$ only the wildlife component will control the shape of the combined kernel, and vice-versa if $x = 0.0$. The process of normalizing the kernels guarantees that the volume of C is constant and equal to the volume

of the local component, L, regardless of what value x takes. The parameter w_ω is the normalized (divided by national average) white tailed deer density of county ω to which i belongs.

Table C.1: The parameters controlling the transmission processes and within-herd (WH) dynamics for bTB simulations with USDOSv2.1.1 and the range of values used for sensitivity analysis.

Parameter	**Default Value**	**Sens. analysis range.**
Between premises transmission parameters		
Local kernel scale (ϕ).	0.05	[0.01, 0.25]
Local kernel shape (γ).	0.00146	[2.92e-4, 7.3e-3]
Wildl. kernel, quarterly means, μ_1, μ_2, μ_3, μ_4.	73.39, 67.21, 70.03, 112.13	-
Wildl. kernel, quarterly standard deviation, σ_1, σ_2, σ_3, σ_4.	280.60, 233.25, 223.69, 307.68	-
Relative weight of wildlife component, x.	0.5	[0, 1.0]
Within-herd bTB model parameters		
Birth rate of dairy premises.	0.05	[0.01, 0.25]
Mortality rate of beef premises.	0.02	[0.004, 0.1]
Mortality rate of dairy premises.	0.05	[0.01, 0.25]
Import rate of beef premises.	0.49	[0.098, 2.45]
Import rate of dairy premises.	0.09	[0.018, 0.45]
Base bTB transmission rate.	3.0	[0.6, 15.0]
Cattle-to-cattle contact rate.	1.0	[0.2, 5.0]
Mean and rate of gamma distributed transition rate *exposed 1* $\rightarrow$ *exposed 2*.	9.75, 0.21	-
Mean and rate of gamma distributed transition rate *exposed 2* $\rightarrow$ *infectious*.	1.6, 1.85	-

C.4 On-farm diagnostics

The tuberculin skin test, also known as the caudal fold test (CFT), is an antemortem test to detect an immune response to *Mycobacteria sp.* in animals with tuberculosis [106]. About 72 hours after tuberculin is injected into animals affected with tuberculosis (any strain), a characteristic swelling reaction appears at the point of injection. Animals with detectable swelling are recorded as responders. Additional tests are required for responders because the tuberculin cross-reacts with several *Mycobacteria sp.* Cattle that respond to the CFT must be followed with additional tests, such as the comparative cervical test (CCT). The CCT consists of injecting bovine purified protein

derivative (PPD) tuberculin and avian PPD tuberculin at separate sites in the mid-cervical area. The probable presence of bovine tuberculosis (*M. bovis*) is determined by comparing the response of the two tuberculins at 72 hours (plus or minus 6 hours) following injection. Animals that respond to the PPD tuberculin on the CCT are classified as suspects or reactors. While histopathology, diagnostic bacteriology, and PCR assay of formalin-fixed tissue are all supplemental diagnostic procedures approved for use in bTB eradication, culture of the organism remains the gold standard for a confirmatory diagnosis.

Diagnostic resource constraints come into effect before the premises moves to the status Started. Once a premises is identified for diagnostic testing by a certain type of test it moves onto the test type-specific waitlist. Then the availability of resources for that diagnostic type is checked to determine if there are sufficient resources to test the premises. If resources are available the premises moves to the Started status. If resources are limited and the premises cannot be tested, it will stay on the waitlist until resources become available. Premises are tested in the order in which they were identified as diagnostic test targets.

C.5 Number of infected animals shipped to slaughter

The number of infected animals that were shipped to slaughter from a premises in a timestep had two main components: the number of infected animals to ship and the rate of shipment to slaughter.

We first calculated the proportion of a premises' inventory that would ship to slaughter each year (see Table C.2). The estimated proporiton is based on Excel models capturing the annual dynamics of the U.S. beef and dairy cattle inventory (USDA, personal communication). These models were built using NASS data [107]. Using the January 1 total inventory, plus data on the number of calves born, cattle slaughtered, and cattle in various size and age classes, the model reproduced the January 1 inventory of the following year. When there were missing data on size/age classes or transition rates between classes, subject matter expertise was used to fill in gaps and reproduce the next year's total.

We used these Excel models to determine the annual proportion of inventory going to slaughter for beef and dairy farms. We calculated the number of animals in five classes (cows, male calves, female calves, heifers, and bulls) on hypothetical cow-calf and dairy operations with 500 cows. The number of calves was computed based on birth rates, and heifer numbers were determined by the proportion of the national breeding female inventory that is heifers versus cows. A small number of bulls were included (10 for dairy and 20 for cow-calf operations) to account for high rates of artificial insemination in dairies [108] and low ratios of bulls per female on cow-calf operations [109]. We gathered the proportion of each class slaughtered in a year from the Excel models once we had generated an inventory for each class. We used this to calculate the total proportion of the operation's inventory expected to ship to slaughter.

Farms in USDOS are categorized as "beef" or "dairy", each of which encompasses multiple premises types. The major beef premises types include cow-calf operations as well as stockers, grazers, and backgrounders, while "dairy" consists largely of dairies and heifer raiser (also called 'calf ranch') operations. Inventory from stockers/backgrounders/grazers and heifer raisers does not generally go directly to slaughter, going either back to a dairy (from heifer raisers) or on to a feedlot (stockers/backgrounders/grazers). We therefore counted the slaughter proportion for these premises as zero, then calculated the mean proportion of inventory to slaughter for beef and dairy. Data are lacking on stocker/backgrounder/grazer and heifer raiser operations, which appear to be more fluid than traditional cow-calf and dairy operations and sometimes share a physical location with them [110]. Because we did not have data on the breakdown of beef and dairy premises types, we assumed that cow-calf and dairy operations each represented 90% of their category, while stockers/backgrounders/grazers and heifer raisers represented 10%.

The proportion of total feedlot inventory sent to slaughter was included in the 2011 NAHMS Feedlot studies [111, 112]. Because the average animal stays in a feedlot for only six months, the annual total feedlot inventory is approximately twice the inventory at any given time. We accounted for this by doubling the proportion of a feedlot's inventory to slaughter.

We next calculated the rate of shipment to slaughter. USAMM does not model slaughter shipments because ICVIs (on which USAMM is based) are not required for slaughter shipments. However, NAHMS studies of cow-calf, dairy, and feedlot operations [108, 109, 111, 112] report the proportion of shipments that go directly to slaughter. We used these data to scale up USAMM-predicted shipment rates into a predicted shipment rate accounting for all shipment types, $\lambda_{slaughter}^{YEAR}$. We then calculated the rate of shipments directly to slaughter. This rate was used to determine whether a slaughter shipment occurred in a given timestep.

Given that one or more slaughter shipments occurred in a time step, the number of animals on each such shipment was modeled as a binomial random variable, avoiding sampling zero animals, $k \sim 1 + Bin(n-1, p)$ with n equal to the herd size of the sending premises, and p given by

$$p = min(1, \frac{m}{\lambda_{slaughter}^{YEAR}}) \tag{C.3}$$

where m is the proportion of a premises entire herd sent to slaughter each year, and $\lambda_{slaughter}^{YEAR}$ is treated as the expected number of slaughter shipments in a year. This gives the expected proportion of a premises herd size sent to slaughter on each slaughter shipment event. This quantity can be larger than one, and in that case it was truncated to 1.0 in which case all infected animals were guaranteed to be removed off the premises. Otherwise the animals sent on the slaughter shipment were sampled from a hypergeometric distribution given by the slaughter shipment size and the number of animals in the different infection classes at the sending premises (see section C.2 for details on that process).

C.6 Probability of detection at slaughter

Once the number of animals going to slaughter in a timestep had been determined, we applied the probability of detecting each individual animal, which accounted for where an animal is slaughtered, the probabilities of lesion presence and submission at slaughter, confirmatory test sensitivity, and the traceback capability to the origin premises. Each of these is an independent

probability, with the exception that lesion sample submission probability depends on the slaughter facility to which an animal is sent.

County-level probabilities that animals on farms in that county would be sent to each federally-inspected slaughter facility were estimated based on farm, feedlot, and slaughter plant locations, and shipment patterns. Because slaughter shipments do not require an ICVI, slaughter shipments were not modeled by USAMM. In order to represent the majority of slaughtered cattle (approximately 80 percent), we assumed that animals on farms are shipped to feedlots based on the patterns predicted by USAMM, and that feedlots shipped to slaughter facilities based on distance. The distance dependence is estimated from the information about the average distance feedlots ship to slaughter in the NAHMS feedlot surveys [111, 112]. Advances in USAMM capabilities and additional work to obtain data on the routes cattle take to slaughter have already identified additional refinements that can be made to improve these slaughter destination probabilities.

All cattle slaughtered in U.S. slaughter plants are visually inspected for evidence of tuberculosis. Tuberculosis lesions may be found in any organ or body cavity of diseased animals. In early stages of the disease, these lesions are difficult to find, even during postmortem examination. But in later stages, the nodules or lumps caused by bovine TB become evident in the lungs and associated lymph nodes. Involvement of the lymph nodes of the head and intestinal tract is also common. Due to a lack of experimental evidence on the probability of any given infected animal having visible lesions, we use a previously stated assumption that this value of P(Lesion of detectable size|Infected) is 0.75 [113] and generated a beta distribution.

The probabilities that each slaughter plant submits lesions for additional testing were estimated at the state level based on the annual totals for number of animals slaughtered and the number of lesions submitted. We assume a background rate of lesions in uninfected animals of 1 in 2,000 for adult cattle. This threshold is based on the rules formulated to ensure that carcasses are carefully inspected; each slaughter plant should submit granulomatous-like lesion(s) from at least 1 per 2,000 adult cattle slaughtered at the facility [114]. Although there is not a similar requirement for fed cattle, we assume a background rate of lesions of 1 in 20,000 animals. The state totals for adult

and fed cattle slaughtered annually were then scaled to determine the number of expected lesions in those populations. For states that submitted more lesions than expected, we set the submission probability to 1, and for those that submitted less than the expected number of lesions, we set the submission probability as the ratio of observed submissions to expected, with 1 added to each to adjust them so that all states have a non-zero probability of lesion submission:

$$p_{submit} = min(1, \frac{n_{submitted} + 1}{n_{expected} + 1}) \tag{C.4}$$

TB-suspect lesions detected at slaughter are submitted to the National Veterinary Services Laboratories (NVSL) for confirmatory testing via histopathology, PCR, and culture. Final disposition, i.e., declaring an animal "positive", is based on confirming animals by culture. To model this process, we used a combined sensitivity value for histology [115, 116] and culture [103].

An animal confirmed as bTB-infected will trigger an investigation into its origin. A successful traceback investigation is defined as a traceback that identifies a herd where an animal spent at least four months and which was not a feedlot [114]. In USDOS therefore, successful traces require tracing back to a beef or dairy farm. In addition, we applied the criterion that the animal had to be of U.S. origin, given USDOS simulates infection seeded in the U.S.

Table C.2: bTB Joint Probability Parameters. This table provides values for the components of the joint probability for detection of a bTB-infected animal at slaughter. The proportion of shipments and inventory to slaughter are used to determine the number of animals an infected premises will send to slaughter (see section C.5). The slaughtershed matrix and probabilities of a detectable lesion, lesion submission, positive test (sensitivity), and traceback are described in section C.6.

Parameter	**Default Value**	**Reference**
Proportion inventory to slaughter (annual)		
Dairy Farm	0.109	C.5
Beef Farm	0.048	C.5
Feedlot	1.908	C.5
Proportion shipments to slaughter (direct)		
Small Dairy Farm	0.102	C.5
Medium Dairy Farm	0.204	C.5
Large Dairy Farm	0.312	C.5
Small Beef Farm	0.024	C.5
Medium Beef Farm	0.017	C.5
Large Beef Farm	0.064	C.5
Extra Large Beef Farm	0.080	C.5
Small Feedlot	0.651	C.5
Medium Feedlot	0.933	C.5
Large Feedlot	0.960	C.5
Slaughtershed Matrix		
See input file (varies by county and slaughter plant)		C.6
P(Lesion of detectable size | Infected)		
α_{sens}	30	C.6
β_{sens}	10	C.6
P(Lesion submitted | Lesion of detectable size)		
See input file (varies by slaughter plant)		C.6
P(Test positive | Lesion submitted)		
α_{sens}	46	C.6
β_{sens}	5	C.6
P(Successful traceback | Test positive)		
α_{sens}	45	C.6
β_{sens}	51	C.6

C.7 Sensitivity county selection

The sample of counties was selected based on premises density, number of in-shipments, number of out-shipments, and premises clustering values. 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 USDOS model [44]. We include these six counties for comparison and because of their importance in the cattle industry [43]. Simulations were seeded or started in each of the 86 selected counties 10 times for each of the 10 FLAPS realizations, which leads to each county being seeded 100 times. Each time a county is seeded a farm is selected at random to be the initial infection. All simulations were run using the maximum population size estimates.

Appendix D

Chapter 3: Supplemental Results

Table D.1: Breakdown of outbreaks that did and did not reach the maximum duration (300 months).

Scenario	Under Max Duration	Max Duration	% Max
Base	5996	2604	30.3
SP:Current	8504	96	1.1
SP:Current-Slaughter:100	8530	70	0.8
SP:Current-Slaughter:100-Trace:60-70	8540	60	0.7
SP:Current-Trace:300-70	8524	76	0.9
SP:Current-Trace:300-90	8537	63	0.7
SP:Current-Trace:60-70	8524	76	0.9
SP:Current-Trace:60-90	8524	76	0.9

Table D.2: Breakdown of outbreaks that did and did not have epidemic extent (EE) >1.Epidemic extent is the number of counties affected by the outbreak

Scenario	Epid Extent = 1	Epid Extent >1	% EE = 1
Base	5546	3054	64.5
SP:Current	7615	985	88.5
SP:Current-Slaughter:100	7588	1012	88.2
SP:Current-Slaughter:100-Trace:60-70	7552	1048	87.8
SP:Current-Trace:300-70	7578	1022	88.1
SP:Current-Trace:300-90	7541	1059	87.7
SP:Current-Trace:60-70	7516	1084	87.4
SP:Current-Trace:60-90	7619	981	88.6

Table D.3: Breakdown of outbreaks that did and did not have more than 1 IP.

Scenario	**>1 IP**	**1 IP**	**% 1 IP**
Base	3255	5345	62.2
SP:Current	1086	7514	87.4
SP:Current-Slaughter:100	1114	7486	87
SP:Current-Slaughter:100-Trace:60-70	1156	7444	86.6
SP:Current-Trace:300-70	1113	7487	87.1
SP:Current-Trace:300-90	1163	7437	86.5
SP:Current-Trace:60-70	1185	7415	86.2
SP:Current-Trace:60-90	1098	7502	87.2

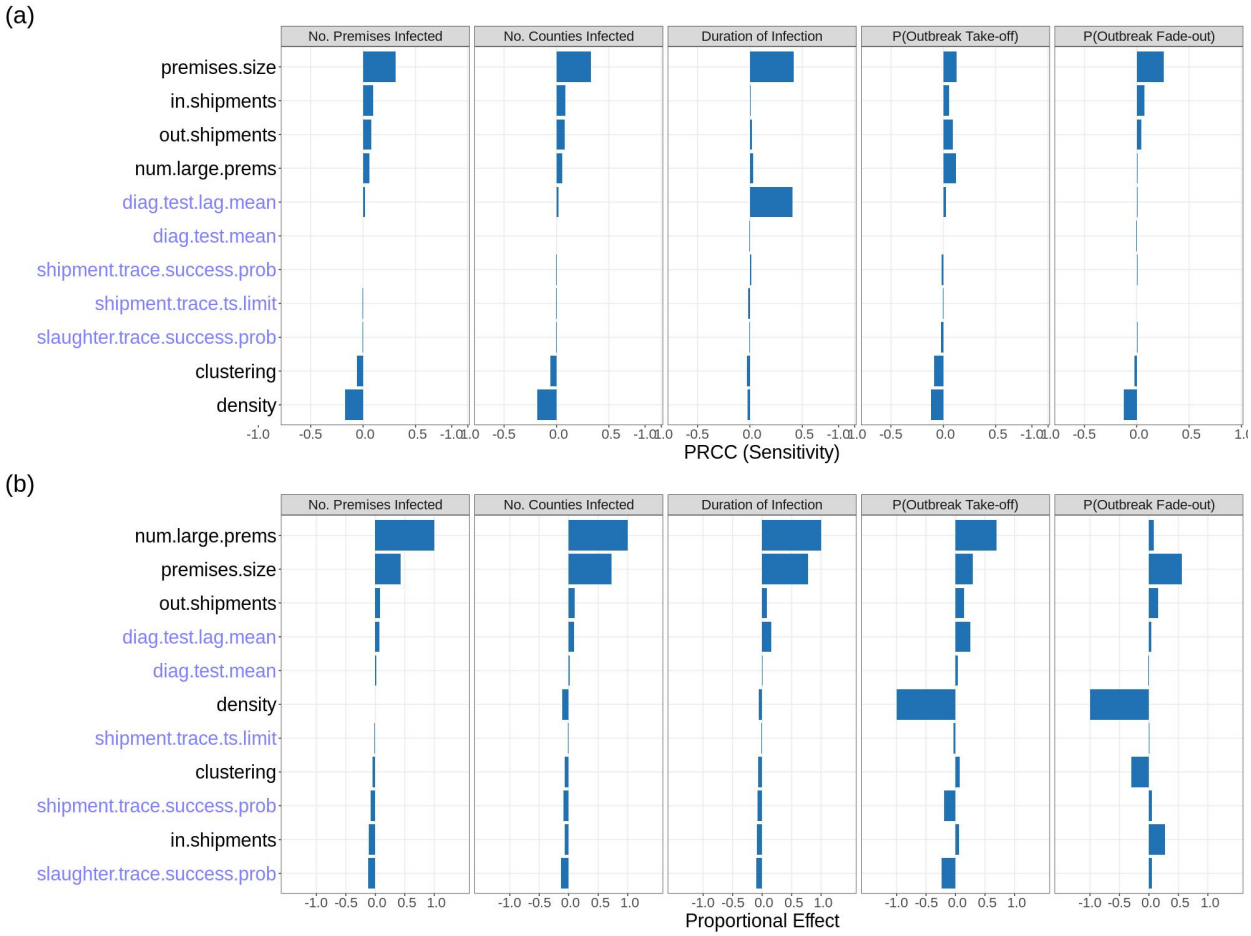


Figure D.1: Sensitivity analysis of diagnostics and control parameters. Labels for parameters related to county demography are in black and control and diagnostic parameters are in blue. (a) Effect sizes from PRCC analysis and (b) Proportional effect sizes from regression analysis.

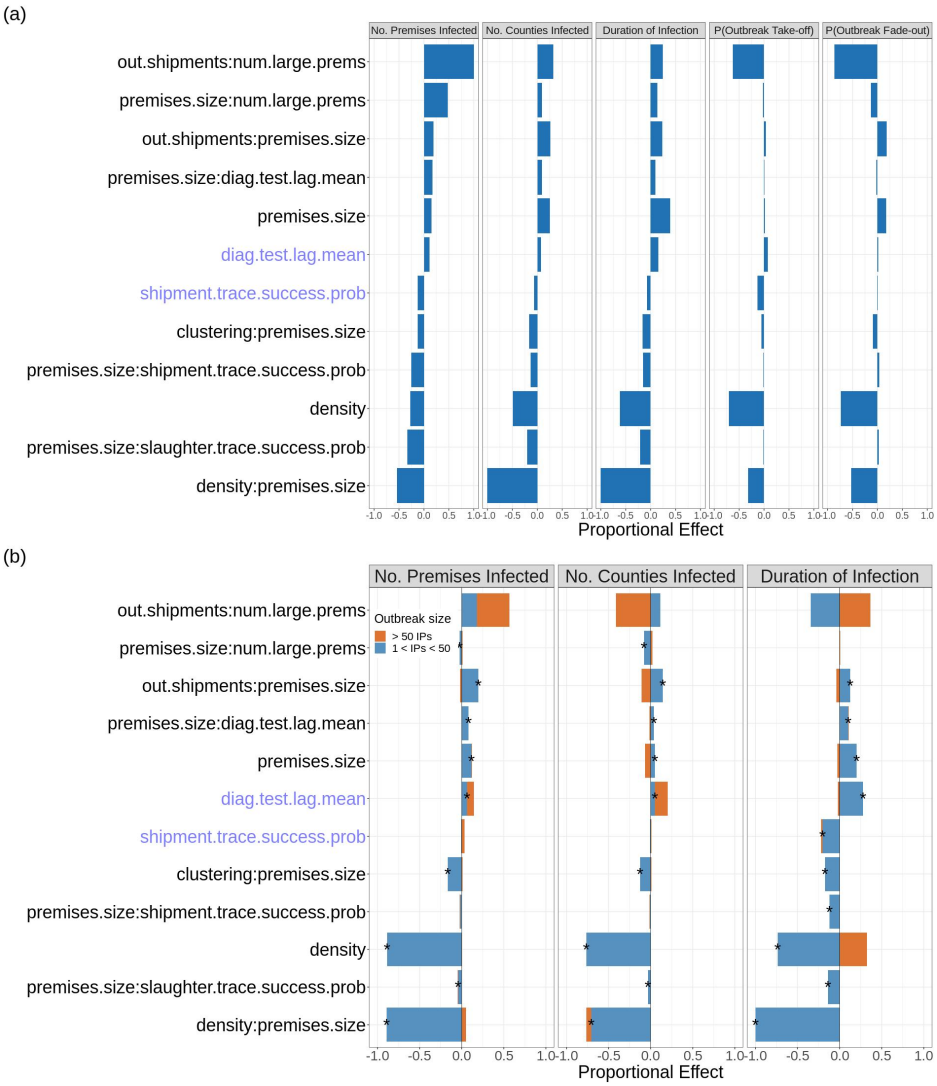


Figure D.2: Sensitivity analysis of diagnostics and control parameters. Labels for parameters related to county demography are in black and control and diagnostic parameters are in blue. (a) Proportional effect of parameters on outbreak metrics across all outbreaks, including those that take-off and fade-out. All parameters except for premises size is significant ($p < 0.05$) across number of the infected premises, counties, and outbreak duration or P(Take-Off) and P(Fade-Out). (b) Proportional effect sizes of parameters for outbreaks that fade-out (blue) and take-off (orange). Stars indicate parameter has a significant effect on outbreaks that fade-out ($p < 0.05$). No parameter has a significant effect on outbreaks that take-off. Outbreaks that fade-out infect between two and 50 premises and last less than 300 months. Outbreaks that take-off infect more than 50 premises.

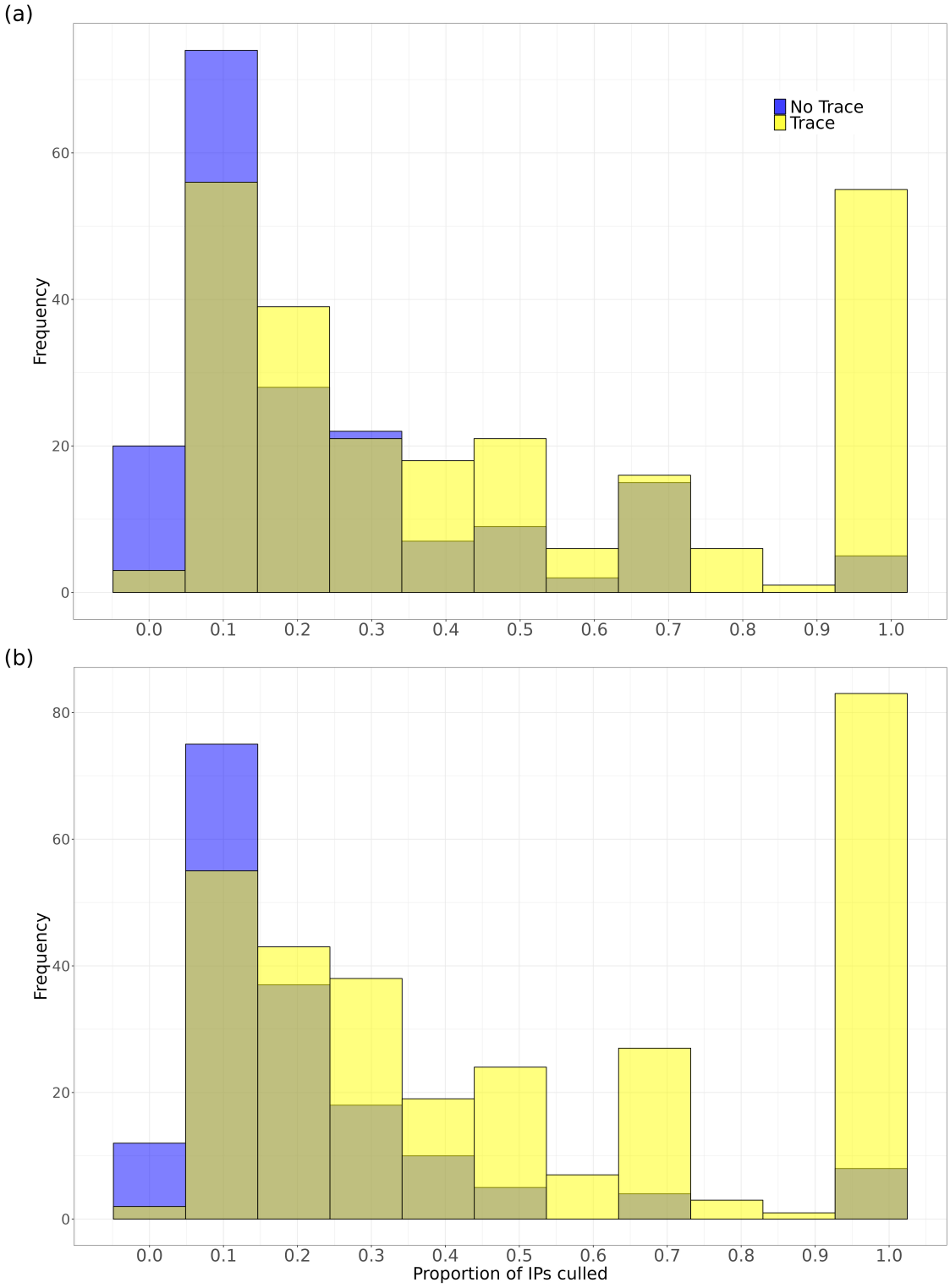


Figure D.3: All reported premises were culled during outbreak simulations. Blue colors are the current diagnostic scenario with no tracing. Yellow colors are the current diagnostic with tracing (Trace: 60,70%, see section 3.2.3). (a) Histogram of the proportion if infected premises reported with and without tracing for a SP: Ideal diagnostic scenario. (b) Histogram of the proportion if infected premises culled with and without tracing for a SP: Ideal diagnostic scenario.