UC Davis

UC Davis Electronic Theses and Dissertations

Title

Agent based modeling to explore intervention strategies for prevention and control of infectious diseases, complex systems modeling in epidemiology

Permalink

https://escholarship.org/uc/item/23s0q56c

Author

Gomez-Vazquez, Jose Pablo

Publication Date

2021

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

Agent based modeling to explore intervention strategies for prevention and control of infectious diseases, dynamic system modeling in epidemiology

By

JOSE PABLO GOMEZ-VAZQUEZ
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Epidemiology

in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:

_____

Beatriz Martínez-Lopez, Chair

_____

Heejung Bang

_____

Manuel Jose Sanchez-Vazquez

Committee in Charge

2022

Abstract

Advances in computational performance and the advent of big data have allowed the emergence of new methodologies for modeling infectious diseases as complex systems representing aspects such as non-linearity, emergence, and feedback loops, among others, with increasing spatio-temporal resolution. Agent based models have been used in many other disciplines such as social sciences, ecology, city planing, and, more recently, epidemiology. With the objective of better integration of data and theory, we used agent based modeling and global sensitivity analysis of complex models under different epidemiological scenarios and with varying degrees of data availability and quality.

In the first chapter, we integrated data from publications between February 2020-February 2021 and from phone interviews in a typical nursing home in California to develop an agent based model to explore the impact of non-pharmaceutical interventions and vaccination in the prevention and control of COVID-19 in nursing homes.

In the second chapter, we used information from the literature and from sow farm production records in the Midwestern United States to develop a model that evaluates the effect of herd management and vaccination in the control of porcine reproductive and respiratory syndrome (PRRS), an endemic disease in the US pork industry.

In the third chapter, we used data provided by the National Veterinary Services of Ecuador (AGROCALIDAD) to evaluate the impact of simulated re-introductions of foot-and-mouth disease (FMD), which is in the last phase of disease eradication in Ecuador, and to evaluate strategies for better prevention and control of FMD.

The findings for each of the presented chapters can be used to support disease eradication efforts of communicable disease outbreaks through approaches centering local epidemiological dynamics under different settings.

Acknowledgements

Since I arrived Davis in 2016 I have met amazing people that have challenged the way I think and made me feel like at home. First I want to thank my advisor Beatriz who has always believed in my ideas and supported me. She has been a very inspiring mentor, a huge influence in my career development and always provided a very welcoming environment for me to grow in both professional and personal, I have not enough words to express my gratitude towards her.

I also want to thank my collaborators that have trusted me and provided me the opportunity to work with them. I was very lucky to have awesome collaborators from the academia, industry and governmental institutions for the work presented in this dissertation, and without them this work would not be possible. Thanks to Miriam Nuño, Yuri Garcia and Alex Schmidt who contributed with their expertise in chapter 1. Thanks to Maria Jose Clavijo, who very patiently explained me how different aspects of the swine production systems works in the US for the development of the model for the second chapter. I also want to thank Alexandra Burbano, Alejandro Vaca, and the rest of team of Agrocalidad Ecuador, who has been providing their expertise to help me guide the modeling efforts from chapter 3. Thanks to my committee members Heejung Bang and Manuel Jose Sanchez-Vazquez who have provided valuable input not only for my dissertation, but also in many other aspects of my career.

I would also like to thank my peers and friends from the GGE and CADMS, they have made my experience very enjoyable. A special thanks to my partner Sarah for the moral support and listening to me talk about statistics and modeling even on weekends and holidays. I would like to thank my amazing family who despite the distance has always been there to motivate me and provide a supporting and loving environment for me to learn and develop in both my personal and professional goals.

And last but not least, I want to thank my sponsor CONACYT-UC MEXUS who has provided me with a wonderful life-changing opportunity to focus on my research interests while having a constant source of funding that complemented my stipend during the time I was working on my PhD.

Contents

Section 1

Introduction

Mathematical modeling in epidemiology has been used to understand the transmission dynamics of diseases since 1920's [Abbey, 1952]. One of the first contributions to this area was by Kendric and McKendrick's, that proposed a compartmental model where the population is divided into compartments and the population transition between compartments is modeled using ordinary differential equations (ODE) [Kermack and McKendrick, 1927]. Initially the model proposed by Kendric and McKendricks included only 3 disease states or compartments, (*S-susceptible*, *I-infected* and *R-recovered*) and was deterministic. This approach has been expanded and adapted to different situations adding or removing compartments for different disease status or characteristics of the population (i.e. age, sex, among others) and introducing stochasticity.

Equation based models have been used widely in epidemiology because are relatively simply to implement and can be expanded more compartments to represent better the heterogeneity of the population. However, these type of models still assume that the population will be homogeneously mixed within each compartment and the transition rates between compartments are constant over the simulation time, which can be unrealistic for capturing individual variations for certain diseases [Epstein et al., 2008]. Woolhouse suggested that 20% of the host population contributes at least 80% of the net transmission potential [Woolhouse et al., 1997].

Multiple approaches to ODE compartmental models have been used to address the heterogeneity of the population. Some of the most popular approaches in the last couple of years include network based models and spatial models. Network based models treat the population as nodes and edges, where the nodes represent the individuals (or group of individuals) and the edges the contacts between individuals. Once the network has been defined, simulations can be made to represent the disease transmission. To investigate the influence of spatial dynamics on the transmission of diseases, researchers have also integrated geographical information

systems to create more complex models [Randhawa et al., 2021, Mao and Bian, 2010, Martínez-López et al., 2010].

Recently, agent-based models (ABM) have been used in epidemiology to more accurate model the transmission dynamics of infectious diseases. ABM integrates concepts used in previous modeling approaches such as mathematical methods to inform the progression of the disease in an individual or complex networks to represent contact patterns between individuals.

In this section we will do a brief introduction to some of the applications of ABM in epidemiology and basic concepts, then throughout the chapters presented in this dissertation, we explored the applications of ABM under different epidemiological scenarios, with two epidemic diseases (COVID-19 and foot and mouth disease) and one endemic disease (porcine reproductive and respiratory syndrome). All the chapters aim to provide an insight not only in the overall impact of the disease, but in the effect of the interventions on preventing and controlling the outbreaks.

In chapter 1 we developed an ABM to support the design and deployment of COVID-19 prevention and control interventions in long term care facilities, which has been among the most affected groups by the pandemic [CMS, 2021]. Given the continued challenges of the implementation of robust protective measures in long term care facilities, the uncertainty involved in the vaccine efficacy in vulnerable population and new circulating strains, in this study we aim to quantify the effect of testing rates and different vaccination strategies in the COVID-19 morbidity and mortality in a long-term care setting under different scenarios. The model presented in chapter 1 was carefully designed and calibrated based on interviews with long term care facilities staff and data obtained from publicly available sources.

In chapter 2 we developed a model to explore the impact of herd management and vaccination strategies for prevention and control of porcine reproductive and respiratory syndrome (PRRS), which is an endemic disease that affects the swine industry in the United States. PRRS was introduced in early 1990s in the US [Mardassi et al., 1994, Meng et al., 1994] and since then it has established as an endemic disease that generates severe economic losses every year [Holtkamp et al., 2013, Nathues et al., 2017]. The main challenges on the disease eradication relies on the genetic diversity of the PRRS virus, therefore, the field strains can vary widely in the virulence, antigenic response and the protection immunity provided from the vaccine [Halbur et al., 1996b,a, Mengeling et al., 1996]. Using the model developed in chapter 2, we explore the impact of the disease in a typical sow farm in the Midwestern US and the effect of interventions such as herd management and vaccination have on the disease impact.

For chapter 3 we explored the impact of a potential reintroduction of foot-and-mouth (FMD) disease to

Ecuador and strategies for disease control. Foot and mouth disease is a viral disease that affects cloven hoofed animal, including several livestock species. Several countries in Latin america, including Ecuador, have been advancing towards the eradication of the disease in the last decade. The ABM developed in this chapter is a computationally efficient disease spread model that represent both local and long distance disease spread dynamics. This approach allows to explore the effect of interventions such as restriction of movements, emergency vaccination and culling of infected farms for controlling the outbreak and identify vulnerable areas.

1.1 ABM in epidemiology

In an ideal world, when we design an experiment, we would like to have pairs of subjects that are comparable to each other and assign them to either a treatment or control group to evaluate the effect of the treatment. Due to logistics of the implementations or ethical considerations, this is not always possible. Although there are several statistical methods meant to control for confounder variables and reduce the potential bias that can be introduced in our experiment due to external factors, it is always necessary to have some degree of assumptions to guide the analysis. The acceptable weights that observed data and the assumptions we make about a phenomena will vary depending on the subject of study. Traditional epidemiological methods (i.e. directed acyclic graphs and regression) often assume linear relationships and unidirectional causal relationships between exposure and outcomes. Nevertheless, infectious disease dynamics can present aspects characteristic of complex systems such as non-linear relationships, emergence of macro patterns that arise from micro level behavior, and feedback loops [Hawe and Shiell, 2000, Galea et al., 2010]. Some of these aspects can be addressed with methodologies such as multilevel models and Bayesian frameworks, however, ABM provides an approach to develop tailor made models to address specific diseases in specific populations. ABMs can be essential part of an epidemiological study when is not feasible to run an experiment due to ethical or logistic aspects [Hernán, 2015] and can be used to study the counterfactual when a solid model is developed [Marshall and Galea, 2015].

The freedom that ABM offers in the model formulation provides the opportunity to integrate different methodologies and concepts from other modeling approaches. For example, to represent the heterogeneity of the population and spatial relationships while maintain computational efficiency in large populations, individuals can be aggregated in neighborhoods, farms or other unit of aggregation and SIR approaches can be used to represent the disease transmission within units of aggregation [Kano et al., 2020, Bradhurst et al., 2015]. Network dynamics can also be integrated in ABM to represent the complex interrelationships

of the agents in a simulation [Arruda et al., 2017, Barrett et al., 2008]. The flexibility in ABM also allows to obtain high resolution spatio-temporal outcomes, which can be useful to simulate targeted interventions for specific time points or group of agents in the simulation. High resolution ABM can be particularly challenging because there is not always enough data available for validating the model and the results can remain questionable in terms on how good the model represents the reality, but with the advances on data availability this will become less of a problem in the future.

In the past, ABM in epidemiology have been used for two main reasons: model general disease behaviors, and model specific disease in specific populations. For example, Epstein et al. [Epstein et al., 2008] developed a generic disease spread model to explore the influence of human behaviors such as fleeing from the area of an outbreak in the diseases spread. Models for specific diseases in generic populations can also be used to unravel macro patterns that arise from micro behaviors. For example, Kano et al. [Kano et al., 2020] developed a model to explore the impact of COVID-19 in economic activities. More localized disease spread dynamics have also been studied wit ABM, this can provide insights in how local landscape characteristics [Dion et al., 2011] or socioeconomic aspects [Aleta et al., 2020] can influence the spread of a disease in a specific population.

1.2 Basic concepts in agent based modeling

An agent can represent any entity that have some degree of autonomy [Crooks et al., 2017], this could include individual people, animals, buildings, farms, among others. In ABM we assign specific characteristics to the agents in a simulation under a set of rules that determine how the agents interact with each other and their environment, this allows to capture interactions at individual level and the impact it has at multiple spatial and temporal scales. ABM allow us to use multiple sources of information including quantitative data measurements and qualitative theory to combine our observations and hypotheses within a single integrative framework. Depending of the interest of the modeler, different characteristics of the population such as: contact structure, spatial distribution, or other demographic traits can be represented in the model.
Due to the flexibility and freedom ABM offers, there is a lack of clear definitions and standard protocols that can often lead to confusion on the different components of the model and comparing to other models. In an effort to standardize some definitions of ABM in epidemiology, Marshall and Galea defined ABMs as follows [Marshall and Galea, 2015]:

For each agent $i = 1, ..., N$, where N is the total population, a set of $m = 1, ..., M$ individual characteristics is described at time $t = 1, ..., T$. This can be represented in a $N \times M$ matrix $\mathbf{S}^t$:

$$\mathbf{S}^t = \begin{bmatrix} S^t_{1,1} & S^t_{1,2} & ... & S^t_{1,M} \\ S^t_{2,1} & S^t_{2,2} & ... & S^t_{2,M} \\ \vdots & \vdots & \ddots & \vdots \\ S^t_{N,1} & S^t_{N,2} & ... & S^t_{N,M} \end{bmatrix}$$

where each row describes the values of each agents characteristics or traits at time t. These characteristics can be defined as continuous (i.e. age, probability of death), dichotomous (i.e. infectious yes/no, sex) or categorical (i.e. stage of development, age group).

At each time step, each agent i interacts with a subset of the population described by an agent-agent interaction matrix $\mathbf{K}^t$ where each element $k^t_{i,j} \epsilon \{0, 1\}$ indicates whether agent i interacts with agent j during time step t, depending on the context, these interaction might or not be symmetrical (i.e. unidirectional contacts vs bidirectional). In addition to the interactions network, the agents can also be placed in different environments represented by a matrix $\mathbf{E}^t$ where each agent is located within one $p = 1, ..., P$ possible environmental states at time t. The effect of the spatial location in of the agent can be captured by both the agent-agent interaction matrix (i.e. agents in close proximity are assumed to interact) and the environmental state matrix (i.e. the spatial location can represent the relationship of the agent with the environment). The model is initialized populating the baseline agent trait matrix $\mathbf{S}^0$, interaction matrix $\mathbf{K}^0$ and environmental states $\mathbf{E}^0$ with values defined by the modeler. A set of rules $\mathbf{Z}$ will determine how the agents interact with each other and the environment. Assuming that the rules are stable and independent of agent behavior, the evolution of the model can be described as:

$$\begin{aligned} s^t_{i,m} &= f(\mathbf{S}^{t-1}, \mathbf{K}^{t-1}, \mathbf{E}^{t-1}, \xi_{i,m,t}) \\ k^t_{i,j} &= g(\mathbf{S}^{t-1}, \mathbf{K}^{t-1}, \mathbf{E}^{t-1}, \epsilon_{i,j,t}) \\ e^t_{i,p} &= h(\mathbf{S}^{t-1}, \mathbf{K}^{t-1}, \mathbf{E}^{t-1}, \zeta_{i,p,t}) \end{aligned}$$

Where the functions $f(), g()$ and $h()$ with the error terms $\xi_{i,m,t}, \epsilon_{i,m,t}$ and $\zeta_{i,m,t}$ represent the set of rules defined by $\mathbf{Z}$. The set of defined rules $\mathbf{Z}$ can be dynamic, adaptive and reactive to the environment states, and change during the course of one simulation run. Different type of agents can be defined in the simulation and the interactions between them can be as complex as desired.

Outcomes of interest can be defined and computed at any point of the simulation (such as total number of infected, new infections per step, location of the infections, etc.) allowing us to explore the spatio-temporal dynamics of disease spread. The outputs can be obtained repeatedly under different circumstances and comparisons of treatments can be done using controlled random seeds, which allow us to have direct

interpretations as counterfactual outcomes.

In the following chapters we will apply this concepts for the formulation and development of ABMs in epidemiology. The models developed in this dissertation provide an example of how ABM can be used to integrate multiple sources of information to support prevention and control strategies centering local epidemiological dynamics under different settings.

Section 2

I: Testing and Vaccination to Reduce the Impact of COVID-19 in Nursing Homes: An Agent-Based Approach

2.1 Abstract

Background: Efforts to protect residents in nursing homes involve non-pharmaceutical interventions, testing, and vaccine. We sought to quantify the effect of testing and vaccine strategies on the attack rate, length of the epidemic, and hospitalization.

Methods: We developed an agent-based model to simulate the dynamics of SARS-CoV-2 transmission among resident and staff agents in a nursing home. Interactions between 172 residents and 170 staff based on data from a nursing home in Los Angeles, CA. Scenarios were simulated assuming different levels of non-pharmaceutical interventions, testing frequencies, and vaccine efficacy to reduce transmission.

Results: Under the hypothetical scenario of widespread SARS-CoV-2 in the community, 3-day testing frequency minimized the attack rate and the time to eradicate an outbreak. Prioritization of vaccine among staff or staff and residents minimized the cumulative number of infections and hospitalization, particularly in the scenario of high probability of an introduction. Reducing the probability of a viral introduction eased the demand on testing and vaccination rate to decrease infections and hospitalizations.

Conclusions: Improving frequency of testing from 7-days to 3-days minimized the number of infections and hospitalizations, despite widespread community transmission. Vaccine prioritization of staff provides the best protection strategy when the risk of viral introduction is high.

Keywords: Nursing Homes, Testing, Vaccine, COVID-19, Agent-Based Model.

2.2 Introduction

COVID-19 has highlighted many inadequacies in the American healthcare system. Elderly and frail residents of long-term care facilities (LTCFs) have experienced a disproportionate burden of infection and death. Approximately 5% of all US cases have occurred in LTCFs, yet deaths related to COVID-19 in these facilities account for 34% of all US deaths as of February 12, 2021, according to the New York Times [Times, 2020]. Nationwide, there are about 44,736 LTCFs in the United States, 15,116 of which are nursing homes. Together these facilities encompass more than 1.2 million staff and 2.1 million residents based on 2015-2016 estimates [Harris-Kojetin et al., 2019].

Guidance on the prevention and mitigation of COVID-19 in LTCFs was offered by many oversight groups, including the Centers for Disease Control and Prevention (CDC) and the Center for Medicare and Medicaid Services (CMS). Substantial numbers of transmission events from symptom-free individuals made it clear that universal testing, regardless of symptoms, was a critical component of a robust prevention program [Bigelow et al., 2020, Louie et al. [2020], Ouslander and Grabowski [2020]]. Testing frequency was widely debated, as LTCFs had to balance the obvious need with the high cost and low availability of testing, especially early in the pandemic [Blackman et al., 2020, Ouslander and Grabowski [2020], Smith et al. [2020]]. Vaccines provide an incredible tool for preventing COVID-19 outbreaks in LTCFs, but they are not a magic solution, nor will they be distributed into an environment that is wholly prepared to implement new protective measures.

Nursing home residents are a priority group for vaccination, as are health care workers. The CDC launched the Pharmacy Partnerships for Long-Term Care Program in an effort to provide on-site vaccination to residents and staff members in LTCFs [Gharpure et al., 2021b]. Though deployment of vaccines in LTCFs appears successful thus far, there is a growing concern that insufficient levels of vaccine coverage will be reached. As of the end of January 2021, median first dose rates among LTCF residents is 77.8%, but only a median of 37.5% of staff have received at least their first dose [Gharpure et al., 2021a]. It is unclear at this time whether the lower vaccination rates among staff is a result of prioritization of residents, lack of recording alternative sources of vaccination, or staff choice; however, a survey of nursing home staff conducted in the state of Indiana (November 2020) found that 45% of respondents were willing to receive a COVID-19 vaccine immediately once available, and an additional 24% would consider it in the future [Unroe et al., 2020]. While visitors are disallowed and residents only interact directly with a small number of other people, staff are the primary vector for viral introduction [Goldberg et al., 2021, Toth and Khader [2021]]; therefore, low rates of vaccine uptake among staff should be of great concern from the perspective of preventing an outbreak. Additionally, there is limited evidence about the ability of vaccines to reduce asymptomatic

transmission. Preliminary data from the UK suggests a 49.3% reduction in infections from an asymptomatic source [Voysey et al., 2021]. Recent evidence of the circulation of more transmissible SARS-CoV-2 variants also raises concerns about the course of this pandemic, particularly as less than 22% of the US population have received the full vaccine dosage [CDC, 2021a].

Given the continued challenge of implementing robust protective measures in LTCFs, the bevy of unknowns around vaccine deployment, the uncertainty involved with new circulating strains, and the impending lifting of co-recreation and visitor restrictions as states ease recommendations, we sought to quantify the effect of testing rates and differing vaccination strategies on morbidity and mortality in a long term care setting, using a nursing home in Los Angeles, CA as the foundation for an agent-based model (ABM). Our study assumes the continued presence of non-pharmaceutical interventions (NPIs) such as mask mandates for staff and universal testing, and varies the risk of introduction by staff. The main outcome is a model that can be adapted/modified to study the effects of these interventions in varied nursing home settings. Such modelling approaches can provide valuable insight into the design and deployment of combined vaccine and surveillance interventions before primary prospective research can be implemented [Toth and Khader, 2021].

2.3 Methods

2.3.1 Model structure

We developed a stochastic agent-based model to simulate the spread of SARS-CoV-2 in an LTCF, based on the floor plan and occupancy of a nursing home in Los Angeles County, California with 172 residents and 170 staff [Figure 2.1]. The simplified floor map shows the location of bedrooms with a capacity of 3 residents, 5 quarantine rooms reserved for residents with frequent outside traffic and/or capacity to quarantine exposed residents, recreation areas which are currently off limits to resident and staff interactions, and rooms for staff.

Resident and staff agents in our proposed model are represented in epidemiological classes of susceptible but not yet exposed to the disease (S), non-infectious exposed individuals incubating the disease whose infection is currently non-detectable by testing (E), infectious individuals with detectable disease who do not yet exhibit clinical symptoms of illness (I_a)[Feaster and Goh, 2020], infectious individuals exhibiting symptoms of illness (I_s), individuals that have recovered and can no longer infect others (R), symptomatic individuals requiring hospitalization (H), and individuals that succumbed to the disease (D) (Figure 2.2). The model assumes that residents are not replaced with new susceptible agents, and staff with confirmed exposure to

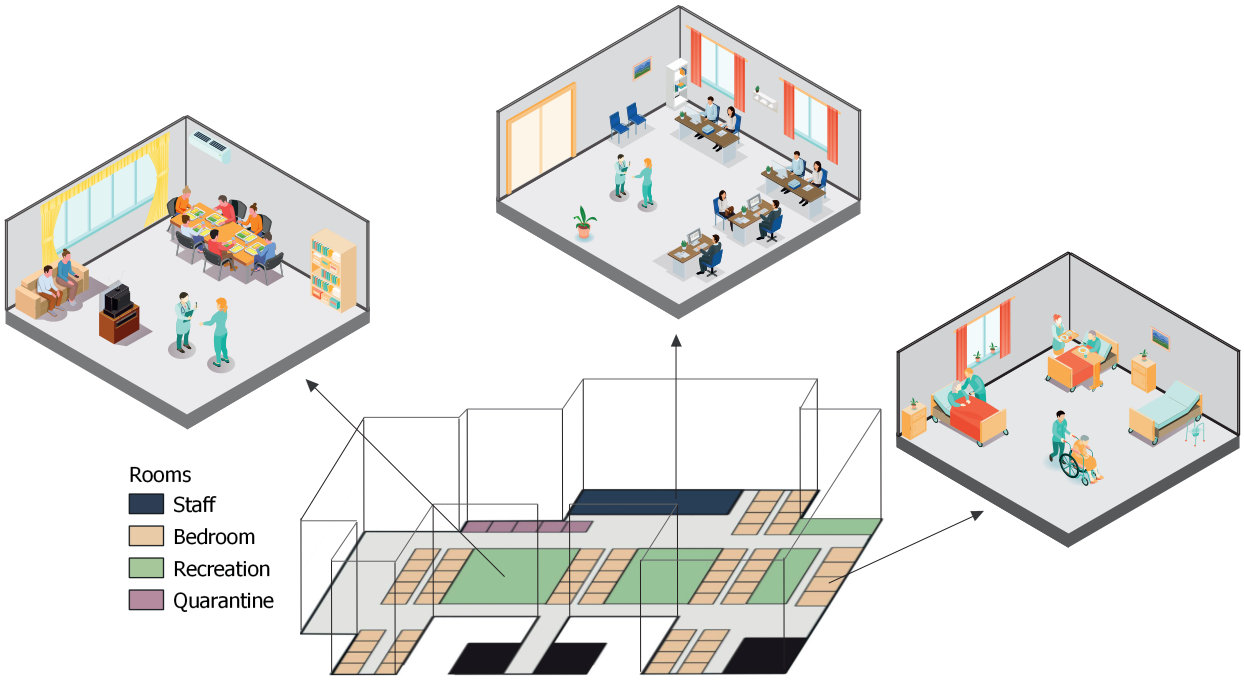

Figure 2.1: Case study of a nursing home in Los Angeles, CA.

the virus are replaced by new staff confirmed negative for SARS-CoV-2 during the period of simulation. Recovered people gain immunity to reinfection lasting 120 days, and the latency period is sampled from a logarithmic normal distribution [He et al., 2020]. Parameters and sources are described in Table 2.1.

2.3.2 Disease dynamics

The transmission of the virus is based on the probability of contact between susceptible people and those who are in presymptomatic, asymptomatic, or symptomatic states. The probability of infecting others on contact was assumed to be the same for each state. Due to default preventive testing and isolation measures, only I_a and I_s agents that have not been detected and isolated may contribute to new infections. A newly-infected individual enters a latency period sampled from a log normal distribution with a mean of 7 days [He et al., 2020]. After that time, 40% of people remain asymptomatic [Feaster and Goh, 2020] until recovery. For those who develop symptoms, 23% [Azar et al., 2020, España et al. [2021]] require hospitalization. The average number of days from the onset of symptoms to hospitalization is 4 days and a person stays in the hospital for an average of 6 days [CDC, 2021b]. Mortality rate was set at 11.8% [Nuno et al., 2021] for hospitalized agents. The average recovery time for asymptomatic agents or those who never required hospitalization is 15 days [Walsh et al., 2020], during which they remain infectious. We assumed that recovery from a primary

Table 2.1: Parameter descriptions, baseline values, and references.

Description	Baseline Value	Ref.
Average time a person remains in the non-infectious latency state (α)	$lognormal(7,3)^b$	[He et al., 2020]
Proportion of asymptomatic people (f)	0.40	[Feaster and Goh, 2020]]
Average recovery time (γ_1)	15 days	[Walsh et al., 2020]
Proportion of hospitalized people (σ_1)	0.23	[Azar et al., 2020, España et al. 2021]
Median number of days from symptom onset to hospitalization (γ_2)	4 (1, 9) days	[CDC 2021b]
Median number of days of hospitalization (γ_3)	6 (3, 10) days	[CDC 2021b]
Percent that die among those hospitalized. (σ_2)	11.8%	[Nuño et al., 2021]
Shedding probability	0.38	[a]
Infection probability	0.38	[a]
Introduction probability	0.1	[a]
Assumptions for the scenarios		
Percentage of staff using PPE	90%	[a]
Percentage of residents using PPE	75%	[a]
PPE Effect (OR_{pi})	0.1467	[a] [Chu et al., 2020]
Test detection probability	80%	[a]
Percentage of Staff tested	90%	[a]
Percentage of Resident tested	33.3%	[a]
Frequency of testing	$Weekly$	[a]
Vaccine effect (OR_v)	0.0493	[a] [Baden et al., 2020]
Vaccine immunity duration	120 days	[a]
Distribution of the staff agent characteristics		
CN Contacts per hour	$Multinom \sim (X_0 = 0.7, X_1 = 0.3)$	
RN Contacts per hour	$Multinom \sim (X_0 = 0.25, X_1 = 0.75)$	
LPN Contacts per hour	$Multinom \sim (X_0 = 0.15, X_2 = 0.2, X_3 = 0.25, X_4 = 0.2, X_5 = 0.2)$	
Work Schedule	$Multinom \sim (X_{morning} = 0.4, X_{night} = 0.2)$	
Staff type	$Multinom \sim (X_{CN} = 0.6, X_{RN} = 0.15, X_{LPN} = 0.15)$	

[a]Explored via sensitivity analysis, [b]fitted to a distribution from data and truncated to a range of plausible values

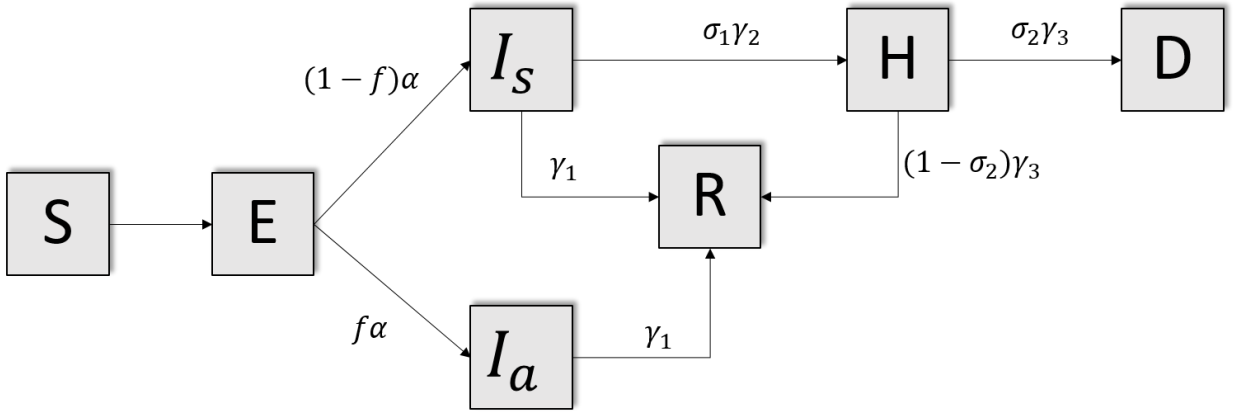

Figure 2.2: Epidemiological classes of the COVID-19 transmission model.

infection provided adequate immunity for the remainder of the simulation.

2.3.3 Staff and resident interactions

Agents in the model include residents and staff only, consistent with the full visitor restrictions. Three residents are assigned to a single room. Five rooms are designated for quarantine/isolation of infected patients or for residents who require outside specialty care, such as dialysis. Residents only interact with two other residents in the same room and with staff, who can be one of three types: Certified Nursing Assistant (CNA), Registered Nurse (RN), and Licensed Practical Nurse (LPN). Since meals are taken in rooms and use of communal space is restricted, residents do not currently interact with residents outside assigned rooms.

Each type of staff has different contact patterns with residents throughout the day. These contact rates are operationalized as contact probabilities defined from a multinomial distribution where each hour a CNA has a 0.7 chance to have 0 contacts and 0.3 chance to have 1 contact with a resident, a LPN has a 0.15 chance of having 0 contacts, 0.2 of two constants, 0.25 chance of having 3 contacts, and so on (Table 2.1). Contact probability parameters were estimated from staff hour-per-resident-day (HRD) data from the CMS Nursing Home Compare data set. We assumed no difference in probability of viral introduction by staff type. Staff are assigned to one of three different work schedules: 40% work in the morning (7am -3pm), 40% in the afternoon (3-11 pm), and 20% work overnight. They spend on average 8 hours inside the nursing home and the rest of the time in the community. Both scheduled time and type of staff are sampled from a multinomial distribution to reflect the distribution in our reference nursing home (Table 2.1).

2.3.4 COVID-19 transmission in the community

Though there is large variability on the impact of COVID-19 in these facilities, tied to historic variability in testing capacity and PPE availability and adherence, the most immediate risk of a COVID-19 outbreak in a nursing home is the level of community transmission of SARS-CoV-2. Since we assumed that visitors are disallowed completely, residents' risk for primary exposure is contact through staff who acquired an infection from the wider community. A critical factor that our model aimed to study was to assess the impact of the probability of viral introduction from the community on the predicted size of internal outbreaks. Each scenario we investigated was simulated across three different probabilities of a staff member introducing the infection: low (5% per day), medium (10% per day), and high (15% per day). These are expressed as 'introduction probability', which is set to 0.1 for the baseline scenario (Table 2.1).

2.3.5 Interventions

We parameterized interventions with variable impacts on the transmission of SARS-CoV-2: PPE use and misuse, regular diagnostic testing, and vaccinations. We considered scenarios where staff were tested every 7 days (baseline), 5 days, and 3 days. Testing of residents in all scenarios assume that one resident per room is tested weekly, systematically cycling through the each resident every three weeks. Reduction in transmission probability from PPE use and vaccination were applied by modifying the shedding and infection probability parameters [Chu et al., 2020]. Vaccine efficacy was translated into odds ratios of infection given exposure from the Pfizer and Moderna phase 3 clinical trial results. For brand- and age-agnostic scenarios, including the baseline scenario, the crude overall odds ratio was set to 0.0493. In scenarios where vaccine brand and recipient age were taken into account, the efficacy of the Moderna vaccine after the second dose was 95.6% (OR 0.0441) for individuals under 65 years old and 86.4% (OR 0.1357) for 65 and older [Baden et al., 2020]. The efficacy of the Pfizer vaccine for individuals under 65 was roughly equivalent to Moderna (OR 0.434), but was 94.7% (OR 0.0619 for individuals 65 years and older [Polack et al., 2020]. For ease of implementation, residents were considered 65 and older, and staff were considered under 65. The vaccine odds ratio has a direct impact on transmission probabilities and reflects the upper bounds for vaccine efficacy according to Equation 2.1. Let p_t be the probability of a transmission event:

$$p_t = \frac{e^{\ln(OR_\omega X_\omega)+\ln(OR_\pi X_\pi)+\ln(OR_\nu X_\nu)}}{1+e^{\ln(OR_\omega X_\omega)+\ln(OR_\pi X_\pi)+\ln(OR_\nu X_\nu)}} \tag{2.1}$$

where the odds ratio ω (OR_ω) represents the global baseline transmission probability of all agents, the odds ratio π (OR_π) represents the transmission reduction from the presence or absence of PPE, and the odds ratio ν (OR_ν) corresponds to the effect of vaccine status on transmission. Probability p_t is computed for all agents at each time step in order to reflect different probabilities of transmission based on the interventions each individual received. For scenarios where a vaccine was implemented, we specified the proportion of residents and staff that received a vaccine and a fixed time interval of 21 days between the first and second dose, with a 60% efficacy after the first dose but before the second.

2.3.6 Model Scenarios

The baseline scenario assumed current CDC infection prevention and control recommendations for nursing homes, including visitor restrictions, daily symptom screening of residents and staff, use of face masks, and weekly testing of staff. We incorporated weekly cyclic testing of one of three residents per room, with

alternating residents being tested each week. When a resident tested positive, they were isolated and the other residents from the same room were tested. Staff who tested positive were 'isolated' (removed from the simulation, as if on paid leave) and replaced with new staff who tested negative. Parameters assumed for the baseline scenario are described on Table 2.1. We simulated a set of scenarios based on staff testing frequency, prioritization of residents or staff for vaccination, and vaccine brand. In each scenario we systematically changed one of these approaches while holding the others at baseline values. Outcomes were estimates of the length of the outbreak, total number of infections (and attack rate), hospitalizations, and deaths across three risks of introduction from the community (low, medium, and high).

2.3.7 Model implementation

The model was implemented in GAMA 1.8.1[Taillandier et al., 2019a]. Code for reproducing this study is available at https://github.com/jpablo91/NH_COVID. Each scenario was simulated 200 times, and the median and 95% confidence intervals for each outcome were reported. For each set of simulations, we used the same seed to conduct sensitivity analysis and make comparisons between scenarios. The model was calibrated with data on confirmed COVID-19 cases reported between May 24, 2020 and February 14, 2021 in California nursing homes with similar resident census, extracted from the Centers for Medicare & Medicaid Services (CMS)[CMS, 2021]. We considered a good fit to be have high R^2 and Pearson's R estimates between the observed and model-predicted cumulative number of confirmed cases.

The model was calibrated with data on confirmed COVID-19 cases reported between May 24, 2020 and February 14, 2021 in California nursing homes with similar resident census, extracted from the Centers for Medicare & Medicaid Services (CMS) [CMS, 2021]. We considered a good fit to be have high R^2 and Pearson's R estimates between the observed and model-predicted cumulative number of confirmed cases.

2.4 Results

2.4.1 Baseline Scenario

In the baseline scenario we assumed PPE mandates, weekly testing, and no vaccination. Baseline attack rate was 0.17 (95% CI: 0.01, 0.39) and a median time to eradication of 28 days (Table 2.2, Figure 2.3). With the

Table 2.2: Description of interventions and parameter values.

	Probability of Introduction		
	Low	Medium	High
	Testing Frequency (ω = Introduction probability)		
	$\omega = 0.05$	$\omega = 0.10$	$\omega = 0.15$
Testing Interval	7 days	7 days	7 days
Testing Interval	5 days	5 days	5 days
Testing Interval	3 days	3 days	3 days
	Vaccine Performance (V_rOR = Odds ratio for the vaccine effect on residents, V_sOR= Odds ratios for the vaccine effect on staff)		
	$\omega = 0.05$	$\omega = 0.10$	$\omega = 0.15$
Equal	$V_rOR = 0.0493$ $V_sOR = 0.0493$	$V_rOR = 0.0493$ $V_sOR = 0.0493$	$V_rOR = 0.0493$ $V_sOR = 0.0493$
Pfizer	$V_rOR = 0.0619$ $V_sOR = 0.0434$	$V_rOR = 0.0619$ $V_sOR = 0.0434$	$V_rOR = 0.0619$ $V_sOR = 0.0434$
Moderna	$V_rOR = 0.1357$ $V_sOR = 0.0441$	$V_rOR = 0.1357$ $V_sOR = 0.0441$	$V_rOR = 0.1357$ $V_sOR = 0.0441$
	Vaccine Prioritization (V_r%=Percentage of residents vaccinated, V_s%=Percentage of staff vaccinated)		
	$\omega = 0.05$	$\omega = 0.10$	$\omega = 0.15$
Equal	$V_r\% = 50\%$ $V_s\% = 50\%$	$V_r\% = 50\%$ $V_s\% = 50\%$	$V_r\% = 50\%$ $V_s\% = 50\%$
Staff Priority	$V_r\% = 30\%$ $V_s\% = 70\%$	$V_r\% = 30\%$ $V_s\% = 70\%$	$V_r\% = 30\%$ $V_s\% = 70\%$
Resident priority	$V_r\% = 70\%$ $V_s\% = 30\%$	$V_r\% = 70\%$ $V_s\% = 30\%$	$V_r\% = 70\%$ $V_s\% = 30\%$

implementation of the vaccine and under the scenario of a high probability of introduction, the attack rate goes down to 0.02 and the time to the eradication of an outbreak was 14 days. (Figure 2.3).

2.4.2 Testing and Vaccine Interventions

The implementation of frequent testing, particularly every 3-days reduced the attack rate by half and allowed containment of the outbreak within 9 days, despite high probability of virus introduction. Estimates and 95% confidence intervals illustrated in Figure 2.4 are provided in Table 2.4. When vaccine was prioritized among staff, residents, or both, the attack did not seem to differ except when the introduction probability was high, in which case the simulated median attack rate was 0.02 when staff were prioritized compared to 0.03 if residents were prioritized or no prioritization was present. Assuming a low probability of introduction, no prioritization provided the best opportunity to control an outbreak, leading to a median of 9 days (95% CI: 7-26) until eradication. We evaluate a vaccine's ability to block transmission for scenarios of vaccine efficacy, staff and residents had the same efficacy, and residents had reduced efficacy compared to staff. We found that the probability of virus introduction was the most significant factor in determining the attack rate and days to the eradication of an outbreak. The attack rate doubled to 0.02 with high transmission probability and the time to the eradication of an outbreak was optimal only for low transmission. In all scenarios of low or moderate probability of transmission, none of the residents were infected.

The model was well calibrated to the cumulative number of cases among residents and staff in California nursing homes, with R^2 and Pearson's R estimates higher than 0.79 (Figure 2.4). Prospectively, our model overestimated confirmed cases among staff, likely due the implementation of new interventions, like increased frequency of testing, put in place after SARS-CoV-2 was introduced in a nursing home. Our model underestimated cases among residents, which may be driven by the fact that some staff have more direct contacts with residents than others.

2.4.3 Sensitivity Analysis

Baseline virus transmission rates, introduction probability, detection probability, PPE implementation and adherence, testing frequency, and vaccine efficacy were all considered for sensitivity analysis. We found that changes in the implementation of PPEs had a greater impact on reducing the attack rate and hospitalizations. Variation in virus transmission rates as well as the introduction probability showed substantial changes in attack rate and hospitalizations. Implementation of highly effective PPEs reduced the attack rate from 0.66 (95% CI: 0.39-0.85) to 0.02 (95% CI: 0-0.20), prevented 221 total infections, 18 hospitalizations, and reduced

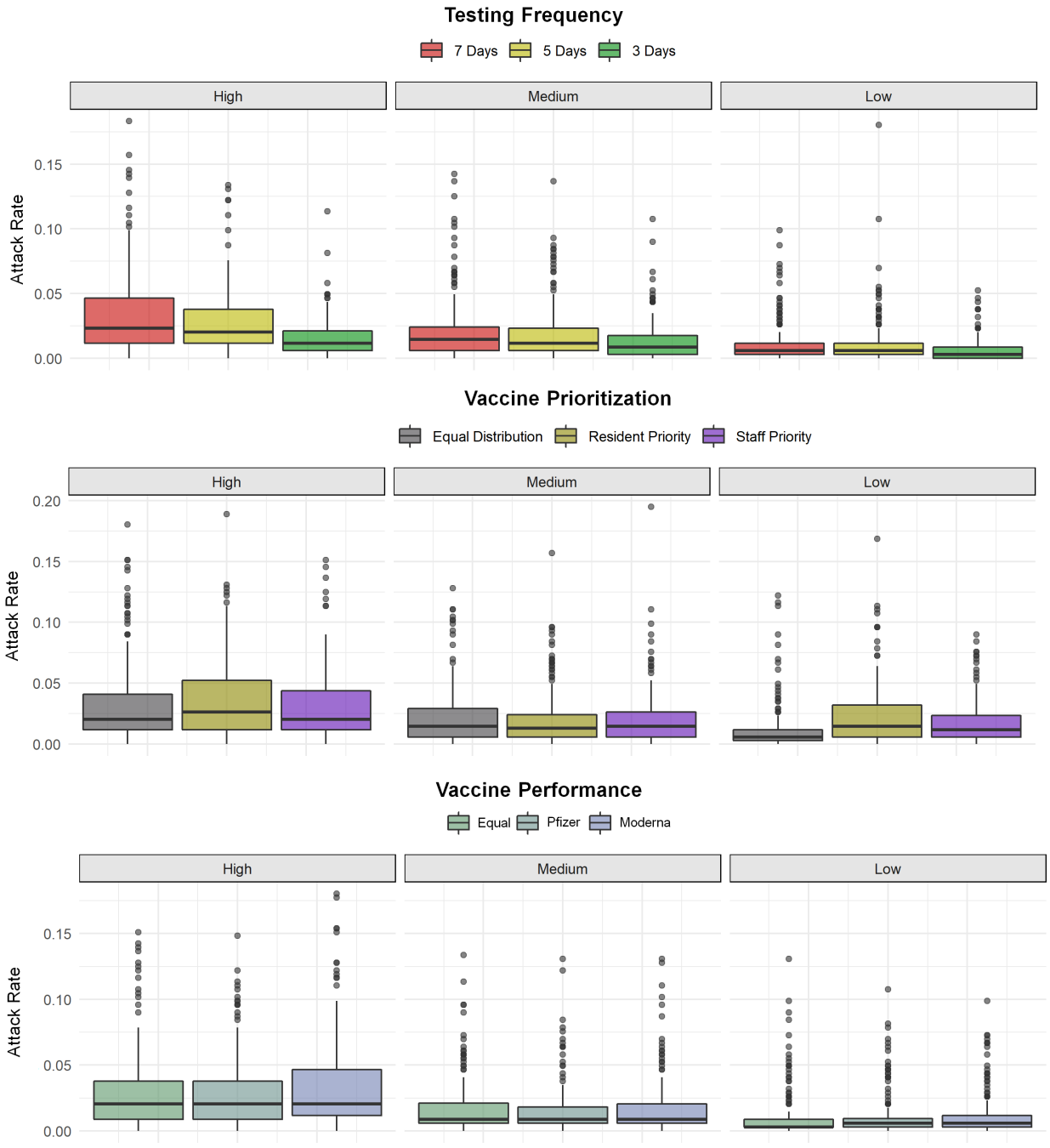

Figure 2.3: Attack rates for interventions under different assumptions of probability of introduction (low, medium, high).

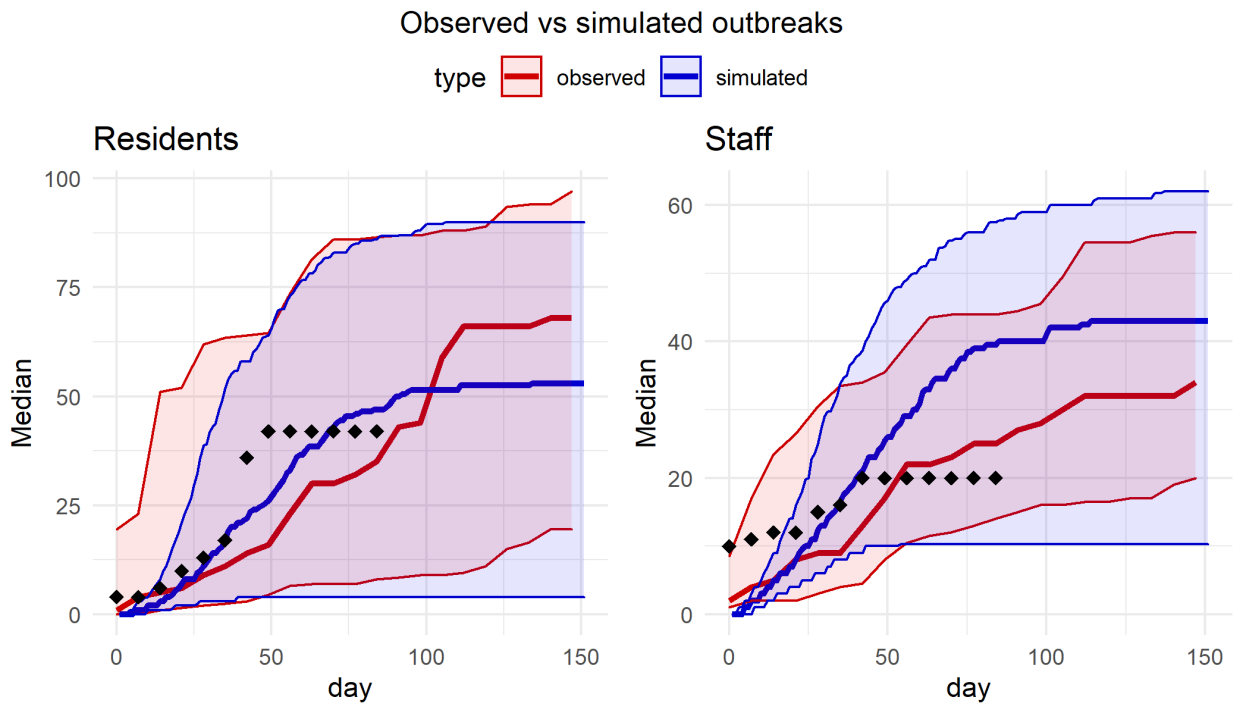

Figure 2.4: Model-predicted and observed number of cumulative incidence of confirmed cases for residents and staff. Dotted data represent the number of cases observed in the nursing home of study. Dark solid lines correspond to the median estimates for cases of staff and residents, and $25th$ and $75th$ percentiles are depicted in the shaded regions.

Table 2.3: Results from the sensitivity analysis summarized by the median and 95% confidence intervals for the various simulations considered.

Target Parameter	Value used	Days to Eradication	Attack Rate	Total Infected	Infected residents	Infected staff	Hospitalizations
Baseline [a]		28 (7, 70)	0.17 (0.01, 0.39)	59 (2, 134)	32 (0, 82)	23 (1,53)	5 (0, 15)
Transmission probability							
Low transmission virus[a]	0.34	21 (7, 63)	0.03 (0, 0.27)	12 (1, 93)	5 (0, 58)	8 (1, 38)	1 (0, 11)
High transmission virus[a]	0.42	28 (7, 63)	0.27 (0.01, 0.47)	93 (2, 163)	56 (0, 100)	37 (1, 65)	9 (0, 18)
Introduction probability							
Low introduction probability[a]	0.05	14 (7, 49)	0.02 (0, 0.32)	7 (0, 110)	3 (0, 72)	5 (0, 42)	1 (0, 14)
High introduction probability[a]	0.15	28 (9, 77)	0.21 (0.01, 0.42)	72 (3, 143)	39 (0, 84)	30 (2, 58)	6 (0, 15)
Detection probability							
Low detection probability (test)[a]	0.7	28 (7, 70)	0.2 (0, 0.47)	68 (1, 161)	38 (0, 97)	30 (1, 62)	5 (0,21)
High detection probability (test)[a]	0.9	21 (7, 70)	0.09 (0, 0.31)	32 (1, 108)	17 (0, 67)	16 (1, 44)	3 (0, 12)
PPE effect							
High effect PPE[a]	0.07	15 (7, 56)	0.02 (0, 0.2)	7 (1, 69)	2 (0, 40)	5 (1, 31)	1 (0, 7)
Low effect PPE[a]	0.34	21 (14, 42)	0.66 (0.39, 0.85)	228 (134, 294)	140 (79, 182)	88 (49, 114)	19 (6, 30)
Testing frequency							
Testing frequency, 5-days[a]	5-days	15 (5, 49)	0.03 (0, 0.22)	10 (1, 74)	3 (0, 44)	7 (1, 30)	1 (0, 9)
Testing Frequency, 3-days[a]	3-days	12 (3, 36)	0.01 (0, 0.15)	5 (1, 51)	1 (0, 34)	4 (1, 21)	1 (0, 5)
Vaccine effect							
Similar age-specific vaccine efficacy	0.04	14 (7, 35)	0.01 (0, 0.05)	4 (1, 17)	0 (0, 9)	3 (0, 11)	0 (0, 2)
Different age-specific vaccine efficacy [Pfizer]	0.06[b],0.04[c]	13 (7, 38)	0.01 (0, 0.06)	4 (1, 20)	0 (0, 9)	3 (0, 11)	0 (0, 2)
Different age-specific vaccine efficacy [Moderna]	0.13[b], 0.04[c]	14 (7, 41)	0.01 (0, 0.07)	5 (1, 24)	1 (0, 14)	3 (1, 14)	0 (0, 3)

[a]No vaccination assumed, [b] Vaccine assumed for resident agents, [c] Vaccine assumed for staff agents

the period to eradicate the outbreak by almost a week. Increasing the probability of an introduction increased the total number of infections from 7 to 72, and 5 additional individuals were hospitalized. Analyses for these outcomes revealed significant decreases attributed to testing and vaccination across different frequency of testing and vaccine efficacy. Prevention of hospitalizations was more effectively accomplished through vaccination and was independent on age-specific vaccine efficacy assumptions.

2.5 Discussion

The importance of careful use of non-pharmaceutical interventions was a critical lesson from the COVID-19 pandemic. Mask policies, limited visitation, and especially universal testing were critical to successful mitigation and prevention plans in the United States. Greater access to PPE and frequent testing surely played a part in reducing the case burden on LTCFs: case rates have dropped from a high of 33,625 nursing home cases/week to the current low of 1,927 cases/week [CMS, 2021]. December 18, 2020 marked the start of the Pharmacy Partnership for Long-Term Care Program in which the CDC partnered with multiple pharmacies to host on-site vaccination clinics for LTCF residents and staff [Gharpure et al., 2021b]. Despite good vaccination progress, nursing home residents remain at high risk. As regulations ease, and with the possibility of requiring yearly vaccinations to prevent future outbreaks, we must consider how surveillance, PPE usage, and vaccine timing and prioritization complement each other. Our study sought to describe the potential combined effects of recommended NPIs and vaccine deployment strategies on the size and duration of a COVID-19 outbreak in a model nursing home.

Results from our model were most evident when we assumed a larger probability of viral introduction.

Table 2.4: Results from scenario modeling using the median and 95% confidence intervals.

Scenario	Days to eradication	Attack Rate	Total Infected	Infected residents	Infected staff	Hospitalizations	Deaths
Introduction Probability & Testing Frequency							
High & 7-days	14 (7, 48)	0.02 (0, 0.1)	8 (1, 34)	2 (0, 16)	6 (1, 21)	0.5 (0, 3)	0 (0, 1)
High & 5-days	15 (5, 41)	0.02 (0, 0.07)	7 (1, 25)	1 (0, 12)	5 (1, 18)	0 (0, 3)	0 (0, 1)
High & 3-days	9 (3, 24)	0.01 (0, 0.04)	4 (1, 14)	0 (0, 6)	3 (1, 11)	0 (0, 2)	0 (0, 0)
Moderate & 7-days	14 (7, 41)	0.01 (0, 0.07)	5 (1, 23)	1 (0, 11)	3 (1, 14)	0 (0, 2)	0 (0, 0)
Moderate & 5-days	10 (5, 35)	0.01 (0, 0.07)	4 (0, 24)	0 (0, 12)	3 (0, 13)	0 (0, 2)	0 (0, 0)
Moderate & 3-days	9 (3, 30)	0.01 (0, 0.04)	3 (0, 15)	0 (0, 6)	2 (0, 10)	0 (0, 1)	0 (0, 0)
Low & 7-days	9 (7, 27)	0.01 (0, 0.04)	2 (0, 14)	0 (0, 9)	1 (0, 7)	0 (0, 2)	0 (0, 0)
Low & 5-days	9 (5, 25)	0.01 (0, 0.04)	2 (0, 13)	0 (0, 8)	1 (0, 7)	0 (0, 2)	0 (0, 0)
Low & 3-days	9 (3, 20)	0 (0, 0.02)	1 (0, 8)	0 (0, 4)	1 (0, 5)	0 (0, 1)	0 (0, 0)
Introduction Probability & Vaccine Prioritization							
High & Equal distribution	14 (7, 42)	0.02 (0, 0.11)	7 (1, 39)	1 (0, 17)	6 (1, 22)	0 (0, 3)	0 (0, 1)
High & Resident	14 (7, 56)	0.03 (0, 0.1)	9 (1, 35)	2 (0, 14)	7 (1, 22)	0 (0, 3)	0 (0, 1)
High & Staff	14 (7, 49)	0.02 (0, 0.09)	7 (1, 30)	1 (0, 15)	5 (1, 18)	0 (0, 3)	0 (0, 0)
Moderate & Equal distribution	14 (7, 42)	0.01 (0, 0.07)	5 (1, 24)	1 (0, 12)	3 (1, 15)	0 (0, 3)	0 (0, 0.05)
Moderate & Resident	14 (7, 35)	0.01 (0, 0.07)	5 (1, 24)	1 (0, 12)	4 (1, 14)	0 (0, 3)	0 (0, 1)
Moderate & Staff	14 (7, 35)	0.01 (0, 0.06)	5 (1, 22)	1 (0, 11)	3 (0, 11)	0 (0, 2)	0 (0, 0.05)
Low & Equal distribution	9 (7, 26)	0.01 (0, 0.04)	2 (0, 15)	0 (0, 9)	1 (0, 8)	0 (0,2)	0 (0, 0)
Low & Resident	14 (7, 42)	0.01 (0, 0.07)	5 (1, 25)	1 (0, 11)	4 (0, 15)	0 (0, 3)	0 (0, 1)
Low & Staff	14 (7, 35)	0.01 (0, 0.06)	4 (1, 19)	1 (0, 10)	3 (0, 10)	0 (0, 2)	0 (0, 0)
Introduction Probability & Vaccine Performance							
High & Similar efficacy	14 (7, 42)	0.02 (0, 0.1)	7 (1, 35)	1 (0, 15)	5 (1, 20)	0 (0, 3)	0 (0, 0)
High & Reduced efficacy (Pfizer)	14 (7, 42)	0.02 (0, 0.1)	7 (1, 33)	1 (0, 15)	6 (1, 18)	0 (0, 4)	0 (0, 0)
High & Reduced efficacy (Moderna)	14 (7, 45)	0.02 (0, 0.12)	7 (1, 40)	1 (0, 19)	6 (1, 21)	0 (0, 4)	0 (0, 1)
Moderate & Similar efficacy	14 (7, 36)	0.01 (0, 0.06)	3 (1, 20)	0 (0, 8)	3 (0, 13)	0 (0, 2)	0 (0, 0)
Moderate & Reduced efficacy (Pfizer)	13 (7, 35)	0.01 (0, 0.06)	3 (1, 20)	0 (0, 6)	3 (0, 11)	0 (0, 2)	0 (0, 0)
Moderate & Reduced efficacy (Moderna)	14 (7, 36)	0.01 (0, 0.06)	3 (1, 21)	0 (0, 9)	3 (0, 14)	0 (0, 2)	0 (0, 0)
Low & Similar efficacy	9 (7, 27)	0 (0, 0.05)	1 (0, 17)	0 (0, 10)	1 (0, 8)	0 (0, 2)	0 (0, 0)
Low & Reduced efficacy (Pfizer)	9 (7, 28)	0.01 (0, 0.05)	2 (0, 16)	0 (0, 9)	1 (0, 7)	0 (0, 2)	0 (0, 0)
Low & Reduced efficacy (Moderna)	9 (7, 28)	0.01 (0, 0.05)	2 (0, 16)	0 (0, 10)	1 (0, 8)	0 (0, 2)	0 (0, 0)

In such cases, increased frequency of universal testing and isolation of positive cases (quarantine or paid leave) lead to larger reductions in attack rate than any other scenario. Prioritizing the vaccination of staff over residents lead to a moderate decrease in attack rate when viral introduction probability was high. Community transmission rate is the strongest predictor of case rates in nursing homes thus far [Konetzka and Gorges, 2020] and staff are the most important vectors through which introduction from the community occurs [Goldberg et al., 2021, Toth and Khader [2021], Escobar et al. [2020]]. Our results support using strategic prioritization of staff for universal testing and vaccination as an important method for reducing the likelihood of an outbreak, especially in situations where community transmission is high.

There are several important challenges that these facilities will continue to face. LTCF administrators reported that staffing remains one of the primary barriers to maintaining high infection control standards [SteelFisher et al., 2021]. Additionally, facilities that had a high degree of disconnectedness via shared staff showed higher case rates in general [Chen et al., 2021]. Expanded paid leave programs may also reduce the need for staff to seek additional employment to make ends meet, generally lowering their personal risk and the risk of introduction events.

Evidence indicates that staff may be more hesitant to get the vaccine than residents [Unroe et al., 2020], and certainly have lower first-dose rates even if unrelated to hesitancy [Gharpure et al., 2021b]. Vaccine mandates are one way to approach ensuring vaccine coverage goals are reached, but may create additional

problems maintaining proper staff levels for delivering quality care. Additionally, nursing staff, including CNAs and LPNs, have high turnover rates in LTCFs. As a result, vaccination rates may fluctuate over time even within the same facility. Maintaining vaccine coverage goals will likely require an active program that includes acquiring confirmation from staff who receive vaccines from a different source (i.e. a local pharmacy or a different job). We have even less data about the risks presented by reopening nursing homes to visitors, prompting questions about vaccine and testing requirements for visitors. An extension to this model that adds a visitor agent could help answer these questions before observational data becomes available.

2.5.1 Strengths and Limitations

We calibrated our model using data from a real-world nursing home. The basal transmission model, in which no agents were vaccinated, generated plausible attack rates when compared to California nursing homes of a similar size. This, plus incorporating parameters from real-world data, provides external validity to the changes observed in our model. A particular strength of ABM is to show how complex outcomes can emerge from simple sets of rules; our model took advantage of this approach to show how interactions between staff and residents manifest the outbreak patterns observed in vivo. However, this model is primarily useful as an exploration of the impact of multiple interventions and introduction probabilities on an outbreak once introduction has occurred, and is therefore not meant to model the processes that lead to an introduction in the first place. Simulations were run for 150 days or until the facility was disease-free for up to 7 days; thus, it is also not able examine the impact of multiple introductions over longer periods of time or waning immunity from recovery or vaccination in its current form.

Not all data-derived parameters were made equally. The estimated effect of PPE use on transmission varied widely, thus making a reliable parameter difficult to define and the model sensitive to changes. Testing was also oversimplified in our model, as we assumed instantaneous results and all tests were equally sensitive. Additionally, we assumed that the effects of immunity, natural or from vaccination, was constant over the course of an outbreak and did not wane over time. We also assumed that staff agents had an equal chance of interacting with each resident agent, which is not reflective of intervention strategies that silo staff into daily routines focused on a specific subset of residents, such as dedicated staff for specific wards within the nursing home or for positive, isolated individuals.

2.6 Acknowledgements

This research was supported by CONACYT-UC MEXUS and a Seed Fund Award 2020-0000000022 from CITRIS and the Banatao Institute at the University of California. No third-party support was provided for this work. We would like to thank our liaison at our example nursing home in Los Angeles for sharing staffing information, floor plans and for providing valuable first-hand experience while we designed our study.

Section 3

II: Evaluation of vaccination and control strategies of porcine reproductive and respiratory syndrome (PRRS) in sow farms usingan agent-based approach

3.1 Abstract

INTRODUCTION: Porcine reproductive and respiratory syndrome (PRRS) is an endemic disease in many countries including the United States. The disease is responsible for severe economic losses every year in swine production systems because of the impact on both the reproduction and the development stages of the animals. The control and eradication of the disease has been very challenging mostly because of the rapid spread and the capacity of the virus to quickly mutate making the vaccine development very difficult. Here we propose a modeling approach that estimates the impact of PRRS on a swine farm and evaluates the effect of different intervention strategies in the disease control after the introduction in a naïve population.

METHODS: We developed a high-resolution within-farm disease spread agent-based model to simulate PRRS transmission and evaluate the impact of different PRRS control strategies. Our model recreates the reproduction dynamics in a typical sow farm, evaluates the impact of the disease in the production, and the effect of different intervention strategies for disease control (i.e. vaccination, acclimation of replacement gilts, herd closure). Our model is parametrized based on literature review, observed PRRS outbreaks and production parameters goals. For parameters with high uncertainty, we evaluated our model using a global sensitivity analysis framework based on random forest and regression trees, which estimates the influence of different combinations of parameters on the model outcomes.

RESULTS: The expected cumulative sow incidence in our model ranged from 6.3% to 42%. We present the impact of the disease under different scenarios using random forests and regression trees as part of our sensitivity analysis. Herd closure was the most influential parameter in our model reducing the cumulative incidence of sows in 60% and the time to disease elimination in 46% when implemented. Other parameters with high influence included the vaccine efficacy and the probability of introduction.

CONCLUSIONS: Our model highlights the importance of a better understanding of the circulating viral strains and the vaccine development efforts when interventions such as herd closure can not be implemented. We believe that our modeling framework allows better understanding and hypothesis testing about transmission dynamics and supports the implementation interventions to advance with PRRS prevention and control.

3.2 Introduction

Porcine reproductive and respiratory syndrome (PRRS) is a swine disease caused by Porcine reproductive and respiratory syndrome virus, which has two different genotypes (PRRSV-1 strain Lelystad and PRRSV-2 strain VR-2332) from the Arteriviridae family [Zimmerman et al., 2019]. The disease was identified as an emergent swine disease almost simultaneously in the early 1990s in Europe [Meulenberg et al., 1993] and the US [Mardassi et al., 1994, Meng et al., 1994], and since then it has become endemic on several regions in Europe, America and Asia. The two main genotypes are PRRSV-1, which is mostly present in America and Asia, and PRRSV-2 which is mostly present in Europe. PRRS is responsible for severe economic losses, which in US is estimated to be over 600M USD every year [Holtkamp et al., 2013, Nathues et al., 2017].

The disease is characterized for reproductive and respiratory problems, which translates into decreased number of weaned piglets in sow farms and underweight animals at the nurseries and finishers. PRRSV is genetically very diverse, and the field strains of PRRSV can vary widely in the virulence and the antigenic response [Halbur et al., 1996b,a, Mengeling et al., 1996]. The virus is shed in the environment via multiple secretions including: oral, nasal, urine, semen and feces [Zimmerman et al., 2019]. Some of the infected pigs might become persistently infected and shed the virus for prolonged periods of time, which plays a very important role on the disease becoming endemic once has been introduced into a susceptible herd. The main pathways of introduction into a susceptible farm include spreading from neighboring farms via airborne or fomites, movement of infected pigs, and semen from infected boars.

In the US, the main prevention and control mechanisms for controlling the disease rely on vaccination and biosecurity. Although there are several PRRS vaccines available, the vaccine efficacy against the diversity of circulating PRRSV strains had shown mixed results [Ding et al., 2021, Chase-Topping et al., 2020, Alexopoulos et al., 2005, Scortti et al., 2006]. In general, the vaccines has been successful in reducing the viral shedding and the symptoms, but does not prevent the infection. Previous exposure to the disease has a big influence on how the disease affects the infected animals and the success of the vaccine reducing the impact [Trevisan et al., 2021]. Another consideration of the PRRS vaccination is that current serology based tests can not differentiate between the antibodies produced by infection from the antibodies produced by the vaccine [Zimmerman et al., 2019].

In terms of biosecurity, cleaning and disinfection along with herd management are the most commonly used strategies. Some of the herd management practices that have been successful on reducing the PRRS impact includes herd closure, gilt acclimation and correct management of the newborns. Other strategies such as partial depopulation or targeted testing and elimination of infected animals have also been suggested but

due to the economic impact, is rarely considered.

With the objective of improving surveillance and prevention of the disease, multiple efforts have been implemented including the PRRS herd classification system [Holtkamp et al., 2011] and the Swine Health Monitoring Project (MSHMP). The PRRS classification system consists in assigning a status to the farms based on the history of PRRS viral circulation assessed via serology and PCR, which is used as a criteria when finding trade partners to move animals between farms. Farms with status of free of the disease will avoid trading animals with farms where the disease is present. The MSHMP incorporates this information along with the estimated herd prevalence of farms in some of the states in the US to provide updates on the viral circulation for certain regions, which allow the producers to identify high risk movements. One of the biggest challenges with the surveillance of PRRS is that the data to inform this surveillance systems is collected voluntarily so not all farms perform routine testing to determine the disease status. PRRS infection is often unnoticed (i.e does not produce clinical signs), therefore, assessment of population status PRRS is key for early detection and disease control.

Several modeling efforts have been done to improve the understanding of the impact of PRRS to the swine industry [Arruda et al., 2017, Galvis et al., 2021, Thomann et al., 2020, Thakur et al., 2015a,b]. Most of these have explored the between-farm spread of the disease and few have explored the within-farm spread of the disease [Phoo-ngurn et al., 2019, Colomer et al., 2019, Evans et al., 2010]. Colomer used a population dynamic P model (PDP) to explore the role of herd management in reducing the impact of the disease at both breeding and nursery; although the model proved to be very flexible for herd management strategies such as cross fostering, it did not included other interventions such as vaccination strategies. Phoo-ngurn used a compartmental Susceptible-Infected-Recovered ordinary differential equation (ODE) model to explore the effect of vaccination on PRRS reduction, but the model did not explored any other interventions such as herd management or improved biosecurity. Research has shown that the success in disease control and prevention will depend on how the vaccination is implemented and other biosecurity measures, which highlights the importance of evaluating the interaction of multiple control strategies.

Agent based models provide a flexible framework where we can assign individual characteristics to the population and represent the heterogeneity that could be relevant in terms of disease transmission and exploring the different implementations of the interventions used for disease control both at population and individual level. For example, it has been observed that the transmission of PRRS can vary within litters [Houben et al., 1995]. Agent based models allow us to define the behavior of the population more explicitly as opposed to other modeling approached where the behavior of the population is assumed to be homogeneous within groups (i.e. ODE or PDP models). In this work we aim to: 1) estimate the impact of

PRRS in a typical sow farm of the Midwest US, and 2) estimate the effect of the implementation of different interventions in reducing the PRRS impact. We believe our modeling framework will be useful to support decision making and better prevent and control PRRS breaks on farms.

3.3 Methods

3.3.1 Population Structure

We developed a high resolution within-farm disease spread stochastic agent-based model to evaluate the impact and different prevention and control strategies of PRRS in a sow farm. The population in the model includes 300 sows and multiple generations of their respective offspring followed up until they are sent to the nursery. Figure 1a shows the population flow through the sow farm.

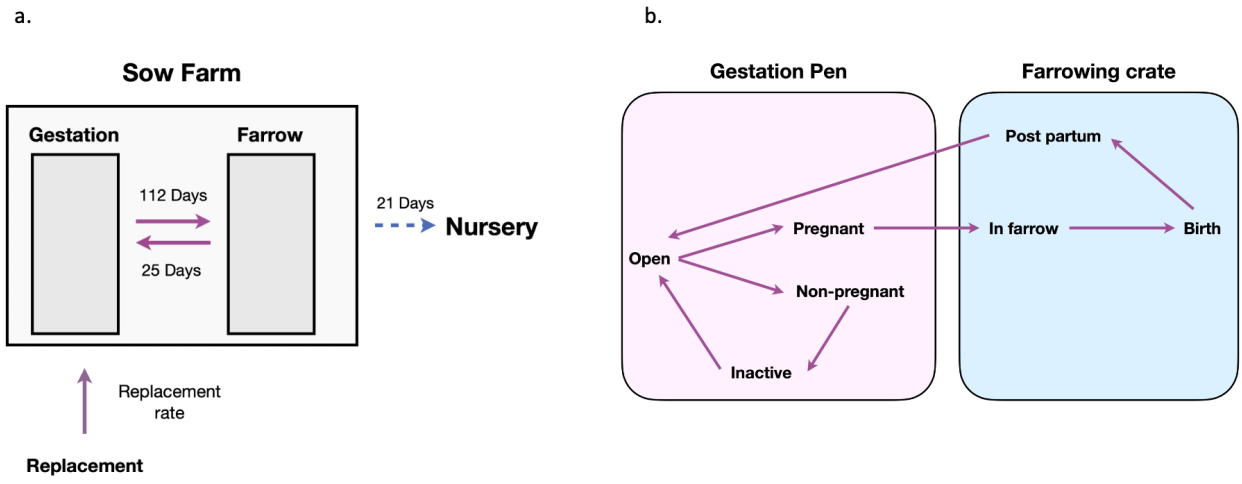

Figure 3.1: Population structure. 1a. Different locations inside the sow farm and the flow of the animals in the farm; 1b. the sow reproductive cycle as represented in our model.

3.3.2 Population Dynamics

3.3.2.1 Production Cycle

We recreated the sow reproductive cycle, which in our model last 21 days when the animals are not inseminated. When the animal is successfully inseminated a full production cycle is the 116 days of gestation plus 21 days of postpartum. Sows are kept in groups during the gestation and moved to individual crates for farrowing. The first 3 days of the cycle the animals will remain inactive, then during the cycle days 4 to 8 the sow can get inseminated and if the insemination is successful, the sow will become pregnant. The pregnancy of the animals in our model is assumed to be 116 days, after the day 112 of pregnancy the sow is moved from the gestation pen to an individual farrowing crate. Then the sow will stay in the farrowing crate until 21 days after birth. After the 21 days of postpartum, the sow is moved back to the gestation pen and they start the cycle again. If the sow is not inseminated, it will stay 21 days inactive in the gestation pen until they start the reproduction cycle again (Figure 1b). After 21 days in the farrowing room, the piglets will be moved out to the nursery. Sows are constantly being replaced based on a replacement rate. Parameters for the production cycle of the sows were assumed to follow the target production parameters for a typical commercial sow farm in the US.

3.3.2.2 Disease Dynamics

The disease spread is represented using different disease states for each agent (Figure 3.2). Infected animals transmit the disease to the susceptible based on a probability of transmission (β) and the infection distance of 1 meter [Wills et al., 1997]. Once a susceptible animal has been exposed to an infection source, we recreate the viral load and built up of the immune response as described by [Lopez and Osorio, 2004]. When the animal has been exposed, the viral load starts to increase and peaks at 12 days post infection. After 7-9 days post infection, the immune response start to appear and increases as the viral load decreases. This dynamic of the viral load and immune response in our model determines the probability of shedding which is associated by the value of β_s. For the vaccinated animals, this viral shedding is reduced by a parameter (δ_v) as shown in Figure 3.2. After day 30 of the simulation we introduce an infected animal, and through the whole simulation time we also included a parameter that defines the probability of an infected replacement gilt being introduced.

To represent the impact of the disease, the infected sows will have a reduced reproductive performance including lower pregnancy rates [Neuman et al., 2005, Dee et al., 1996], and higher farrowing mortality

[Scortti et al., 2006]. For purposes of comparing different scenarios we record variables such as: cumulative incidence for both sows and piglets, and time to elimination of the disease.

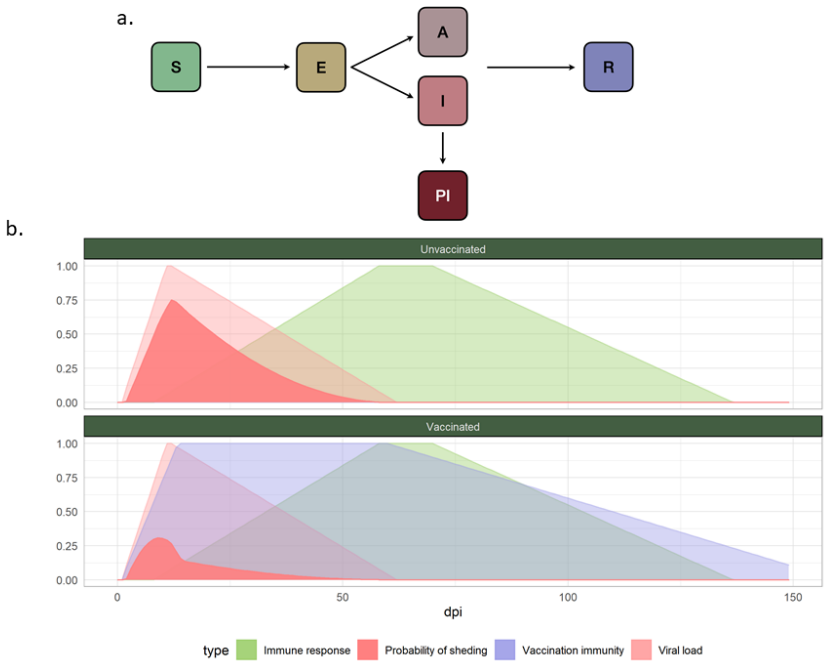

Figure 3.2: Disease states represented in our model. a. the transition between disease states representing: S = susceptible, E = exposed, A = infectious asimptomatic, I = infectious symptomatic, PI = persistently infected and R = recovered; b. Time series of the Immune response, viral load and vaccination immunity and its relationship on the probability of shedding trought the infection process of an unvaccinated and a vaccinated animal.

3.3.2.3 Interventions

We explored different interventions for prevention and control of the disease in our model. Some of the interventions explored included sow vaccination, vaccination of newborns, herd closure, and testing and acclimation of replacement gilts. The vaccination in our model is applied for a given number of sows depending on the proportion of animals to vaccinate V_p, and a re-vaccination happens once a year. The piglets that are born under the scenarios of newborn vaccination will also receive a vaccine dose, the number of piglets to vaccinate will also depend on the V_p. The vaccine does not prevent the infections, it will only reduce the symptoms and the shedding of the virus by the parameter δ_v. To represent the herd closure in our model, once the disease has been detected, the replacement of gilts is stopped until the disease is eliminated. The vaccination and testing of replacement gilts are also explored in the model, the replacement gilts will be tested and vaccinated in a quarantine pen before being introduced with the rest of the animals under these

Table 3.1: Parameters used for the model.

Parameter	Value	Reference
Production parameters		
Number of sows	300	
Pregnancy rate	90%	[a]
Median Number of piglets	9.13	[a]
Farrowing mortality	14%	[a]
Days in farrowing	21 days	[a]
Replacement rate	20% of the inventory per year	[a]
Disease parameters		
Infection distance	1 m	(Wills et al. 1997)
Infection probability	(16, 20, 24%)	[b]
Abortion probability	10%	(Neuman et al. 2005),
Vertical transmission probability	35%	(Neuman et al. 2005; Dee et al. 1996),
Asymptomatic probability	1%	(Dee et al. 1996), [b]
Born alive when infected	-59%	(Scortti et al. 2006)
Farrowing mortality when infected	+18%	(Scortti et al. 2006)

[a]based on production target. [b]Explored via sensitivity analysis scenarios.

3.3.3 Model implementation and analysis of the outcomes

We ran 2000 simulations for a period of one year using a controlled random seed. Parameters were obtained from literature and from the target production parameters for a typical commercial sow farm in the US as shown in Table 3.1. To calibrate our model, we compared the proportion of infected sows in a year to the MSHMP 2021 report [MSHMP, 2021]. For each of the simulations we sampled selected parameters from a list of possible values representing low, moderate and high estimates or yes/no for the implementation of interventions (Table 3.2). We used random forest (RF) to explore influence of the parameters in the outcome of interest, and classification regression trees (CART) to provide a graphical understanding of how the parameters interact to affect the outcomes selected, similar to the process described by [Harper et al., 2011] for global sensitivity analysis (GSA) of complex models. Code for reproduction of the results is available in https://github.com/jpablo91/PRRS_Modelling. The model was implemented in GAMA 1.8.1 [Taillandier et al., 2019b] and the analysis of model outcomes in R [R Core Team, 2020].

Table 3.2: Parameters explored for global sensitivity analysis and the sample spcae defined for low, moderate and high estimates for the PRRS intra farm model.

Parameter	Definition	Sample space
Shedding_p	Daily probability that when infected, an animal will transmit the disease to others within range	(0.16, 0.2, 0.24)
Vaccination_p (V_p)	Proportion of animals vaccinated	(0.72, 0.9, 1.00)
V_Shedding (δ_v)	Effect of the vaccine reducing the viral shedding	(0.64, 0.8, 0.96)
P_asymptomatic	Probability of an infected animal being asymptomatic	(0.01, 0.012, 0.015)
P_introduction	Probability of introducing an infected animal when replacing sows	(0.04, 0.05, 0.06)
Replacement Testing	Whether or not to perform testing of replacement sows	(yes, no)
Vaccination Replacement	Whether or not to perform vaccination of replacement sows	(yes, no)
PigletVaccination	Whether or not to perform newborn vaccination	(yes,no)
HerdClosure	Implementation of Herd closure	(yes, no)

3.4 Results

The estimated sow cumulative incidence ranged between 6.3% to 42% with a median of 19%. When compared to the MSHMP 2021 report, we obtained outbreaks of similar sizes in overall magnitudes, data was not available to make a more in depth comparison of the outbreaks in terms of sequence of events. The farrowing mortality incidence varied much less, between 11% and 15%, unfortunately there was no data available on farrowing mortality to compare our simulation results to observed data. The time to elimination of the disease ranged between 190 and 358 with a mean of 303 days until elimination of the disease, 75% of the iterations showed a long elimination time ($>$ 358 days to elimination) which could be considered as the disease establishing on the farm and becoming endemic. RF and CART results show that the model predictions are sensitive to complex combinations of parameter estimates. The influence of the parameters and these complex interactions between them is presented in Figure 3. Depending on the outcome analyzed, the classification and trees generated explained between 65% and 75% of the variance. For the cumulative sow incidence and time to disease elimination, herd closure was the parameter with the greatest influence. The implementation of herd closure reduced in average the sow cumulative incidence from 23% to 6.3% and the time to disease elimination from 358 to 109 days after the introduction. For the case of farrowing mortality, the proportion of asymptomatic animals was the most influential parameter.

To summarize the impact of the interventions, we looked at the proportionate reduction in each outcome (sow cumulative incidence, farrowing mortality and time to disease elimination) for the scenarios with the different implementation of interventions (Figure 4). When comparing the interventions, we see that testing of the replacement gilts had the greatest effect in reducing the Sow cumulative incidence (-67%), farrowing mortality (-15.92%) and time to disease elimination (-55.69%).

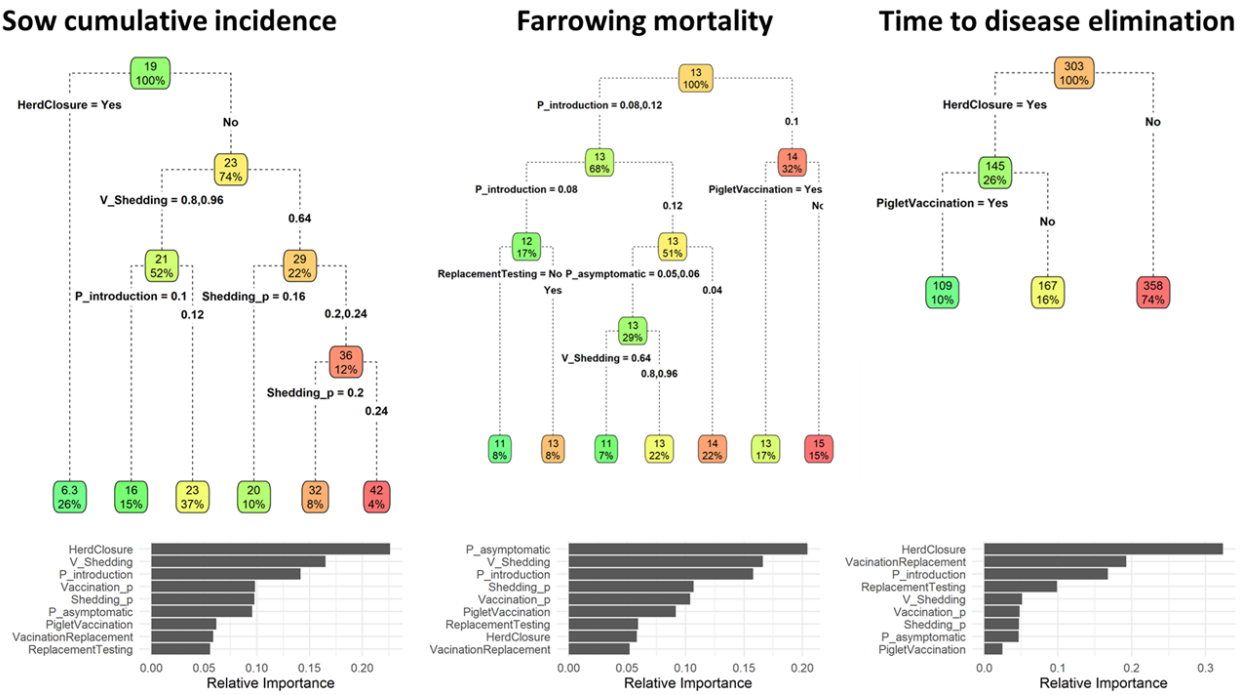

Figure 3.3: Global sensitivity analysis. Classification trees showing the interactions between the parameters explored using global sensitivity analysis for each of the outcomes analyzed (top). Normalized relative importance of the parameters used for the sensitivity analysis (bottom). Description of the parameters canbe found on Table 2.

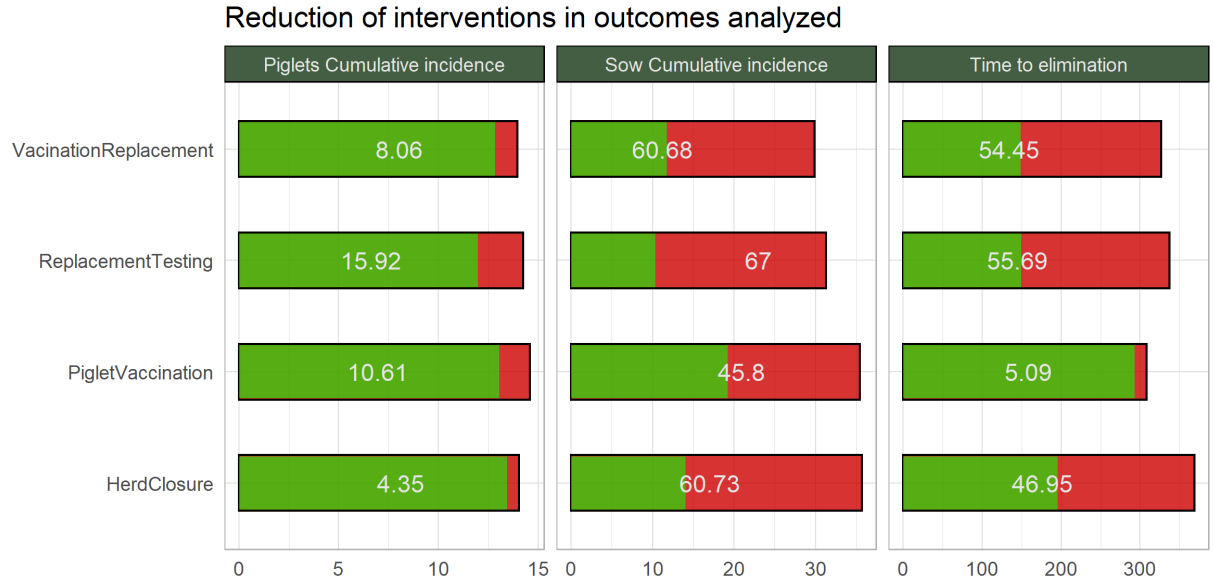

Figure 3.4: Reduction in the cumulative incidence of sows, farrowing mortality and time to disease elimination presented as the proportionate reduction for each of the outcomes analyzed

3.5 Discussion

Despite being one of the most economically important diseases in the swine industry, the transmission dynamics of PRRS remain poorly understood. In this study we attempt to cover multiple scenarios where the uncertainty around the virulence and effect of vaccination are considered. We developed a new simulation model using an agent based approach that allow to simulate different diseases transmission scenarios and can be easily adapted to different settings (i.e. other swine diseases such as porcine epidemic diarrhea or African swine fever). Our model allowed to explicitly include the disease progression with much more detail than previous models have done for this setting. This approach also allow us to be more flexible in terms of the interventions applied to control the disease and model more specific scenarios. We illustrate our model performance using a small-medium farm, since we included a population of 300 sows, but the model is computationally efficient and was able to run several iterations in a personal computer without issues. Therefore, the model can be definitively expanded and adapted to settings for larger farms and include more agents to represent bigger farms, but that would require more computational power and time, which was not of our interest for this publication. Future studies might explore the escalation of this modeling approach for bigger populations or different combination of strategies, which potentially will require cloud computing in order to run several iterations of the model.

The data used to calibrate our model infection parameters was from the MSHMP 2021 report, which is somehow biased towards the production sites that are reporting the PRRS status, presumably the ones more aware of the disease that are continuously working on improvement of PRRS prevention and with likely better biosecurity practices. Additional data on the sequence of events would have been very useful to calibrate better the model, but this data is not easy to obtain for PRRS since during standard practices of an outbreak only a proportion of the population is sampled for surveillance of the disease. Another limitation of this publication is that we did not explicitly simulated the movements of personnel and trucks, which its known to play an important role in PRRS introduction into a site; but we believe that the probability of introduction parameter used in our model can be used to approximate this (i.e. places where there is more pig movements or other contacts between farms would be considered with higher introduction probabilities).

The variable importance for the parameters explored in our model is not unexpected, but it provides a reasonable explanation on how the parameters interact with each other to affect the outcomes analyzed. The parameter influence is somehow balanced, except for the herd closure effect on time to disease elimination, none of the parameters had a variable contribution larger than 25%. The modeling approach allowed us to implement the interventions in a more flexible way that previous models have done and explore the

interactions between different combination of interventions.

Herd closure accounted for >20% of the relative importance for both the sow cumulative incidence and time to disease elimination. Herd closure can be difficult to implement in sow farms especially in small sow farms where the space and resources are limited. Our model suggests that for scenarios where herd closure can not be implemented, a high vaccine efficacy and a low probability of introduction can still reduce the sow cumulative incidence almost in half. Parameters such as viral shedding and the effect of the vaccine in our model can be interpreted as an approximation to the wide genetic diversity of the virus. Our model was sensible to both parameters which highlights the importance of the selection of an appropriate vaccine that is more efficient against the circulating virus strains in the area and keeping high biosecurity levels to minimize the probability of introduction. Although PRRS testing has been improving during the last years, there is a need to characterize better the circulating strains in order to more efficiently manage the swine trade and avoid exposing animals to different PRRS strains. In this regard, the use of tools such as Disease BioPortal (https://bioportal.ucdavis.edu) that allows a better visualization, monitoring and tracing of the circulating strains across sites and production systems could effectively help to support decision making and better prevent and control PRRS spread, saving producers millions of dollars annually.

3.6 Acknowledgements.

This research was supported by CONACYT-MEXUS and the National Science Foundation BigData:AI (Award No. 1838207) and Convergence Accelerator-Track D (Award No. 2040680). A special thanks to Maria Jose Clavijo who provided her expertise in the swine industry production systems and PRRS control to guide the modeling efforts.

Section 4

III: Spatial-explicit agent-based modeling to inform targeted surveillance and emergency response against foot-and-mouth disease in the last phase of eradiation programs

4.1 Abstract

Foot-and-Mouth Disease continues to be one of the most economically important diseases for the livestock industry due the international trade restrictions and the production losses in the affected countries. Despite the intense local, national and international efforts for FMD prevention and control, FMD remains endemic in many countries in South and central America, most of Africa, Asia and Eastern Europe. In this study we used data from animal demographics in Ecuador including location of farms, vaccination coverage and movement patterns to evaluate the spatio-temporal dynamics of FMD at local and national level. Our model also asses the interventions to control the disease impact, such as emergency vaccination, culling and movement restrictions. Model outcomes include the total number of infected farms, culled animals and farms to vaccinate in a disease emergency scenario to control de spread. Risk maps were generated for different introduction scenarios. Our results suggest that reducing the average number of days to detection and removal of infected farms from 21 to 7 days can reduce the overall disease impact in a 53.3%. Scenarios where the index case was introduced in the south region resulted in larger outbreaks. The results presented here intend to support the current FMD eradication program in Ecuador to improve the emergency preparedness and advance faster towards the final steps of the eradication process. Our modelling approach can be easily adapted to different scenarios in other countries and for other transboundary animal diseases such as African Swine fever.

4.2 Introduction

Foot and mouth disease (FMD) is a highly contagious viral disease that affects cloven hoofed animals, including several domestic species such as: cows, pigs, sheep, and goats. Although the disease is usually not fatal, it usually has a huge economic impact for the livestock industry of the affected countries [Knight-Jones and Rushton, 2013, Thompson et al., 2002]. The transmission from an infected to a susceptible animal occurs via respiratory and oral routes and can spread very quickly to other animals in the farm or nearby farms through direct or indirect contacts. Infected animals shed the virus through secretions (saliva, feces, semen, milk, etc.) and the virus can survive for long periods of time in the environment making it easy to be transported on equipment, food supplies, trucks and travel long distances in the air. Other risk factors associated with the disease includes high animal density [Bessell et al. [2010]; Perez2005], mixing with animals from different species [Hayama et al., 2012, Bessell et al., 2010, Dukpa et al., 2011], low biosecurity, and high amount of movements between farms.

The process of eradication of FMD relies on the protection of the susceptible population and rapid response to early detect and rapid control outbreaks. Currently the best tool for control and eradication of FMD is vaccination. There are many factors that can influence the effectiveness of the vaccination program, such as the transportation and application of the vaccine. These factors can make the effectiveness vary widely, and sometimes it can be extremely poor. In the last decade there has been a significant advancement towards the eradication of FMD in South America. Peru and Bolivia have both halted their vaccination programs and obtained disease-free without vaccination status from the World Organization for Animal Health (OIE), in 2017 and 2018 respectively. The South America region has an 88.5% extension of territories considered FMD free, of which 22.8% do not practice vaccination. On the other hand, since 2017 there have been also some steps back in the eradication process. Venezuela lost the status in 2017 after the decay in the vaccination coverage from 95% in 2014 to 53% in 2018 [PANAFTOSA-OPS/OMS, 2019], and Colombia experienced an outbreak with an estimated impact of $300K millions of losses due to trade restrictions and control measures [Agronegocios, 2019].

Many models of FMD have been developed using a wide variety of methodologies to account for uncertainty (deterministic or stochastic), heterogeneity of the population (spatial models, contact structure, population characteristics), and availability of the data. Epidemiological FMD models have been used for three main reasons: to evaluate response to outbreaks [Ferguson et al., 2001, Hayama et al., 2013, Keeling et al., 2001, Morris et al., 2001, Boender et al., 2010], to estimate the impact in naïve populations [Bates et al., 2003, Carpenter et al., 2007, Garner and Beckett, 2005], and to guide the eradication efforts in endemic regions

[Martínez-López et al., 2014]. Models such as AusSpread [Ward et al., 2009], InterSpread Plus [Sanson, 1993], North America Animal Disease Spread Model (NAADSM)[Harvey et al., 2007], Davis Animal Disease Simulation (DADS) and DTU-DADS, use a state-transition microsimulation approach where the resolution level of the population at risk goes down to the farm level and multiple transmission pathways can be modeled, but these models require a considerable amount of computation time and resources, especially for nation-wide disease spread simulations.

Most of the countries where FMD models have been recently developed (e.g. UK, US, Australia) are regions where the disease is absent or was introduced after a long period of absence, and therefore, do not have a current vaccination program. Other countries where the disease is established or that have a current vaccination program have notably less research in this area. In 2017, Pomeroy published an extensive literature review of FMD models and listed only 5 models developed for endemic regions [Martínez-López et al., 2014, Chowell et al., 2006, Estrada et al., 2008, Rich, 2008, Gilbert et al., 2005] of which most don't support scenario modeling and only one uses farm level data[Martínez-López et al., 2014], highlighting the over-representation of models at locations where FMD has an epidemic character and recognizing the need for developing FMD models in endemic regions [Pomeroy et al., 2017].

Most of the models previously developed agree that the success of different intervention strategies will vary depending on the region, which could be due to the different trade patterns and population structure. For example, by the late 1990s some countries in South America, including Argentina, Brazil, Uruguay, and Paraguay successfully controlled the disease and ceased vaccination. When the disease re-emerged in 2000, stamping out was initially tried to control the disease, however, due to the delays in disease reporting and control, stamping out only was not effective and mass vaccination ended up being re instituted [Rich, 2008].). In most of the countries where the disease is endemic preventive vaccination is the main tool for control and eradication, and this represent an extra component that most of the previously developed models are not implementing. Most of the models developed and discussed previously have been developed specifically for countries where the disease has been absent for several years, and some of these models (i.e. NAADSM) explicitly state that they are inappropriate for disease spread simulation of endemic diseases[Reeves et al., 2012]

Ecuador, although did not report FMD outbreaks since 2012, it is still in trying to control and eradicate FMD and is currently vaccinating the bovine herds. In this publication we developed an spatial explicit agent based model with the objective of estimate the impact of a hypothetical re-emergence of FMD in Ecuador under different scenarios. We used our model to identify vulnerable regions and evaluate the effect of interventions and control strategies to support decision making and accelerate the last phase of eradication

in the country.

4.3 Methods

4.3.1 Model framework

We developed a agent based simulation model that recreates the transmission dynamics on a local and national level. To achieve this we aggregate the demographic characteristics fo the population at risk using a hexagonal grid of 10km radius where each cell is used as the basic unit of analysis (Figure 4.1). This allow us to reflect the heterogeneity of the population and incorporate interventions at local level such as culling and restriction of movements within a 10 km radius.

4.3.2 Data

To inform our model we use the following sources of data provided by the Veterinary Services of Ecuador (AGROCALIDAD): 1) *Vaccination records*, AGROCALIDAD performs a biannual vaccination campaign targeting bovines only. AGROCALIDAD reports a vaccination coverage of nearly 100 % of the cattle population for each vaccination campaign, this information provides a more up to date estimation of the distribution of the population in the country than other sources such as the census. Some relevant information we used for our model from this dataset included: the number of animals per farm, location of the farms, and vaccine coverage for years 2019 and 2020. 2) *Movement records*, the SIFAE (Sistema Informático de Fiebre Aftosa en el Ecuador) is a system for traceability and control of animal movements in the country. As part of the legislation for animal trade in the country, every movement must be approved, and only movements from premises where vaccination was performed in the previous vaccination campaign are allowed. We used data from 2019 to inform our model about the movement patterns of the farms aggregated at the grid level such as probabilities of movements to other farms and fairs, origins and destinations, and movements within each hexagonal cell. 3) *Census for other species than cattle*, locations and number of animals per farms for other species such as goats, sheep and camelids was also provided by AGROCALIDAD and incorporated in the model.

4.3.3 Local spread dynamics

To represent the transmission of FMD at a local level we used a compartmental modeling approach where the population for each cell (N_i) is subdivided into susceptible (S_i), exposed (E_i), infected (I_i), removed (R_i) and culled (X_i). Once the disease has been introduced into a cell, the transition between compartments is calculated using the following ordinary differential equations (ODE):

$$
\begin{aligned}
S_i &= -\frac{\beta_i I_i S_i}{N_i} - \frac{\mu_i S_i}{N_i} \\
E_i &= \frac{\beta_i I_i S_i}{N_i} - E_i\sigma - \frac{\mu_i E_i}{N_i} \\
I_i &= E_i\sigma - \gamma_i I_i - \frac{\mu_i I_i}{N_i} \\
R_i &= \gamma_i I_i \\
X_i &= \frac{\mu_i S_i}{N_i} + \frac{\mu_i E_i}{N_i} + \frac{\mu_i I_i}{N_i}
\end{aligned}
$$

The rate at which animals transition from susceptible to exposed (β_i) for each cell is calculated as follows:

$$\beta_i = \beta\omega_1\omega_2\omega_3(1 - v_p)$$

Where β is a global transmission rate, ω_1, ω_2 and ω_3 are the influence of animal density, other species and within cell movements respectively, and v_p is the vaccinated proportion. We assume that places with higher animal density [Bessell et al. [2010]; Perez2005; Branscum et al. [2008]], presence of other species [Hayama et al., 2012, Bessell et al., 2010, Dukpa et al., 2011] and high within cell number of movements [Fasina et al., 2013] will have higher transmission rates. The latency period between exposure to infectious ($1/\sigma$) is assumed to be 5 days [Yadav et al., 2019]. The transition between infected to removed (γ_i) is represented as the inverse of the average number of days to detection and removal of infected farms. We also included a transition from susceptible, exposed and infected farms to culled farms, which is modulated using a parameter for the speed at which the farms are culled (μ_i).

Transmission between spatially adjacent cells is also simulated to represent other disease spread mechanisms such as fomites and airborne transmission. This adjacent cell transmission is affected by the proportion of infected animals. For the infected cells, every step of the simulation a Bernoulli distribution describes the probability of infecting one of the adjacent cells as follows $P(y_{ij} = 1|x_i = 1) = \frac{I_i+2}{N_i+4}$, where $y_{ij} = 1$ is the adjacent transmission between a pair of cells, $x_i = 1$ is that the current cell is infected and $\frac{I_i}{N_i}$ is the proportion of infected farms. All the parameters are local, which means each hexagonal cell is parametrized

individually based on the population characteristics, and parameters such as γ_i, μ_i and between spatially adjacent cells transmission are reactive to the disease status of the hexagonal cell and the interventions implemented in the model.

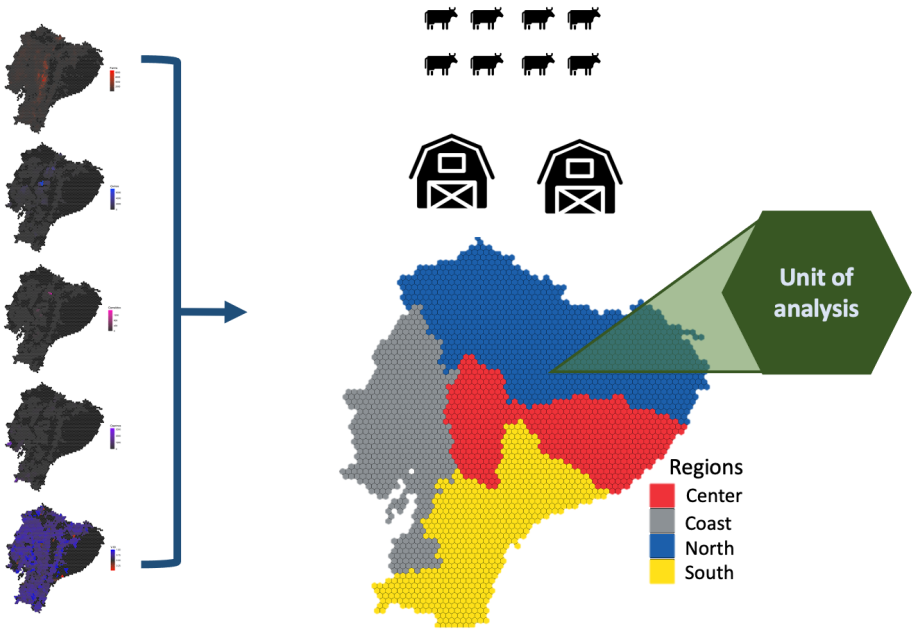

Figure 4.1: Modeling framework. The population characteristics are aggregated in a hexagonal grid, each cell from the grid is treated at the unit of analysis. The country is subdivided in 4 main regions: North, South, Center and Coast with distinctive animal demographics

4.3.4 Long distance spread dynamics.

To represent the transmission of the disease across long distances and between different regions, we used an origin-destination probability matrix calculated using the movement records. Each cell has a list of potential trade partners observed from the movements records and probabilities associated for moving animals from one cell to another in any given day. The probability of exporting infected animals form one farm to another is represented as a function of the proportion of animals infected at the origin as follows: $P(y_{ij} = 1|x_i = 1) = \left(\frac{I_i+2}{N_i+4}\right)(p_{mov,ij})$, where $y_{ij} = 1$ is the long distance transmission between a pair of cells, $x_i = 1$ is that the current cell is infected, $\frac{I_i+2}{N_i+4}$ is the Wilson adjusted proportion of infected farms and $p_{mov,ij}$ is the probability of a movement between the given pair of cells.

4.3.5 Interventions.

The interventions explored in our model followed the guidelines of the emergency plan in the country, where control zones are defined for 10 km radius and surveillance zones are defined for a 25 km radius around the detected farms. The interventions included: restriction of movements, depopulation of farms, emergency vaccination and increased surveillance.

At the beginning of the simulation, a baseline average time to detection of 21 days is assumed. Once a farm has been detected positive, movement restrictions and culling of the population are implemented in the 10 km control zone, and increased awareness and emergency vaccination are implemented in the 25 km surveillance zone. The movement restriction intervention reduces the parameter $p_{mov,ij} = 0$, which effectively stops any movement from the affected cell. Culling implementation is represented increasing the value for the parameter μ_i, which is the rate at which individuals from the compartments S_i, E_i and I_i transition to the compartment X_i. There is a baseline vaccination coverage at the beginning of our simulation according to either, a homogeneous coverage of a 95% across the country or a per cell coverage estimated using the data provided by AGROACALIDAD. Then for scenarios with emergency vaccination in our simulation there will be an increased coverage in the surveillance zone when the disease is detected.

A surveillance zone is defined in a 25 km radius where the awareness of the disease is increased, reflected in reducing the average number of days to detection; and emergency vaccination is implemented, where we assume a vaccination coverage based on the parameter V_{ev} and a vaccine efficacy V_{ef}[Cox and Barnett, 2009].

4.3.6 Model Implementation

We ran 500 simulations for a period of 18 simulated months using a controlled random seed. For each of the simulations we sampled selected parameters from a list of possible values representing low, moderate and high estimates or yes/no for the implementation of interventions (Table 4.2). To asses the impact of the disease we recorded variables such as the total number of infected and culled farms, and we used random forest (RF) to explore influence of the parameters in the outcome of interest, and classification regression trees (CART) to provide a graphical understanding of how the parameters interact to affect the outcomes selected, similar to the process described by [Harper et al., 2011] for global sensitivity analysis (GSA) of complex models. Code for reproduction of the results is available in https://github.com/jpablo91/EcuadorFMD The model was implemented in GAMA 1.8.1 [Taillandier et al., 2019b] and the analysis of model outcomes in R [R Core

Table 4.1: Model parameters.

Parameter	Estimate	Reference
Population parameters		
Number of farms	$280,000$	[a]
Avg. Indegree	49.46	[a]
South	24.69	[a]
North	51.72	[a]
Coast	10.92	[a]
Center	101.41	[a]
Avg. Outdegree		
South	9.18	[a]
North	16.46	[a]
Coast	6.8	[a]
Center	28.02	[a]
Disease parameters		
Latency period ($1/\sigma$)	5 days	(Yadav et al. 2020)
Vaccine efficacy	70%	(Cox and Barnett 2009)
Average days to detection ($1/\gamma_i$)	21 days	[b]
Interventions		
Avg. Vaccination coverage in 2019		
South	80%	[a]
North	75%	[a]
Coast	77%	[a]
Center	83%	[a]
Avg. Vaccination coverage in 2020		
South	80%	[a]
North	80%	[a]
Coast	79%	[a]
Center	73%	[a]

[a] Estimated from data provided by AGROCALIDAD. [b] Estimated from observed events reported by the OIE.

Table 4.2: Parameters explored for global sensitivity analysis.

Parameter	Definition	Sample space
GBetaPh (β)	Global transmission rate for between farm local transmission	(0.2, 0.25, 0.3, 0.35)
IntroductionRegion	Region where the index case was simulated	(Center, Coast, South, North)
V_coverage	Initial vaccination coverage	(homogeneous, 2019, 2020)
V_efficacy	Vaccine efficacy	(0.7, 0.8, 0.9)
CullingRate (μ_i)	Local culling rate when the disease has been detected	(0.0, 0.1, 0.12)
OREab	Influence of the size of farm in the between farm local transmission rate	(0.0, 0.1, 0.2)
OROeb	Influence of the abundance of other species in the between farm local transmission rate	(0.0, 0.1, 0.2)
ORLb	Influence of the within cell movements in the between farm local transmission rate	(0.0, 0.1, 0.2)
Movement restrictions	Whether or not movement restrictions are implemented after the detection of a case	(yes, no)
detection_effect	Average number of days to detection and removal of infected farms after the first case has been detected	(21, 14, 12)
EVCoverage	Coverage of emergency vaccination	(0.8, 0.95)

Team, 2020].

4.4 Results

The number of infected farms varied between 1 to 267 infected farms with a mean of 15, the number of culled farms (for scenarios when culling was implemented) ranged from 2 to 733 with a mean of 47, and the number of farms that required emergency vaccination (when implemented) ranged from 66 to 67,905 with a median of 5,100.

The influence of the parameters explored via sensitivity analysis in the outcomes examined are presented in Figures 4.2, 4.3, 4.4. The parameters most influential parameters for the number of infected farms included the global transmission coefficient (*GBeta*), region of introduction of the index case (*IntroductionRegion*) and the initial vaccination coverage (*V_coverage*). When comparing the initial vaccination coverage, the average number of expected farms goes from 19 to 5.7 when a homogeneous vaccination coverage of 95% is assumed.

For the total culled farms, the most influential parameters included the effect of animal density on the disease transmission (*OREab*) introduction region (*IntroductionRegion*) and the global transmission coefficient (*GBeta*). Some interventions in our model showed to reduce the total number of culled animals drastically, for example the implementation of movement restriction reduced the average number of culled animals from 137 to 50 and the reduction of average number of days to detection from 21 to 7 or 14 reduced the average number of culled farms from 69 to 23.

The parameters most influential for the number of emergency vaccinated farms included the introduction region (*IntroductionRegion*), the influence of the animal density in the transmission coefficient (*IREab*) and the culling rate (*CullingRate*). When the index case was introduced in the Center or North as opposed to

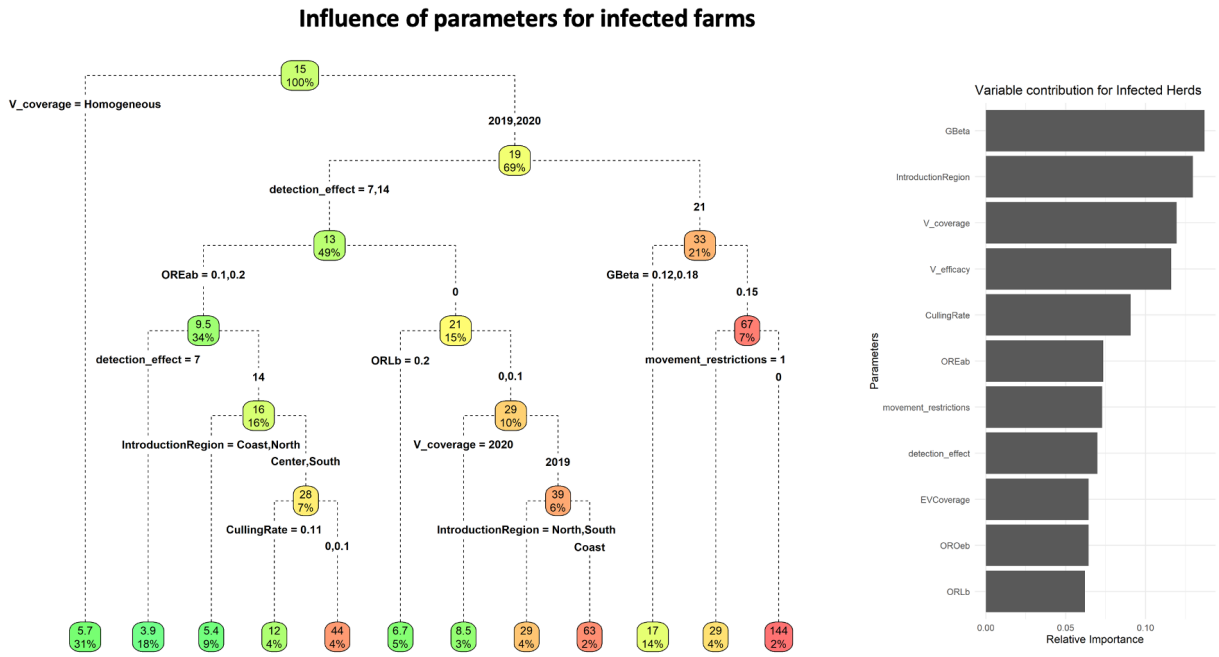

Figure 4.2: Global sensitivity analysis for the number of infected farms

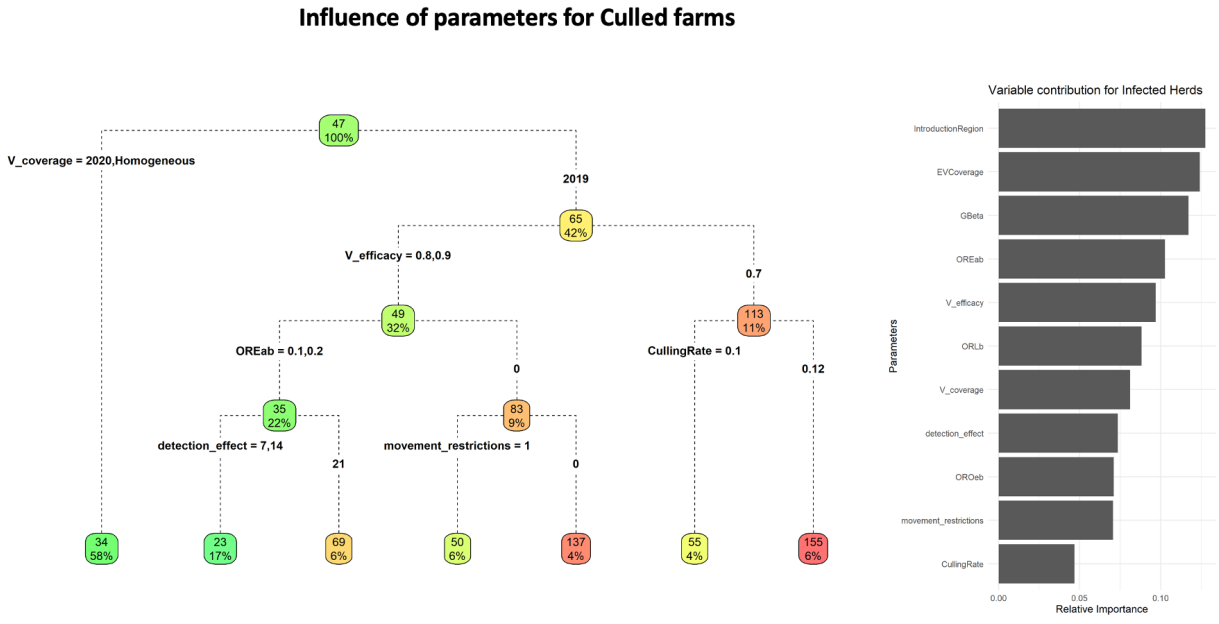

Figure 4.3: Global sensitivity analysis for the total culled farms when culling was implemented.

the Coast or South, the average number of farms vaccinated increased from 2.6 thousands to 7.6 thousands of farms.

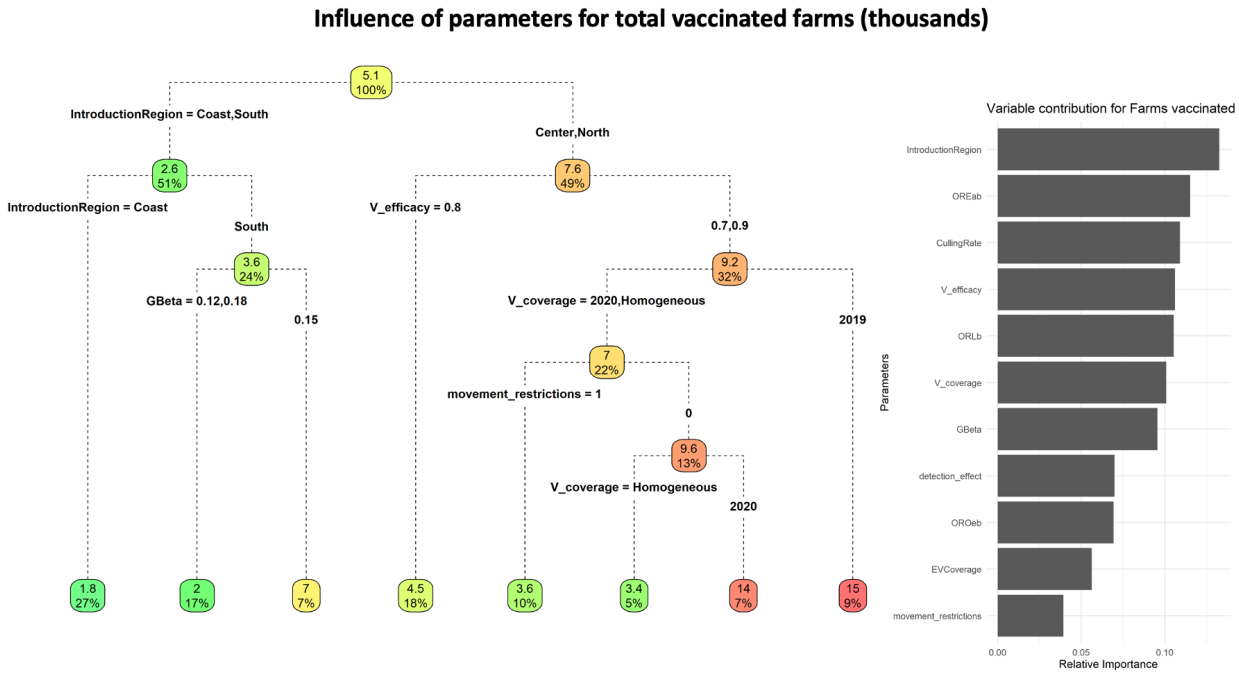

Figure 4.4: Global sensitivity analysis for the number of vaccinated farms when emergency vaccination was implemented.

Based on the number of times a cell was infected for all the simulations, we generated risk maps with the probability of infection under different scenarios of introduction of the index case (Figure 4.5). The average number of infected farms was the highest when the disease was introduced in the south of the country with an average number of infected farms of 21.6. When we look at the resources used to control the outbreaks, the highest number of culled farms happened when the disease was introduced in the North with average number of 38 farms, and the highest number of vaccinated farms was when the disease is introduced in the Center with an average of 4660 farms.

To compare the interventions implemented in detail, we estimated the average proportion in the reduction of farms infected (Figure 4.6). Reducing the average number of days to the detection of an infected case showed the greatest effect in reducing the total number of infected farms (53.23%).

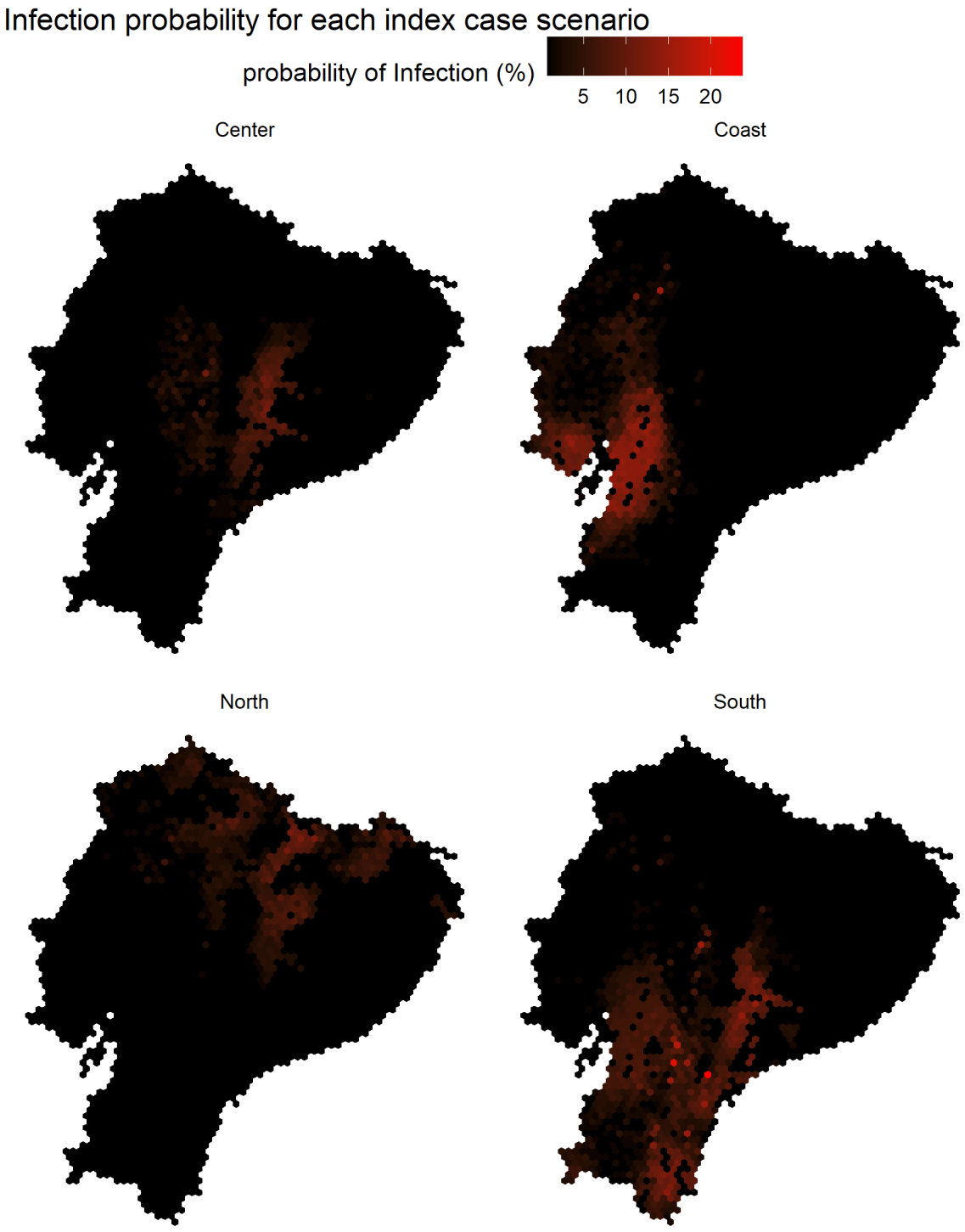

Figure 4.5: Risk maps for the probability of infection based on the region the index case was introduced.

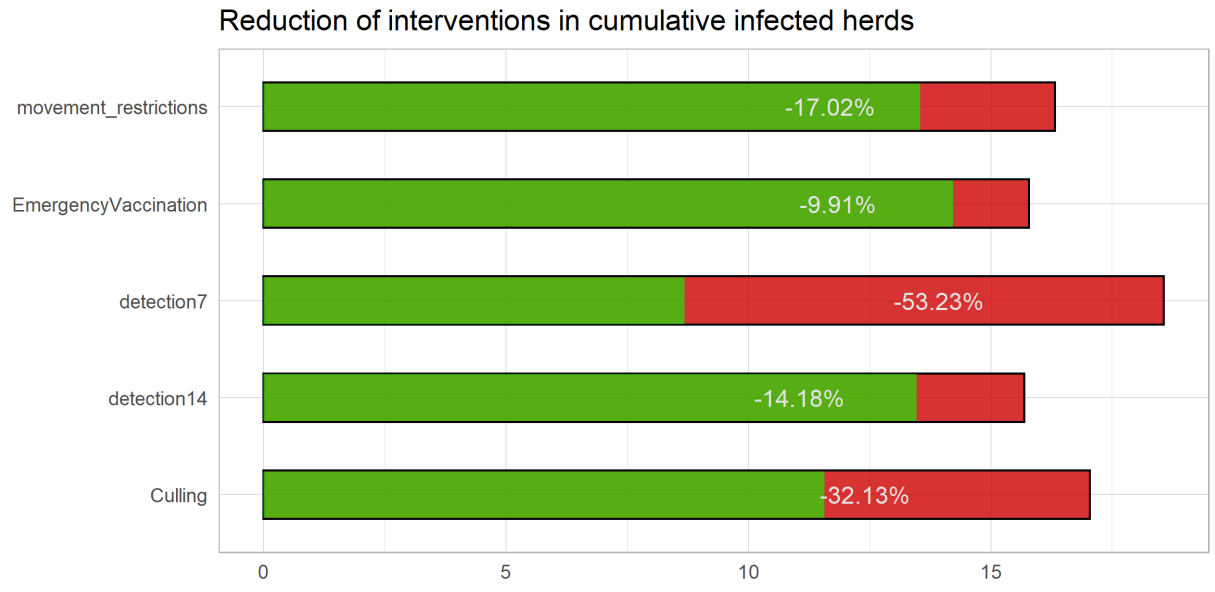

Figure 4.6: Reduction in the total number of infected farms presented as the proportionate reduction for each of the outcomes analyzed.

4.5 Discussion

In this study we present a simulation model for transboundary infectious diseases using census and movement data to inform the risk of spread for FMD in Ecuador. Our modeling approach using hexagonal grids allowed us to incorporate the spatio-temporal transmission dynamics at a local and national level, and the implementation of different strategies for FMD control while decreasing computation power and increasing the speed to run the simulations. The disease spread pattern based on the region of introduction of the index case suggests that an introduction in the South region of the country could result in larger outbreaks, therefore should be targeted for reinforcement of the surveillance and preparedness. When looking at the interventions individually, emergency vaccination had the lowest impact in reducing the total number of infected farms, this might be because we are assuming that the vaccination coverage holds constant for each cell over the simulation period and the vaccination proportion was already >80% for most of the country, so increasing the vaccination coverage in response of the outbreak did not have as much effect as other interventions in our simulations.

Due to the absence of the disease since 2008, we did not have any data available for the external validation of our results and explore model fitting, so we used the global sensitivity analysis for internal validation. The global sensitivity analysis showed some of the expected relationships between the parameters in the

model (i.e. higher transmission coefficient resulted into larger outbreaks, higher vaccination coverage and efficacy resulting into smaller outbreaks). The global sensitivity analysis also unraveled some interesting relationships of the parameters and allowed us to estimate the magnitude and duration of the epidemic for the different scenarios that can happen when the disease is introduced.

One limitation from of our approach include:is that the exact number of affected animals is not estimated., Although the animal density is incorporated with the intention to reflect the heterogeneity in the different disease dynamics for the different size of farms, we did not included this explicitly and we limited our results to describe the number of infected farms as opposed of the number of infected animals. Some of the known risk factors for a increased susceptibility of farms to the disease are incorporated as the parameters, but the parametrization of this was challenging and we limited to just include them on the sensitivity analysis, which only the influence of animal density showed high influence in the number culled and vaccinated farms . Since our model is focused on the cattle population, disease spread in other species is not modeled explicitly here, but we still incorporated the influence of the presence of other species in the between farm disease transmission.

Very few models have been developed in endemic regions and the presented simulation model attempts to fill the gap of knowledge regarding the disease transmission in a population that has been exposed to the virus during for long periods of time. Several countries are investing millions of dollars annually in the eradication process and models developed specifically for their scenarios like the one presented here could be highly beneficial in providing valuable information to advance faster towards the final steps of eradication of the disease.

4.6 Acknowledgements

This research was supported by CONACYT-UC MEXUS and the Hemispheric Institute on the Americas of University of California Davis. A very special thanks to Manuel Jose Sanchez-Vazquez, Alexandra Burbano, Alejandro Vaca, Ginger Aguayo, and the rest of the team from Agrocalidad Ecuador that has provided their expertise and guided the modeling efforts.

Section 5

Conclusion

Infectious disease often involve complex multi-factorial processes. Traditional epidemiological modeling such as compartmental equation based models have proven to be useful for many cases and can be implemented relatively easy, but can be limited when exploring in detail complex relationships involved in disease transmission such as non-linearity, emergence of macro patterns form individual behaviors. In this dissertation we presented an agent based modeling approach to explore in detail the impact of different diseases and prevention and control strategies. We developed a ABM for each of the chapters which involved the implementation and evaluation of the presented models. We presented how can ABM can be used as an integrative framework for both collected data and assumptions made about an event, and how can be useful to support the decision making process.

The three chapters presented challenges in terms of data availability for parametrization and validation of the model. For all the chapters, experts in the subject matter were consulted to represent the disease dynamics as close as possible to reality while maintaining relatively low computing requirements, all the presented models consumed around 30 min per 500 simulations. Having a computationally efficient model is especially useful in situations that require quick action.

At the time of publication of chapter 1, there was still a lot of uncertainty regarding the vaccine efficacy in vulnerable populations. Using the model developed we were able to estimate the impact of COVID-19 in a long term care facility (LTCF) and evaluate the influence of different intervention strategies under different assumptions of the effect of the vaccine and PPE in prevention of infections. Out model was calibrated used observed outbreak data for LTCFs in California, the calibration was somehow limited in the sense that we did not have detailed information regarding with interventions were being implemented in the observed LTCFs,

but we still were able to reflect this uncertainty in our estimations. Using a ABM for this was particularly useful to evaluate the role of testing frequency and community transmission.

Modeling endemic disease such as PRRS can represent a challenge because of the lack of case report data for validation. The effect of the vaccination efficacy against PRRS can vary widely depending on the strain infecting the population and the previous exposure to the disease, the ABM developed aimed to model more accurate the infection dynamics of PRRS including the role of exposure and vaccination immunity in the individuals. Using this approach allowed us to explore in detail other non-pharmaceutical interventions such as herd closure and acclimation of the replacement sows, which resulted in contributed the most for the control of an outbreak.

In chapter 3 we integrated concepts of compartmental, network and spatial models in an agent based framework to represent the spatial and contact patterns heterogeneity of the population while maintaining a constitutionally efficient model for the whole country of Ecuador. Our model estimated vulnerable regions that could be more affected in a re introduction of FMD to the country. We also evaluated the effect of interventions strategies and highlighted the importance of a early detection of the disease. Strategies such as culling and emergency vaccination were also evaluated and we estimated the amount of resources needed in case of an emergency. This information can be very valuable to update the current contingency strategies for disaster epidemiology and guide the surveillance efforts for a more efficient resource allocation.

Using ABM allow us to estimate exactly how many individuals were affected and how many resources were used to control the epidemic, this could provide an insight to evaluate the cost-effectiveness of interventions accounting for multiple factors, which is something we hope to explore more in detail in the future. The model developed can be adapted for different settings and diseases and all the code to reproduce the research presented here is available in their respective repositories via github.com/jpablo91.

ABM is still a relatively recent field in epidemiological modeling, with the increasing availability of higher computation resources ABM have become more commonly used as a tool for decision making. However, there are may challenges and limitations when using these novel methodologies.

The flexibility that ABM offers in the model specification represents both an advantage and a challenge, special attention must be put on the computing resources needed to run the model. Scaling a complex model to a bigger population can be unfeasible when high detail is being modeled, hence, a balance between detail of the model representing the reality and the computing power required must be achieved in order to have an efficient model.

ABM relies heavily on theory and the understanding we have about a system, hence the model will only

be as good as the assumptions made on defining the rules and the data used to parametrize it. With the new advances in data collection and the advent of 'Big Data', more information is being becoming available and the vast amount of information required for parametrizing and validating ABMs is becoming less of a problem. ABM calls for interdisciplinary research in order to integrate better all the aspects involved when representing complex problems, having the support of experts in the topic for each of the chapters of the dissertation was critical for the development of the models.

List of Figures

List of Tables

Bibliography

Helen Abbey. An Examination of the Reed-Frost Theory of Epidemics. *Human Biology*, 24(3):201–233, 1952.

Agronegocios. La fiebre aftosa ha dejado perdidas por 300.000 millones a los ganaderos, jan 2019. URL https://www.agronegocios.co/agricultura/la-fiebre-aftosa-ha-dejado-perdidas-por-300000-millones-a-los-ganaderos-2822309.

Alberto Aleta, David Martín-Corral, Ana Pastore y Piontti, Marco Ajelli, Maria Litvinova, Matteo Chinazzi, Natalie E. Dean, M. Elizabeth Halloran, Ira M. Longini, Stefano Merler, Alex Pentland, Alessandro Vespignani, Esteban Moro, and Yamir Moreno. Modelling the impact of testing, contact tracing and household quarantine on second waves of COVID-19. *Nature Human Behaviour*, 4(9):964–971, 2020. ISSN 23973374. doi: 10.1038/s41562-020-0931-9. URL http://dx.doi.org/10.1038/s41562-020-0931-9.

C. Alexopoulos, S. K. Kritas, C. S. Kyriakis, E. Tzika, and S. C. Kyriakis. Sow performance in an endemically porcine reproductive and respiratory syndrome (PRRS)-infected farm after sow vaccination with an attenuated PRRS vaccine. *Veterinary Microbiology*, 111(3-4):151–157, 2005. ISSN 03781135. doi: 10.1016/j.vetmic.2005.10.007.

A. G. Arruda, Z. Poljak, D. Knowles, and A. McLean. Development of a stochastic agent-based model to evaluate surveillance strategies for detection of emergent porcine reproductive and respiratory syndrome strains. *BMC Veterinary Research*, 13(1):171, dec 2017. ISSN 1746-6148. doi: 10.1186/s12917-017-1091-7. URL http://bmcvetres.biomedcentral.com/articles/10.1186/s12917-017-1091-7.

Kristen MJ Azar, Zijun Shen, Robert J Romanelli, Stephen H Lockhart, Kelly Smits, Sarah Robinson, Stephanie Brown, and Alice R Pressman. Disparities in outcomes among covid-19 patients in a large health care system in california: Study estimates the covid-19 infection fatality rate at the us county level. *Health Aff.*, 39(7):1253–1262, 2020.

Lindsey R Baden, Hana M El Sahly, Brandon Essink, Karen Kotloff, Sharon Frey, Rick Novak, David Diemert, Stephen A Spector, Nadine Rouphael, C Buddy Creech, et al. Efficacy and safety of the mrna-1273 sars-cov-2 vaccine. *NEJM*, 2020.

Christopher L. Barrett, Keith R. Bisset, Stephen G. Eubank, Xizhou Feng, and Madhav V. Marathe. EpiSimdemics: An efficient algorithm for simulating the spread of infectious disease over large realistic social networks. *2008 SC - International Conference for High Performance Computing, Networking, Storage and Analysis, SC 2008*, (January), 2008. doi: 10.1109/SC.2008.5214892.

Thomas W. Bates, Mark C. Thurmond, and Tim E. Carpenter. Description of an epidemic simulation model for use in evaluating strategies to control an outbreak of foot-and-mouth disease. *AJVR*, 64(2):195'204, 2003.

Paul R. Bessell, Darren J. Shaw, Nicholas J. Savill, and Mark E.J. Woolhouse. Estimating risk factors for farm-level transmission of disease: Foot and mouth disease during the 2001 epidemic in Great Britain. *Epidemics*, 2(3):109–115, 2010. ISSN 17554365. doi: 10.1016/j.epidem.2010.06.002. URL http://dx.doi.org/10.1016/j.epidem.2010.06.002.

Benjamin F Bigelow, Olive Tang, Bryan Barshick, Matthew Peters, Stephen D Sisson, Kimberly S Peairs, and Morgan J Katz. Outcomes of universal covid-19 testing following detection of incident cases in 11 long-term care facilities. *JAMA Intern Med*, 181(1):127–129, 2020. doi: \url{10.1001/jamainternmed.2020.3738}.

Carolyn Blackman, Sharon Farber, Richard A. Feifer, Vincent Mor, and Elizabeth M. White. An illustration of sars-cov-2 dissemination within a skilled nursing facility using heat maps. *J Am Geriatr Soc*, 68(10): 2174–2178, 2020. doi: https://doi.org/10.1111/jgs.16642. URL https://agsjournals.onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16642.

Gert Jan Boender, Herman J.W. van Roermund, Mart C.M. de Jong, and Thomas J. Hagenaars. Transmission risks and control of foot-and-mouth disease in The Netherlands: Spatial patterns. *Epidemics*, 2 (1):36–47, 2010. ISSN 17554365. doi: 10.1016/j.epidem.2010.03.001. URL http://dx.doi.org/10.1016/j.epidem.2010.03.001.

Richard A. Bradhurst, Sharon E. Roche, Iain J. East, Paul Kwan, and M. Graeme Garner. A hybrid modeling approach to simulating foot-and-mouth disease outbreaks in Australian livestock. *Frontiers in Environmental Science*, 3, mar 2015. doi: 10.3389/fenvs.2015.00017.

A. J. Branscum, A. M. Perez, W. O. Johnson, and M. C. Thurmond. Bayesian spatiotemporal analysis of

foot-and-mouth disease data from the Republic of Turkey. *Epidemiology and Infection*, 136(6):833–842, 2008. ISSN 09502688. doi: 10.1017/S0950268807009065.

Tim E. Carpenter, Lasse E. Christiansen, Bradley F. Dickey, Clair Thunes, and Pamela J. Hullinger. Potential impact of an introduction of foot-and-mouth disease into the California State Fair. *Journal of the American Veterinary Medical Association*, 231(8):1231–1235, oct 2007. ISSN 0003-1488. doi: 10.2460/javma.231.8.1231.

CDC. Center for disease control covid data tracker. https://covid.cdc.gov/covid-data-tracker/#datatracker-home, 04 2021a. (Accessed on 04/14/2021).

CDC. Covid-19 pandemic planning scenarios | CDC. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html#table-2, 02 2021b. (Accessed on 02/28/2021).

Margo Chase-Topping, Jiexiong Xie, Christopher Pooley, Ivan Trus, Caroline Bonckaert, Kelly Rediger, Richard I. Bailey, Helen Brown, Vasiliki Bitsouni, Maria Belén Barrio, Sylvie Gueguen, Hans Nauwynck, and Andrea Doeschl-Wilson. New insights about vaccine effectiveness: Impact of attenuated PRRS-strain vaccination on heterologous strain transmission. *Vaccine*, 38(14):3050–3061, 2020. ISSN 18732518. doi: 10.1016/j.vaccine.2020.02.015. URL https://doi.org/10.1016/j.vaccine.2020.02.015.

M Keith Chen, Judith A Chevalier, and Elisa F Long. Nursing home staff networks and covid-19. *PNAS*, 118(1):e2015455118, 2021. doi: \url{https://doi.org/10.1073/pnas.2015455118}.

G. Chowell, A. L. Rivas, N. W. Hengartner, J. M. Hyman, and C. Castillo-Chavez. The role of spatial mixing in the spread of foot-and-mouth disease. *Preventive Veterinary Medicine*, 73(4):297–314, 2006. ISSN 01675877. doi: 10.1016/j.prevetmed.2005.10.002.

Derek K Chu, Elie A Akl, Stephanie Duda, Karla Solo, Sally Yaacoub, Holger J Schünemann, Amena El-harakeh, Antonio Bognanni, Tamara Lotfi, Mark Loeb, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of sars-cov-2 and covid-19: a systematic review and meta-analysis. *Lancet*, 2020.

CMS. Covid-19 nursing home data | data.cms.gov. https://data.cms.gov/stories/s/COVID-19-Nursing-Home-Data/bkwz-xpvg/, 03 2021. (Accessed on 03/09/2021).

Ma Àngels Colomer, Antoni Margalida, and Lorenzo Fraile. Improving the management procedures in farms infected with the Porcine Reproductive and Respiratory Syndrome virus using PDP models. *Scientific Reports*, 9(1):1–13, 2019. ISSN 20452322. doi: 10.1038/s41598-019-46339-w.

Sarah J. Cox and Paul V. Barnett. Experimental evaluation of foot-and-mouth disease vaccines for emergency use in ruminants and pigs. *Veterinary Research*, 40(3), 2009. ISSN 09284249. doi: 10.1051/vetres:2008051.

Andrew Crooks, Nicolas Malleson, Ed Manley, and Alison Heppenstall. *Agent-Based Modelling and Geographical Information Systems*. 2017. ISBN 9781473958654. URL https://www.abmgis.org.

Scott A. Dee, Han Soo Joo, Steve Henry, Lisa Tokach, Bong Kyun Park, Tom Molitor, and Carlos Pijoan. Detecting subpopulations after PRRS virus infection in large breeding herds using multiple serologic tests. *Journal of Swine Health and Production*, 4(4):181–184, 1996. ISSN 1537209X.

Yaozhong Ding, Ashenafi Kiros Wubshet, Xiaolong Ding, Zhongwang Zhang, Qian Li, Junfei Dai, Qian Hou, Yonghao Hu, and Jie Zhang. Evaluation of four commercial vaccines for the protection of piglets against the highly pathogenic porcine reproductive and respiratory syndrome virus (hp-PRRSV) QH-08 strain. *Vaccines*, 9(9), 2021. ISSN 2076393X. doi: 10.3390/vaccines9091020.

Elise Dion, Louis VanSchalkwyk, and Eric F. Lambin. The landscape epidemiology of foot-and-mouth disease in South Africa: A spatially explicit multi-agent simulation. *Ecological Modelling*, 222(13):2059–2072, 2011. ISSN 03043800. doi: 10.1016/j.ecolmodel.2011.03.026. URL http://dx.doi.org/10.1016/j.ecolmodel.2011.03.026.

K. Dukpa, I. D. Robertson, J. R. Edwards, T. M. Ellis, P. Tshering, K. Rinzin, and N. Dahal. Risk factors for foot-and-mouth disease in sedentary livestock herds in selected villages in four regions of Bhutan. *New Zealand Veterinary Journal*, 59(2):51–58, 2011. ISSN 00480169. doi: 10.1080/00480169.2011.552852.

Joshua M. Epstein, Jon Parker, Derek Cummings, and Ross A. Hammond. Coupled contagion dynamics of fear and disease: Mathematical and computational explorations. *PLoS ONE*, 3(12), 2008. ISSN 19326203. doi: 10.1371/journal.pone.0003955.

Daniel J Escobar, Maria Lanzi, Pouné Saberi, Ruby Love, Darren R Linkin, John J Kelly, Darshana Jhala, Valerianna Amorosa, Mary Hofmann, and Jeffrey B Doyon. Mitigation of a coronavirus disease 2019 outbreak in a nursing home through serial testing of residents and staff. *Clin. Infect. Dis.*, ciaa1021, 2020. doi: \url{https://doi.org/10.1093/cid/ciaa1021}.

Pedro Pablo España, Amaia Bilbao, Susana García-Gutiérrez, Iratxe Lafuente, Ane Anton-Ladislao, Ane Villanueva, Ane Uranga, Maria Jose Legarreta, Urko Aguirre, Jose Maria Quintana, Miren Orive, Nerea Gonzalez, Ane Anton, Josune Martin, Cristina Muñoz, Jose María Quintana, Mikel Egurrola, Amaia Aramburu, Amaia Artaraz, Leire Chasco, Olaia Bronte, Patricia García, Ana Jodar, Virginia Fernandez, Cristobal Esteban, Naia Mas, Esther Pulido, Itxaso Bengoetxea, Antonio Escobar, Iñigo Gorostiza, Iñaki

Arriaga, José Joaquín Portu, Naiara Parraza, Milagros Iriberri, Rafael Zalacain, Luis Alberto Ruiz, Leyre Serrano, Adriana Couto, Oier Ateka, Arantza Cano, Maria Olatz Ibarra, Eduardo Millan, Mayte Bacigalupe, Jon Letona, Andoni Arcelay, and Iñaki Berraondo. Predictors of mortality of COVID-19 in the general population and nursing homes. *Internal and Emergency Medicine*, 16(6):1487–1496, 2021. ISSN 19709366. doi: 10.1007/s11739-020-02594-8.

C. Estrada, A. M. Perez, and M. C. Turmond. Herd reproduction ratio and time-space analysis of a foot-and-mouth disease epidemic in Peru in 2004. *Transboundary and Emerging Diseases*, 55(7):284–292, 2008. ISSN 18651674. doi: 10.1111/j.1865-1682.2008.01023.x.

C. M. Evans, G. F. Medley, S. J. Creasey, and L. E. Green. A stochastic mathematical model of the within-herd transmission dynamics of porcine reproductive and respiratory syndrome virus (PRRSV): Fade-out and persistence. *Preventive Veterinary Medicine*, 2010. ISSN 01675877. doi: 10.1016/j.prevetmed.2009.11.001.

Folorunso O. Fasina, Dana R. Connell, Oladele A. Talabi, David D. Lazarus, Gabriel A. Adeleke, Taiwo P. Olusanya, and Jorge A. Hernandez. Foot-and-mouth disease virus strains and examination of exposure factors associated with seropositivity of cattle herds in Nigeria during 2007-2009. *Preventive Veterinary Medicine*, 109(3-4):334–342, 2013. ISSN 01675877. doi: 10.1016/j.prevetmed.2012.10.004. URL http://dx.doi.org/10.1016/j.prevetmed.2012.10.004.

Matt Feaster and Ying-Ying Goh. High proportion of asymptomatic sars-cov-2 infections in 9 long-term care facilities, pasadena, california, usa, april 2020. *Emerg Inf Dis*, 26(10):2416–2419, 2020.

N M Ferguson, C A Donnelly, and R M Anderson. Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. *Nature*, 413(6855):542–8, oct 2001. ISSN 0028-0836. doi: 10.1038/35097116. URL http://www.ncbi.nlm.nih.gov/pubmed/11586365.

Sandro Galea, Matthew Riddle, and George A. Kaplan. Causal thinking and complex system approaches in epidemiology. *International Journal of Epidemiology*, 39(1):97–106, 2010. ISSN 03005771. doi: 10.1093/ije/dyp296.

Jason A. Galvis, Cesar A. Corzo, Joaquin M. Prada, and Gustavo Machado. Modelling the transmission and vaccination strategy for porcine reproductive and respiratory syndrome virus. *Transboundary and Emerging Diseases*, page tbed.14007, mar 2021. ISSN 1865-1674. doi: 10.1111/tbed.14007. URL https://onlinelibrary.wiley.com/doi/10.1111/tbed.14007.

M. G. Garner and S. D. Beckett. Modelling the spread of foot-and-mouth disease in Australia. *Australian Veterinary Journal*, 83(12):758–766, 2005. ISSN 00050423. doi: 10.1111/j.1751-0813.2005.tb11589.x.

Radhika Gharpure, Angela Guo, Courtney Krier Bishnoi, Urvi Patel, David Gifford, Ashley Tippins, Aaron Jaffe, Evan Shulman, Nimalie Stone, Elisabeth Mungai, Suparna Bagchi, Jeneita Bell, Arjun Srinivasan, Anita Patel, and Ruth Link-Gelles. Early covid-19 first-dose vaccination coverage among residents and staff members of skilled nursing facilities participating in the pharmacy partnership for long-term care program - united states, december 2020-january 2021. *MMWR*, 70:178–182, 2021a. doi: 10.15585/mmwr.mm7005e2.

Radhika Gharpure, Anita Patel, and Ruth Link-Gelles. First-dose covid-19 vaccination coverage among skilled nursing facility residents and staff. *JAMA*, 2021b.

M. Gilbert, S. Aktas, H. Mohammed, P. Roeder, K. Sumption, M. Tufan, and J. Slingenbergh. Patterns of spread and persistence of foot-and-mouth disease types A, O and Asia-1 in Turkey: A meta-population approach. *Epidemiology and Infection*, 133(3):537–545, 2005. ISSN 09502688. doi: 10.1017/S0950268804003516.

Scott A Goldberg, Jochen Lennerz, Michael Klompas, Eden Mark, Virginia M Pierce, Ryan W Thompson, et al. Presymptomatic transmission of severe acute respiratory syndrome coronavirus 2 among residents and staff at a skilled nursing facility: Results of real-time polymerase chain reaction and serologic testing. *Clin. Infect. Dis.*, 72(4):686–689, 2021.

P. G. Halbur, P. S. Paul, M. L. Frey, J. Landgraf, K. Eernisse, X. J. Meng, J. J. Andrews, M. A. Lum, and J. A. Rathje. Comparison of the antigen distribution of two US porcine reproductive and respiratory syndrome virus isolates with that of the lelystad virus. *Veterinary Pathology*, 33(2):159–170, 1996a. ISSN 03009858. doi: 10.1177/030098589603300205.

Patrick G. Halbur, Prem S. Paul, Xiang Jin Meng, Melissa A. Lum, John J. Andrews, and John A. Rathje. Comparative pathogenicity of nine US porcine reproductive and respiratory syndrome virus (PRRSV) isolates in a five-week-old cesarean-derived, colostrum-deprived pig model. *Journal of Veterinary Diagnostic Investigation*, 8(1):11–20, 1996b. ISSN 10406387. doi: 10.1177/104063879600800103.

Elizabeth B. Harper, John C. Stella, and Alexander K. Fremier. Global sensitivity analysis for complex ecological models: A case study of riparian cottonwood population dynamics. *Ecological Applications*, 21 (4):1225–1240, 2011. ISSN 10510761. doi: 10.1890/10-0506.1.

L Harris-Kojetin, M Sengupta, JP Lendon, V Rome, and C Caffrey. Long-term care providers and services users in the united states, 2015–2016. *Vital Health Stat*, 2019.

Neil Harvey, Aaron Reeves, Mark A. Schoenbaum, Francisco J. Zagmutt-Vergara, Caroline Dubé, Ashley E. Hill, Barbara A. Corso, W. Bruce McNab, Claudia I. Cartwright, and Mo D. Salman. The North American Animal Disease Spread Model: A simulation model to assist decision making in evaluating animal disease incursions. *Preventive Veterinary Medicine*, 82(3-4):176–197, 2007. ISSN 01675877. doi: 10.1016/j.prevetmed.2007.05.019.

Penelope Hawe and Alan Shiell. Social capital and health promotion: A review. *Social Science and Medicine*, 51(6):871–885, 2000. ISSN 02779536. doi: 10.1016/S0277-9536(00)00067-8.

Y. Hayama, N. Muroga, T. Nishida, S. Kobayashi, and T. Tsutsui. Risk factors for local spread of foot-and-mouth disease, 2010 epidemic in Japan. *Research in Veterinary Science*, 93(2):631–635, 2012. ISSN 00345288. doi: 10.1016/j.rvsc.2011.09.001. URL http://dx.doi.org/10.1016/j.rvsc.2011.09.001.

Y. Hayama, T. Yamamoto, S. Kobayashi, N. Muroga, and T. Tsutsui. Mathematical model of the 2010 foot-and-mouth disease epidemic in Japan and evaluation of control measures. *Preventive Veterinary Medicine*, 112(3-4):183–193, nov 2013. ISSN 01675877. doi: 10.1016/j.prevetmed.2013.08.010.

Xi He, Eric HY Lau, Peng Wu, Xilong Deng, Jian Wang, Xinxin Hao, Yiu Chung Lau, Jessica Y Wong, Yujuan Guan, Xinghua Tan, et al. Temporal dynamics in viral shedding and transmissibility of covid-19. *Nat. Med.*, 26(5):672–675, 2020.

Miguel A. Hernán. Invited commentary: Agent-based models for causal inference-reweighting data and theory in epidemiology. *American Journal of Epidemiology*, 181(2):103–105, 2015. ISSN 14766256. doi: 10.1093/aje/kwu272.

Derald J. Holtkamp, Bob Morrison, Dyneah M Classen, Lisa Becton, Steve Henry, Max T Rodibaugh, Raymond R Rowland, Harry Snelson, Barb Straw, Paul Yeske, and Jeff Zimmerman. Terminology for Classifying Swine Herds by PRRS Status. *Journal Of Swine Health And Production*, 19(February):44–56, 2011. ISSN 1434-1220.

Derald J. Holtkamp, James B. Kliebenstein, Eric J. Neumann, Jeffrey J. Zimmerman, Hans F. Rotto, Tiffany K. Yoder, Chong Wang, Paul E. Yeske, Christine L. Mowrer, and Charles A. Haley. Assessment of the economic impact of porcine reproductive and respiratory syndrome virus on United States pork producers. *Journal of Swine Health and Production*, 21(2):72–84, 2013. ISSN 1537209X.

S. Houben, K. van Reeth, and M. B. Pensaert. Pattern of Infection with the Porcine Reproductive and Respiratory Syndrome Virus on Swine Farms in Belgium. *Journal of Veterinary Medicine, Series B*, 42 (1-10):209–215, 1995. ISSN 14390450. doi: 10.1111/j.1439-0450.1995.tb00704.x.

Takeshi Kano, Kotaro Yasui, Taishi Mikami, Munehiro Asally, and Akio Ishiguro. An agent-based model for interrelation between COVID-19 outbreak and economic activities. *arXiv*, (December 2019):1–15, 2020.

M. J. Keeling, M. E.J. Woolhouse, D. J. Shaw, L. Matthews, M. Chase-Topping, D. T. Haydon, S. J. Cornell, J. Kappey, J. Wilesmith, and B. T. Grenfell. Dynamics of the 2001 UK foot and mouth epidemic: Stochastic dispersal in a heterogeneous landscape. *Science*, 294(5543):813–817, 2001. ISSN 00368075. doi: 10.1126/science.1065973.

W.O Kermack and A.G McKendrick. A contribution to the mathematical theory of epidemics. Proceedings of the Royal Society of London . Series A , Containing Papers of a Mathematical and physical Character, Vol. 115, No. 772. *Society*, 115(772):700–721, 1927.

T. J.D. Knight-Jones and J. Rushton. The economic impacts of foot and mouth disease - What are they, how big are they and where do they occur?, nov 2013. ISSN 01675877.

R Tamara Konetzka and Rebecca J Gorges. Nothing much has changed: Covid-19 nursing home cases and deaths follow fall surges. *J Am Geriatr Soc*, 2020. doi: \url{https://doi.org/10.1111/jgs.16951}.

O. J. Lopez and F. A. Osorio. Role of neutralizing antibodies in PRRSV protective immunity. *Veterinary Immunology and Immunopathology*, 102(3):155–163, 2004. ISSN 01652427. doi: 10.1016/j.vetimm.2004.09.005.

Janice K Louie, Hyman M Scott, Amie DuBois, Natalya Sturtz, Wendy Lu, Juliet Stoltey, Godfred Masinde, Stephanie Cohen, Darpun Sachdev, Susan Philip, Naveena Bobba, and San Francisco Department of Public Health COVID-19 Skilled Nursing Facility Outbreak Response Team Aragon, Tomas. Lessons From Mass-Testing for Coronavirus Disease 2019 in Long-Term Care Facilities for the Elderly in San Francisco. *Clin. Infect. Dis.*, 07 2020. ISSN 1058-4838. doi: 10.1093/cid/ciaa1020. URL https://doi.org/10.1093/cid/ciaa1020. ciaa1020.

Liang Mao and Ling Bian. Spatial-temporal transmission of influenza and its health risks in an urbanized area. *Computers, Environment and Urban Systems*, 34(3):204–215, 2010. ISSN 01989715. doi: 10.1016/j.compenvurbsys.2010.03.004. URL http://dx.doi.org/10.1016/j.compenvurbsys.2010.03.004.

H. Mardassi, S. Mounir, and S. Dea. Identification of major differences in the nucleocapsid protein genes of a Quebec strain and European strains of porcine reproductive and respiratory syndrome virus. *Journal of General Virology*, 75(3):681–685, 1994. ISSN 00221317. doi: 10.1099/0022-1317-75-3-681.

Brandon D.L. Marshall and Sandro Galea. Formalizing the role of agent-based modeling in causal inference and epidemiology. *American Journal of Epidemiology*, 181(2):92–99, 2015. ISSN 14766256. doi: 10.1093/aje/kwu274.

B. Martínez-López, A. M. Perez, and J. M. Sánchez-Vizcaíno. A simulation model for the potential spread of foot-and-mouth disease in the Castile and Leon region of Spain. *Preventive Veterinary Medicine*, 96 (1-2):19–29, 2010. ISSN 01675877. doi: 10.1016/j.prevetmed.2010.05.015.

B. Martínez-López, B. Ivorra, E. Fernández-Carrión, A. M. Perez, A. Medel-Herrero, F. Sánchez-Vizcaíno, C. Gortázar, A. M. Ramos, and J. M. Sánchez-Vizcaíno. A multi-analysis approach for space-time and economic evaluation of risks related with livestock diseases: The example of FMD in Peru. *Preventive Veterinary Medicine*, 114(1):47–63, apr 2014. ISSN 01675877. doi: 10.1016/j.prevetmed.2014.01.013.

X. J. Meng, P. S. Paul, and P. G. Halbur. Molecular cloning and nucleotide sequencing of the 3'-terminal genomic RNA of the porcine reproductive and respiratory syndrome virus. *Journal of General Virology*, 75(7):1795–1801, 1994. ISSN 00221317. doi: 10.1099/0022-1317-75-7-1795.

W L Mengeling, A C Vorwald, K M Lager, and S L Brockmeier. Comparison among strains of porcine reproductive and respiratory syndrome virus for their ability to cause reproductive failure. *American journal of veterinary research*, 57(6):834–9, jun 1996. ISSN 0002-9645. URL http://www.ncbi.nlm.nih.gov/pubmed/8725809.

Janneke J.M. Meulenberg, Marcel M. Hulst, Emile J. de Meijer, Peter L.J.M. Moonen, Annelien den Besten, Eric P. de Kluyver, Gert Wensvoort, and Rob J.M. Moormann. Lelystad Virus, the Causative Agent of Porcine Epidemic Abortion and Respiratory Syndrome (PEARS), Is Related to LDV and EAV. *Virology*, 192(1):62–72, jan 1993. ISSN 00426822. doi: 10.1006/viro.1993.1008. URL http://repositorio.unan.edu.ni/2986/1/5624.pdfhttps://linkinghub.elsevier.com/retrieve/pii/S0042682283710081.

R. S. Morris, J. W. Wilesmith, M. W. Stern, R. L. Sanson, and M. A. Stevenson. Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. *Acta Horticulturae*, 566(Sanson 1993):337–347, 2001. ISSN 05677572. doi: 10.17660/ActaHortic.2001.566.43.

MSHMP. Morrison Swine Health Monitoring Project PRRS yearly cumulative incidence, 2021. URL https://vetmed.umn.edu/centers-programs/swine-program/outreach-leman-mshmp/mshmp/mshmp-prrs-figures.

H. Nathues, P. Alarcon, J. Rushton, R. Jolie, K. Fiebig, M. Jimenez, V. Geurts, and C. Nathues. Cost of porcine reproductive and respiratory syndrome virus at individual farm level – An economic disease model.

Preventive Veterinary Medicine, 142:16–29, 2017. ISSN 01675877. doi: 10.1016/j.prevetmed.2017.04.006. URL http://dx.doi.org/10.1016/j.prevetmed.2017.04.006.

Eric Neuman, James Kliebenstein, Colin Jhonson, and John Mabry. Assessment of the economic impact of porcine reproductive and respiratory syndrome on swine production in the United States. Technical report, 2005.

Miriam Nuno, Yury Garcia, Ganesh Rajasekar, Diego Pinheiro, and Alec J Schmidt. Covid-19 hospitalizations in five california hospitals. *medRxiv*, 2021.

Joseph G. Ouslander and David C. Grabowski. Covid-19 in nursing homes: Calming the perfect storm. *J Am Geriatr Soc*, 68(10):2153–2162, 2020. doi: https://doi.org/10.1111/jgs.16784. URL https://agsjournals.onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16784.

PANAFTOSA-OPS/OMS. Informe de situacion de los programas de erradicacion de la fiebre aftosa en sudamerica y panama. Technical report, Centro Panamericano de Fiebre Aftosa. Organizacion Panamericana de la Salud. Organizacion Mndial de la Salud, 2019.

Phithakdet Phoo-ngurn, Chanakarn Kiataramkul, and Farida Chamchod. Modeling the spread of porcine reproductive and respiratory syndrome virus (PRRSV) in a swine population: transmission dynamics, immunity information, and optimal control strategies. *Advances in Difference Equations*, 2019(1), 2019. ISSN 16871847. doi: 10.1186/s13662-019-2351-6. URL http://dx.doi.org/10.1186/s13662-019-2351-6.

Fernando P Polack, Stephen J Thomas, Nicholas Kitchin, Judith Absalon, Alejandra Gurtman, Stephen Lockhart, John L Perez, Gonzalo Pérez Marc, Edson D Moreira, Cristiano Zerbini, et al. Safety and efficacy of the bnt162b2 mrna covid-19 vaccine. *NEJM*, 2020.

L. W. Pomeroy, S. Bansal, M. Tildesley, K. I. Moreno-Torres, M. Moritz, N. Xiao, T. E. Carpenter, and R. B. Garabed. Data-Driven Models of Foot-and-Mouth Disease Dynamics: A Review, jun 2017. ISSN 18651682.

R Core Team. R: A Language and Environment for Statistical Computing, 2020. URL https://www.r-project.org/.

Nistara Randhawa, Hugo Mailhot, Duncan Temple Lang, Beatriz Martínez-López, Kirsten Gilardi, and Jonna A.K. Mazet. Fine scale infectious disease modeling using satellite-derived data. *Scientific Reports*, 11(1):1–11, 2021. ISSN 20452322. doi: 10.1038/s41598-021-86124-2. URL https://doi.org/10.1038/s41598-021-86124-2.

Aaron Reeves, Kelly A Patyk, and Ashley E. Hill. *User's Guide for the North American Animal Disease Spread Model 4.0*. NAADSM Development Team, 2012. URL www.naadsm.org.

Karl M. Rich. An interregional system dynamics model of animal disease control: applications to foot-and-mouth disease in the Southern Cone of South America. *System Dynamics Review*, 24(1):67–96, 2008. ISSN 08837066. doi: 10.1002/sdr.385. URL http://doi.wiley.com/10.1002/sdr.385.

R L Sanson. *The development of a decision support system for an animal disease emergency*. PhD thesis, 1993.

Mariela Scortti, Cinta Prieto, Isabel Simarro, and José M. Castro. Reproductive performance of gilts following vaccination and subsequent heterologous challenge with European strains of porcine reproductive and respiratory syndrome virus. *Theriogenology*, 66(8):1884–1893, 2006. ISSN 0093691X. doi: 10.1016/j.theriogenology.2006.04.043.

David RM Smith, Audrey Duval, Koen B Pouwels, Didier Guillemot, Jerome Fernandes, Bich-Tram Huynh, Laura Temime, and Lulla Opatowski. Optimizing covid-19 surveillance in long-term care facilities: a modelling study. *BMC Med.*, 18(386), 2020.

Gillian K SteelFisher, Arnold M Epstein, David C Grabowski, Karen E Joynt Maddox, E John Orav, and Michael L Barnett. Persistent challenges of covid-19 in skilled nursing facilities: The administrator perspective. *J Am Geriatr Soc*, 2021. doi: \url{https://doi.org/10.1111/jgs.17062}.

P Taillandier, B Gaudou, A Grignard, QN Huynh, N Marilleau, P Caillou, D Philippon, and A Drogoul. Building, composing and experimenting complex spatial models with the gama platform. *Geoinformatica*, 23(2):299–322, 2019a.

Patrick Taillandier, Benoit Gaudou, Arnaud Grignard, Quang-Nghi Huynh, Nicolas Marilleau, Philippe Caillou, Damien Philippon, and Alexis Drogoul. Building, composing and experimenting complex spatial models with the GAMA platform. *GeoInformatica*, 23(2):299–322, apr 2019b. ISSN 1384-6175. doi: 10.1007/s10707-018-00339-6. URL http://link.springer.com/10.1007/s10707-018-00339-6.

Krishna K. Thakur, Crawford W. Revie, Daniel Hurnik, Zvonimir Poljak, and Javier Sanchez. Simulation of between-farm transmission of porcine reproductive and respiratory syndrome virus in Ontario, Canada using the North American Animal Disease Spread Model. *Preventive Veterinary Medicine*, 118(4):413–426, 2015a. ISSN 01675877. doi: 10.1016/j.prevetmed.2015.01.006. URL http://dx.doi.org/10.1016/j.prevetmed.2015.01.006.

Krishna K. Thakur, Javier Sanchez, Daniel Hurnik, Zvonimir Poljak, Sheldon Opps, and Crawford W. Revie. Development of a network based model to simulate the between-farm transmission of the porcine reproductive and respiratory syndrome virus. *Veterinary Microbiology*, 180(3-4):212–222, 2015b. ISSN 18732542. doi: 10.1016/j.vetmic.2015.09.010. URL http://dx.doi.org/10.1016/j.vetmic.2015.09.010.

Beat Thomann, Jonathan Rushton, Gertraud Schuepbach-regula, and Heiko Nathues. Modeling Economic Effects of Vaccination Against Porcine Reproductive and Respiratory Syndrome : Impact of Vaccination Effectiveness , Vaccine Price , and Vaccination Coverage. 7(August):1–9, 2020. doi: 10.3389/fvets.2020.00500.

D Thompson, P Muriel, D Russell, P Osborne, A Bromley, M Rowland, S Creigh-Tyte, and C Brown. Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001. *Revue scientifique et technique (International Office of Epizootics)*, 21(3):675–87, dec 2002. ISSN 0253-1933. URL http://bvs1.panaftosa.org.br/local/file/textoc/Thompson.pdfhttp://www.ncbi.nlm.nih.gov/pubmed/12523706.

The New York Times. More than one-third of u.s. coronavirus deaths are linked to nursing homes. https://www.nytimes.com/interactive/2020/us/coronavirus-nursing-homes.html, 03 2020. (Accessed on 03/09/2021).

Damon JA Toth and Karim Khader. Efficient sars-cov-2 surveillance strategies to prevent deadly outbreaks in vulnerable populations. *BMC Med.*, 19(25), 2021.

Giovani Trevisan, Clayton Johnson, Neil Benjamin, Laura Bradner, and Daniel C. L. Linhares. Description of changes of key performance indicators and PRRSV shedding over time in a naïve breeding herd following a PRRS MLV exposure. *Transboundary and Emerging Diseases*, (September):1–6, 2021. ISSN 1865-1674. doi: 10.1111/tbed.14327.

Kathleen T Unroe, Russell Evans, Lindsay Weaver, Dan Rusyniak, and Justin Blackburn. Willingness of long-term care staff to receive a covid-19 vaccine: A single state survey. *J Am Geriatr Soc*, 2020.

Merryn Voysey, Sue Ann Costa Clemens, Shabir A Madhi, Lily Y Weckx, Pedro M Folegatti, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, et al. Safety and efficacy of the chadox1 ncov-19 vaccine (azd1222) against sars-cov-2: an interim analysis of four randomised controlled trials in brazil, south africa, and the uk. *Lancet*, 397(10269):99–111, 2021.

Kieran A Walsh, Karen Jordan, Barbara Clyne, Daniela Rohde, Linda Drummond, Paula Byrne, Susan Ahern, Paul G Carty, Kirsty K O'Brien, Eamon O'Murchu, Michelle O'Neill, Susan M Smith, Máirín Ryan, and Patricia Harrington. SARS-CoV-2 detection, viral load and infectivity over the course of an infection.

Journal of Infection, 81(3):357–371, 2020. ISSN 0163-4453. doi: https://doi.org/10.1016/j.jinf.2020.06.067. URL https://www.sciencedirect.com/science/article/pii/S0163445320304497.

Michael P. Ward, Linda D. Highfield, Pailin Vongseng, and M. Graeme Garner. Simulation of foot-and-mouth disease spread within an integrated livestock system in Texas, USA. *Preventive Veterinary Medicine*, 88 (4):286–297, 2009. ISSN 01675877. doi: 10.1016/j.prevetmed.2008.12.006.

Robert W. Wills, Jeff J. Zimmerman, Sabrina L. Swenson, Kyoung Jin Yoon, Howard T. Hill, Dwaine S. Bundy, and Michael J. McGinley. Transmission of PRRSV by direct, close, or indirect contact. *Journal of Swine Health and Production*, 5(6):213–218, 1997. ISSN 1537209X.

M.E.J. Woolhouse, C. Dye, J.F. Etard, T. Smith, J.D. Charlwood, G.P. Garnett, P. Hagan, J.L.K. Hii, P.D. Ndhlovu, R.J. Quinnell, C.H. Watts, S.K. Chandiwana, and R.M. Anderson. Heterogeneities in the transmission of infectious agents. *Proceedings of the National Academy of Sciences of the United States of America*, 94(January):338–342, 1997.

Shankar Yadav, Carolina Stenfeldt, Matthew A. Branan, Karla I. Moreno-Torres, Lindsey K. Holmstrom, Amy H. Delgado, and Jonathan Arzt. Parameterization of the Durations of Phases of Foot-And-Mouth Disease in Cattle. *Frontiers in Veterinary Science*, 6(August):1–14, 2019. ISSN 22971769. doi: 10.3389/fvets.2019.00263.

Jeffrey J. Zimmerman, Scott A. Dee, Derald J. Holtkamp, Michael P. Murtaugh, Tomasz Stadejek, Gregory W. Stevenson, Montserrat Torremorell, Hanchun Yang, and Jianqiang Zhang. Porcine reproductive and respiratory syndrome viruses (porcine arteriviruses). In *Diseases of Swine*, chapter 41, pages 685–708. 2019. ISBN 9781119350927. doi: 10.1002/9781119350927.ch41.