Investigating the efficacy of vaccine strategies in Turkey using a mathematical epidemiological model.

by

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Contents

List of Tables

List of Figures

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Declarations

The work presented here is my own, except where stated otherwise. The thesis has been composed by myself and has not been submitted for any other degree or professional qualification.

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Abstract

Many regions of the world experience regular outbreaks of Foot-and-Mouth Disease (FMD), a virulent livestock disease which causes great amounts of economic damage. Mathematical models are a fundamental component of many epidemiological studies, however there is limited work on endemic FMD due to the complicated dynamics of the endemic disease and a lack of good data. We probe the dynamics of this disease using a model developed with these dynamics, along with high quality data from Turkey.

First, we develop a stochastic spatial metapopulation model which takes into account the dynamics of endemic FMD, test identifiable parameters with the available data from Turkey, and parameterise the model using the Approximate Bayesian Computation Sequential Monte Carlo (ABC-SMC) model fitting algorithm. Second, we assess plausible control policies for their effectiveness in reducing disease circulation and potential for disease eradication. The optimal control policy combinations are found to be reactive ring vaccination with biannual mass vaccination, but reactive movement bans are ineffective. The parameter sensitivity of these control policies are then identified.

Third, we use the model to explore potential carrier transmission and compare this to transmission via movements of infected livestock. The rate of carrier transmission sufficient to contribute to persistence of the disease is found to be very low, such that failure to observe transmission experimentally is unsurprising. Movement transmission alone is found to be insufficient for persistence, however the assumption of vehicle contamination allows persistence also.

Finally, we explore the interaction of the assumed persistence drivers of carrier transmission and contaminated livestock shipments, and assess control policies in the presence of these disease transmission mechanisms. It is shown that pessimistic assumptions of carrier transmission alter the optimal control policy to reactive ring vaccination alone, but contaminated livestock shipments make no difference to the optimal control policies.

Abbreviations

ABC Approximate Bayesian Computation

ABC-SMC Approximate Bayesian Computation Sequential Monte Carlo

BHK Baby Hamster Kidney Cell

DIVA Differentiation Infected from Vaccinated Animals

EuFMD European Commission for the Control of Foot-and-Mouth Disease

FMD Foot-and-Mouth Disease

FMDV Foot-and-Mouth Disease Virus

IQR Interquartile Range

LHS Latin Hypercube Sampling

LMIC Low and Middle Income Countries

MB Movement Ban

MCMC Markov Chain Monte Carlo

MDA Maternally Derived Antibodies

MLE Maximum Likelihood Estimation

MV Mass Vaccination

NSP Non-Structural Protein(s)

ODE Ordinary Differential Equation

OIE World Organisation for Animal Health

OPF Oro-pharyngeal Fluid

PCP Progressive Control Pathway

PD_{50} 50% Protective Dose

P(E) Probability of Elimination

PRCC Partial Rank Correlation Coefficient

RV Ring Vaccination

R_0 Reproductive Ratio

SAT South African Territories

SMC ABC Sequential Monte Carlo Approximate Bayesian Computation

TCID50 Median Tissue Culture Infectious Dose

TTE Time To Elimination

VE Vaccine Efficacy

WRLFMD World Reference Laboratory for Foot-and-Mouth Disease

Chapter 1

Introduction

1.1 The Global Context of Foot-and-Mouth Disease

1.1.1 History of FMD

It is generally agreed that the earliest known description of FMD was by the monk Fracastorius in 1545, suggesting that the disease has been extant for approximately 500 years (J. Arzt et al. 2011). Despite this long history however, the first true insights into the disease did not come until 1898, when Loeffler and Frosch demonstrated that the etiological agent of the disease was a virus and in so doing helping to found the field of virology (Brown 2003).

Research on FMD has always been hampered by the biosecurity requirements of working with the virus, and the seven serotypes and myriad strains that circulate globally (J. Arzt et al. 2011). Initial research efforts focused on identifying a suitable experimental animal to grow the virus in, eventually identifying guinea pigs and then mice in 1927 and 1951 respectively. Although the problem of large scale production of the virus was solved by 1947, efforts at a vaccine continued to be held back by the multitude of serotypes which circulated globally, as protection against one serotype does not confer protection against any other. Indeed, there have been cases where protection was not offered against different strains within the same serotype, such as the 1965-66 European outbreaks (Brown 2003). Modern vaccines generally include multiple serotypes to work around this problem (Luis L Rodriguez and Marvin J Grubman 2009).

With the problem of large-scale production of vaccine solved, many states began to implement vaccination of cattle and swine to prevent the circulation of FMD within their borders. Mexico eliminated FMD through the use of vaccination

in 1952, joining the rest of North America in being free from the disease (Naranjo and Cosivi 2013). By 1991 in Europe, the European Community had judged that the disease was under control and that there was no indigenous focus for the disease on the continent, as such banning preventative vaccination against FMD in 1991 (Leforban 1999). Occasional introductions over the decade following were quickly controlled, with the exception of the 2001 outbreaks in the UK and the Netherlands (Bouma, A. R. W. Elbers, et al. 2003). However, the disease has never re-established itself as endemic to the continent of Europe. In South America, the first national FMD elimination programs were established in the 1960s and 1970s, progressing to regional elimination efforts in the 80s. By 2009 however, the disease remained present on the continent (Naranjo and Cosivi 2013). Today the majority of the continent (with the exception of Venezuela) is recognised by World Organisation for Animal Health (OIE) as free from the disease with vaccination, as shown in Figure 1.2.

However, the disease remains endemic in many Asian and African countries. For a variety of reasons including lack of good quality data and the more complex dynamics of multiple circulating serotypes, less research has focused on the disease in endemic areas. The areas still at risk for FMD are split into regional pools, which tend to share a number of serotypes. There are seven such pools, outlined in Figure 1.1. Due to the virulence and ease of transmission of Foot-and-Mouth Disease Virus (FMDV), it therefore remains as a constant threat for reintroduction to those areas of the world currently free of the disease.

In those countries where FMD remains endemic, efforts to control or combat FMD vary, and there are major difficulties in bringing the disease under control. Indeed, in 2014 only 2 laboratories existed in Africa that could diagnose FMD and carry out vaccine-matching (Brito et al. 2017). In an effort to encourage and streamline the path of a country to being free from FMD, the Progressive Control Pathway (PCP) was introduced in 2012 by European Commission for the Control of Foot-and-Mouth Disease (EuFMD) and OIE. The PCP introduces stages, outlined in Figure 1.3, by which a country can progressively learn about the presence of the disease within their borders, introduce control measures to reduce the impact of the disease, and eventually proceed to being free of the disease (K. Sumption, Domenech, and Ferrari 2012).

1.1.2 International & Economic FMD Policy

International policy regarding FMD is governed by OIE, the disease being listed in the Terrestrial Animal Health Code (OIE 2021). OIE formulates rules about the

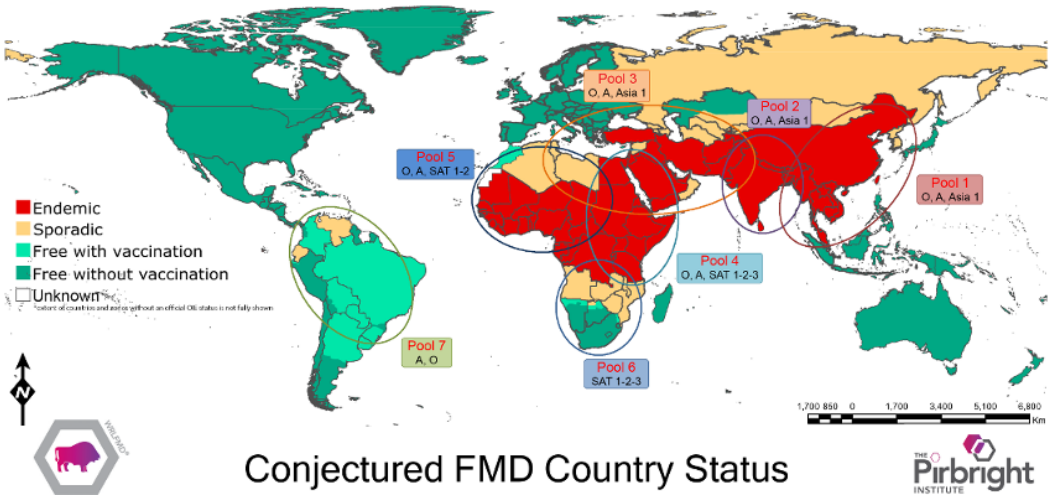

Figure 1.1: Conjectured Global FMD Status & Regional Serotype Pools, 2021, by the World Reference Laboratory for Foot-and-Mouth Disease (WRLFMD) at Pirbright. Each pool lists the serotypes that typically circulate in that region. Countries where the disease is endemic are found only in Asia and Africa. Venezuela is considered to have sporadic outbreaks.

Source: `https://www.foot-and-mouth.org/sites/foot/files/quick_media/WRLFMD_status.png`

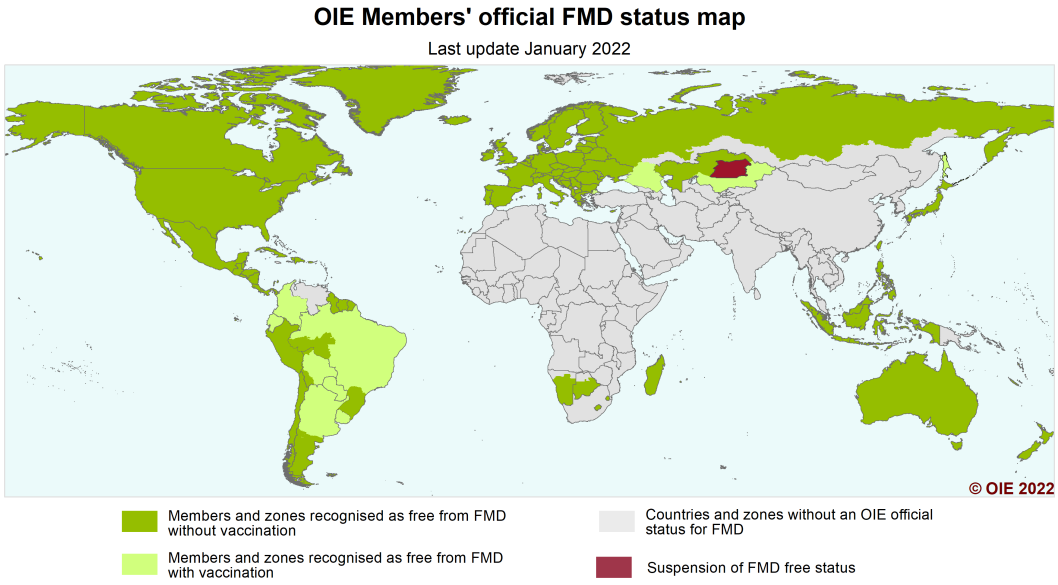

Figure 1.2: *OIE Member's Official FMD Status Map (Jan 2022).*

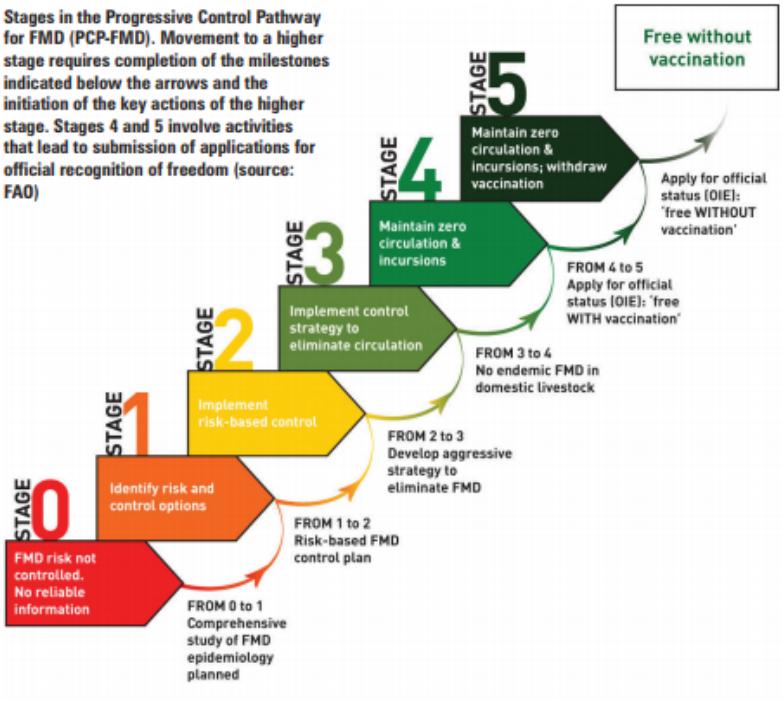

Figure 1.3: *The stages of the Progressive Control pathway for FMD. Source: K. Sumption, Domenech, and Ferrari 2012*

treatment and classification of a countries FMD-status, voted on by its 182 member countries, and is the arbiter of whether a region is officially free from FMD. OIE also maintains relations with the few non-member states for collecting and validating disease occurrence information.

The OIE recognises two classifications of regions as free from the disease. The first is "Free from FMD without vaccination", the second is "Free from FMD with vaccination", and distinguishes between those regions where mass vaccination is regularly applied to control the spread of the disease (OIE 2021). Countries not FMD-free cannot trade live animals with those countries that are free from the disease. Trade of livestock products are also restricted; countries experiencing regular outbreaks can only export heat-treated meat and even those countries who are FMD-free with vaccination can only export de-boned meat subject to stringent bio-security measures (James and Rushton 2002). Being classified as free from the disease is therefore important for unrestricted access to lucrative markets, as most of the richest economies are free from FMD (T. J. D. Knight-Jones and J. Rushton 2013).

The response to an outbreak of a country free from FMD has important consequences on a countries access to international trade in the event of an epidemic,

which has implications for how the epidemic is managed. When a policy of culling only is pursued to manage the epidemic, Free status is regained 3 months after the end of the outbreak. If vaccines are used to contain the spread of the disease, and the vaccinated animals are subsequently slaughtered, this also applies. However, if the vaccinated animals are allowed to live, this period where restrictions still apply is extended to 6 months, due to the fear that unnoticed carriers might initiate subsequent outbreaks (Arnold et al. 2008; OIE 2021). This can have large economic effects, and incentivizes the slaughter of animals to reduce the period when access to international markets is restricted.

Countries that are free from FMD experience losses related to their surveillance and enforcement systems required to remain free of the disease. In the event of disease incursions, they also experience the direct losses of vaccination and/or culling of livestock, as well as expensive restrictions on trade in an economy use to access to international markets (T. J. D. Knight-Jones and J. Rushton 2013).

Regions where the disease is endemic experience losses in potential revenue due to the aforementioned trade barriers, impairment of their food security, and indirect losses from the prevention of the adoption of more efficient production methods by FMD. Direct losses are related to the costs of measures to monitor, prevent, and bring under control FMD (T. J. D. Knight-Jones and J. Rushton 2013).

1.1.3 FMD in the Republic of Turkey

The Republic of Turkey is a region where FMD is considered to be endemic, as seen in Figure 1.1. More specifically, Thrace (in Europe) is considered free from FMD with vaccination, while Anatolia (in Asia) is considered to be at PCP Stage 2. The region is considered important due the size of the cattle industry in the area, and its proximity to FMD-free Europe. Unlike many countries where the disease is endemic however, the country has a comprehensive reporting system and mass vaccination program. Over the past 20 years serotypes O, A, and Asia-1 have circulated in the region (T. J. D. Knight-Jones, S. Gubbins, et al. 2016). During the period data is available the Turkish surveillance system relied on passive surveillance (farmers reports), but over the last decade have added active surveillance measures such as seroprevalence studies and risk-based surveillance efforts (unpublished communication). Control policies include biannual mass vaccination in at-risk provinces, as well as reactive ring vaccination and movement bans around detected infected farms. The data used in this thesis is from the Republic of Turkey, and the setting and details of the data are discussed in detail in Chapter 2.

Published research on FMD in Turkey is sparse. The earliest reference to research in the area appears to be Nazlioglu in 1967, who assessed the economic losses the disease was causing. In 1992 Zog *et al* developed a model to update the financial losses. In 2005 and 2008, it was estimated that FMD-induced production losses in dairy and fattening cattle totalled losses of $294/head for milking cattle, $152/head for dairy heifers, and $197/head for beef cattle - demonstrating the large impact that FMD can have (Senturk and Yalcin 2005; Şentürk and Yalçin 2008).

In the past 20 years, there have been four published modelling frameworks used to assess FMD in the Republic of Turkey. Gilbert et al. (2005) analysed spatial and temporal trends in the spread of FMD in the region, finding that from 1997-2002 the disease had retreated into persistence islands and become more associated with long-range transportation of live animals, as opposed to the previous dynamic of short-range transmission. In 2008 Branscum et al also used a Bayesian spatio-temporal model to analyse the same trends, and found that the disease appeared to be waning in Western Anatolia and waxing in Eastern Anatolia (Branscum et al. 2008).

Finally, in 2016 two modelling frameworks were developed by Theo Knight-Jones *et al*, 2016. One attempted to assess the probability of FMD spread from wild boars, the other modelled the coverage and decay of vaccination protection in a simulated population of cattle using the previously used vaccination strategy (T J D Knight-Jones, Robinson, et al. 2016; T. J. D. Knight-Jones, S. Gubbins, et al. 2016). However, this model used the previous vaccination strategy of biannual vaccination with a single-dose of a ≥ 3 50% Protective Dose (PD_{50}) vaccine, instead of the latest strategy of a two-dose course of a $\geq 6PD_{50}$ vaccine, and did not account for the effect of cattle movements throughout the country.

1.2 Natural History of Foot-and-Mouth Disease

FMDV is the causative agent of FMD, and consists of a single-strand, plus-sense RNA genome of approximately 8,500 base-pairs. This is enclosed in icosahedral capsid made up of four structural proteins (Marvin J. Grubman and Baxt 2004). FMD is one of the most infectious animal diseases in the world and can infect up to 70 different animal species, including all species of domesticated cloven-hoofed animals and many undomesticated species (J. Arzt et al. 2011; Marvin J. Grubman and Baxt 2004). Seven serotypes of FMD are known: O; A; C; Asia-1; South African Territories (SAT)1; SAT2; SAT3 (Fig. 1.4), with each serotype including a varying number of strains or sub-types (Domingo et al. 2002).

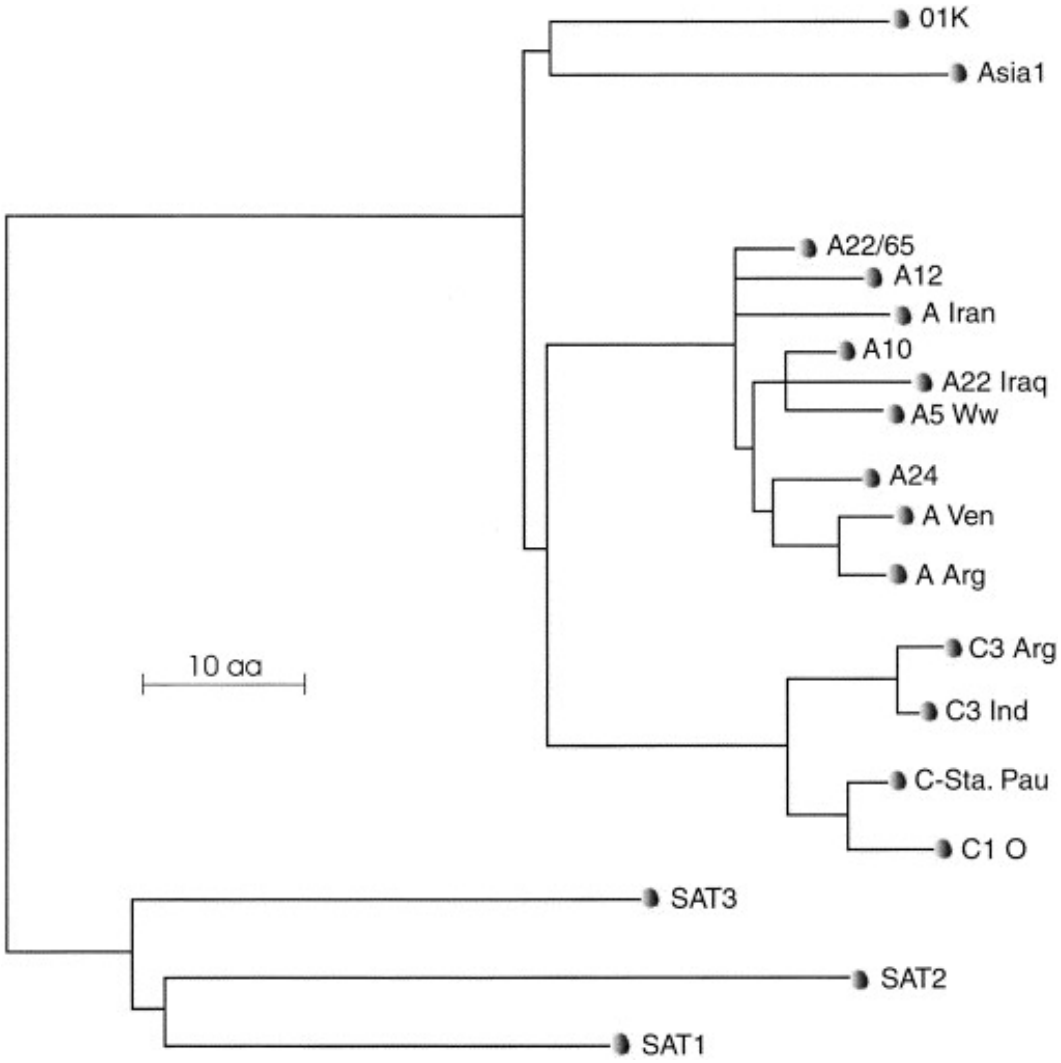

Figure 1.4: *Phylogenetic relationships between the 7 serotypes of FMD. (Domingo et al. 2002)*

FMD exhibits high morbidity but low mortality. The most common symptoms, for which the disease takes its name, are lesions on the feet, mouth and tongue of affected animals. Common but less visible symptoms include a drop in milk production, fever, and excessive drooling. Less common symptoms include lameness and miscarriages (Marvin J. Grubman and Baxt 2004). Although most adult animals recover from the disease, mortality typically being less than 5%, death is more common in younger animals (Şentürk and Yalçin 2008). The severity of disease varies by the species infected, the individual susceptibility of the host, the infecting strain, and the infecting dose (R P Kitching, Hutber, and Thrusfield 2005). It is generally considered impossible to carry out intensive cattle or swine agriculture in regions where the disease is endemic (James and Rushton 2002).

FMDV can infect many different species, including most domesticated cloven-hoofed animals and many other wild species such as deer (Marvin J. Grubman and Baxt 2004; Schaftenaar 2002). The course of the disease can be different in different species. In cattle, upon infection with FMD the incubation period of the disease can extend up to 12 days, but is most commonly 2-3 days. Virus can be excreted in the milk of infected cattle 2-4 days before any lesions form. Excretion of the virus (and hence infectiousness) generally ceases by around 5 days after the appearance of lesions. Clinical signs typically disappear 10 days after their first appearance (Mardones et al. 2010; Yadav et al. 2019). Cattle are highly susceptible to infection via inhalation, whereas swine are more easily infected via oral exposure (J. Arzt et al. 2011). Once infected however, swine excrete more infectious doses per day by an order of magnitude (up to 500 million ID_{50}/day). Sheep and goats are generally only mildly symptomatic if at all, and are less infectious (S. Alexandersen, Quan, et al. 2003).

In cattle, immunity following infection varies but can potentially last up to four and a half years, although the immunity is generally serotype-specific and does not induce sterilizing immunity. In swine however, it typically lasts only 3-6 months. Little research has been done on this area for sheep or goats (T. R. Doel 2005, 1999).

1.2.1 Transmission

FMD is one of the most infectious animal diseases in the world, with estimates of the basic reproductive ratio Reproductive Ratio (R_0), the average number of secondary infections from an infected animal in a naive herd, sometimes exceeding 70 (T. J. D. Knight-Jones and J. Rushton 2013; Woolhouse et al. 1996).

There are three main routes of infection. The most common route is via the inhalation of aerosolized virus particles which have been exhaled in an infected

animals breath. Swine require up to 6000 Median Tissue Culture Infectious Dose (TCID50) to become infected in this manner, whereas cattle and sheep can require as little as 10 TCID50. Contrasting this, once infected swine produce much more aerosolized virus, estimated at up to 400,000,000 TCID50 from a single pig in a day. Over the same time period, cattle are estimated to release up to 120,000 TCID50 (R P Kitching, Hutber, and Thrusfield 2005).

In favourable environmental conditions, the aerosolized release of virus can potentially spread the disease over distances of many kilometres. In 1981 aerosol from an infected herd in Brittany, France, was detected as far as the Isle of Wight more than 250 km away (A. I. Donaldson et al. 1982).

FMD may also spread through oral ingestion of the remains of previously infected animals, for example when this is added to animal feed. In 2001 this occurred in the UK, leading to a major outbreak (Bourn et al. 2002).

Finally, the virus can persist in the environment in the form of fomites. High temperatures, dry conditions, or pH values below 6 or above 10 can reduce the time these virus particles do survive in the environment. Nevertheless if kept moist and at a neutral pH the virus can potentially survive for days, weeks, or even months on surfaces. As such, virus-laden clothing or uncleaned tools or vehicles which have come close to infected animals present the risk of further onward spread. This route was determined to be the cause of outbreaks in Denmark in 1982, and Italy in 1983 (R P Kitching, Hutber, and Thrusfield 2005). This sort of contamination also played an important role in the 2001 UK outbreak, and generally occurs through indirect contacts such as farm-to-farm movements of personnel (L.M et al. 2011). Due to the difficulty of obtaining this contact data, research on this route is limited, however work has demonstrated that being limited to subsets of the full information can lead to significantly different results (Rossi et al. 2017). Additionally, it has been shown that environmental R arising from this contamination is approximately 2, enough to sustain an epidemic without direct contact (Bravo de Rueda et al. 2015).

1.2.2 Carrier Animals

Essentially all naive cattle show symptoms of FMD, lesions around the mouth, tongue and feet, as well as a fever and possible lameness, during the period where they are clinically infectious. Following this phase, some proportion of the cattle fully clear the infection and generate immunity against the infecting strain or serotype, and the rest remain persistently infected, referred to as carriers. Experimental evidence suggests that close to 50% of cattle become carriers, although field studies find lower proportions (C. Stenfeldt et al. 2016; Carolina Stenfeldt

and Jonathan Arzt 2020; Carolina Stenfeldt, Heegaard, et al. 2011; Paul Sutmoller, McVicar, and Cottral 1968). Carrier cattle display no symptoms, but have detectable levels of virus recoverable from the oropharyngeal fluid (ORF) more than 28 days post-infection. This period can potentially last up to 3 years, although most evidence suggests around 6 months to 1 year is likely (Carolina Stenfeldt and Jonathan Arzt 2020; Tenzin et al. 2008).

It is unclear whether or not carrier animals are infectious and can transmit to other susceptible animals (Soren Alexandersen, Zhidong Zhang, and Alex I. Donaldson 2002; Carolina Stenfeldt and Jonathan Arzt 2020). There is no evidence from well-studied epidemics in FMD-free countries, such as in the UK in 2001, because all known or suspected infected animals are generally culled. Multiple experimental studies have failed to find evidence of transmission or viral shedding from carrier animals, and it has never been observed in the field (Soren Alexandersen, Zhidong Zhang, and Alex I. Donaldson 2002; Moonen et al. 2004). Recent field experiments observing animals in Vietnam and India observed no transmission from carriers (Bertram, Vu, et al. 2018; Bertram, Yadav, et al. 2020; Hayer et al. 2018). A summary of the research by Tenzin et al. (2008) however, noted that after calculating a rate of transmission after synthesising multiple studies, transmission from carrier could still not be entirely ruled out. More recently, research has demonstrated that the virus taken from the ORF can be infectious (Jonathan Arzt et al. 2018).

Sheep may also become persistently infected with FMD, but swine are not capable of maintaining persistent FMDV infection (Carolina Stenfeldt and Jonathan Arzt 2020).

If persistently-infected livestock are capable of infecting susceptible animals, the probability of such an event must be low. However, if such transmission does occur, it has potential policy implications. The possibility of carrier animals triggering a new outbreak after a contained outbreak is one of the reasons why the OIE mandated trade ban lasts for 6 months if vaccinate-to-live is used, but only 3 months for vaccinate-to-kill policies.

1.2.3 Vaccination

The first practical vaccine against FMD was developed by Waldemann in 1937, and used virus from epithelium and vesicular fluid of tongues from deliberately infected cattle. In the intervening decades, much research and development has been carried out on vaccines, and today vaccine is formulated by infecting Baby Hamster Kidney Cell (BHK)-21 suspension cells with carefully selected virus, although research into vaccines continues (Singh et al. 2019). The extracted virus is then inactivated and

concentrated, purified, and then adjuvants and preservatives added (T. R. Doel 2003). The inactivated vaccines are generally formulated depending on the strain required and the species to be vaccinated, commonly containing more than one strain to cover more than one serotype. Strains selected are tested against field isolates and reference vaccine strains (D J Paton et al. 2005). The use of vaccines purified of Non-Structural Protein(s) (NSP) allows discrimination between those animals vaccinated and those who have been exposed to infection. These Differentiation Infected from Vaccinated Animals (DIVA) tests have been available since 1998, although the purification process may leave trace remnants and animals may still develop antibodies to NSPs after multiple vaccinations, so caution is appropriate (R P Kitching, Hutber, and Thrusfield 2005; Mackay et al. 1998).

Vaccinated livestock respond rapidly to their first dose of a vaccine, and depending on vaccine composition reach peak antibody titres 14-28 days post-vaccination, though subclinical infection remains possible (T. R. Doel 2003). Younger animals commonly receive a booster dose 3-4 weeks after their first vaccine dose to induce a greater immune response (T. J. D. Knight-Jones, S. Gubbins, et al. 2016; Park et al. 2021). High potency vaccines are able to reduce the time until protection to within 3-4 days. Calves from non-vaccinated cattle appear to respond as effectively as adult cattle after 1-2 weeks of age. Maternally Derived Antibodies (MDA) against FMDV however, interferes with the immune response of young animals to the vaccine, possibly up to several months of age, which must be accounted for in vaccination programs (R. P. Kitching and Salt 1995; Nicholls, Black, and M. M. Rweyemamu 1984).

Vaccines generally confer approximately 6 months of immunity against the serotype used, comparable with the duration of natural immunity in swine but less than has been observed for natural immunity in cattle (T. R. Doel 2003; Lyons et al. 2019). A single dose of vaccine does not prevent the vaccinated animal from becoming sub-clinically or persistently infected (Parthiban et al. 2015; Carolina Stenfeldt, Eschbaumer, et al. 2016). The effect of reinfection on the duration of immunity is not well studied, however E. El-Sayed et al. (2012) finds natural immunity lasting 32-36 weeks where T. R. Doel (2005) reports protective immunity up to several years. This, in combination with the known benefit of booster vaccinations, suggests that reinfection will stimulate a greater duration of the immune response.

Vaccination has successfully been used as a tool in integrated control programs for FMD, as demonstrated by the decline and subsequent elimination of the disease in many areas of the world over the past 70 years. This may effectively be achieved even without the vaccination of all livestock. For example, during the

time of mass vaccination in Europe it was common to focus on cattle, due to their abundance and high value, and vaccinate only a few of the sheep or pigs. Nonetheless the disease was eradicated (T. R. Doel 2003). Many countries free from FMD today maintain emergency vaccine stocks, for use in the event of an epidemic. In many cases, these vaccines will be used to slow the spread of the disease before the vaccinated animals are subsequently culled to speed the return to official FMD-free status, as in the Netherlands in 2001 (Bouma, A. Elbers, et al. 2003). In contrast, the 2001 UK policy response involved culling alone, with no emergency vaccination (Bourn et al. 2002). Whether culling or vaccination is the optimal policy for control of FMD depends on the goal of the policymaker and their resource constraints, but if stopping an epidemic is the main concern vaccination is best used as a prophylactic before an animal is infected due to the time delay to protection, and culling of currently infected animals is best for preventing the further spread of the virus.

1.3 Modelling Infectious Diseases

Mathematical and mechanistic models of infectious disease can play an important role in infectious disease epidemiology. Mathematical models are mathematical descriptions of a situation based on initial hypotheses, which produce results and conclusions that may be compared against experimental evidence. This production of comparable results usually requires numerical simulations, usually on a computer. For epidemiology, the general process is to formulate assumptions about how a disease spreads and translate this into a mathematical problem (Brauer 2009).

Mathematical models have great use in epidemiology because experiments in epidemiology with controls are often difficult, expensive, or ethically dubious to carry out. Models can offer a method of investigating the underlying mechanisms of a disease that reduces or eliminates these concerns. In doing so, it can often suggest or support control mechanisms for the disease. In more recent years, the rapid deployment of such models have aided in predictions of ongoing outbreaks as well as comparing control measures (Brauer 2008; Matt J. Keeling, Hill, et al. 2021). As such, mathematical models offer a very useful tool, with a wide range of applicability.

The foundations of mathematical modelling of infectious disease lie in the work of Ronald Ross, the British medical doctor who won the Nobel prize in 1902 for discovering that *Anopheles* mosquitoes are the host vector for malaria. In 1911 he modelled the spread of malaria using differential equations, through this mathematical reasoning demonstrating that the cessation of malarial spread required only

the reduction in the *Anopheles* population below a certain threshold, rather than complete eradication (Ross 1911).

This contribution was then developed by Kermack and McKendrick in 1927, using partial differential equations to predict the spread of disease within a population. Although their model structured the population in terms of age-at-first-infection, the simple case where infectiousness did not vary by age led to the first compartmental SIR model (Kermack, McKendrick, and Walker 1927).

In the second half of the 20th Century the field was revitalised, most notably by Anderson and May (Anderson and May 1979; May and Anderson 1979). The field remained focused on the theory underpinning mathematical modelling in this period, most likely due to the lack of computing power available to simulate their ideas.

Modern efforts at formalising mathematical models about the spread of disease have the benefit of large amounts of computing power, which can allow the use of such models as predictions during the crises being analysed, for example during the 2001 UK FMD epidemic or the 2020 COVID19 pandemic (Anastassopoulou et al. 2020; Brauer 2008; Kao 2002; Matt J. Keeling, Hill, et al. 2021). A common target for this type of work is to predict the R_0, which is the average number of secondary infections that is expected from a primary case in a completely susceptible population (Heesterbeek 2002). This ratio is useful for the information it contains about the spread of the disease, if $R_0 > 1$ then the number of infected hosts is increasing, if $R_0 < 1$ then the number of infected hosts is decreasing. Consequently, disease control policies are targeting this ratio.

1.3.1 Compartmental ODE models

The compartmental Ordinary Differential Equation (ODE) model, first developed as an SIR model in Kermack, McKendrick, and Walker (1927), is very common in epidemiological research. This model divides the population under study into compartments which correspond to a disease status, and they move between these compartments at different rates. There are many formulations of these compartmental models, for example the SI model, which includes a susceptible population S and an infectious population I, with movement $S \rightarrow I$ at rate λ. SIR models add a recovered compartment R, to allow individuals to recover (or die) from the disease, with recovery rate γ for $I \rightarrow R$ (shown in Figure 1.5). Other formulations include SEIR, which includes an exposed/latent compartment, with $E \rightarrow I$ proceeding at rate σ; SIS to allow infectious individuals to become susceptible again ($S \rightarrow I \rightarrow S$); and SIRS or SEIRS to allow recovered (and immune) individuals to lose their immu-

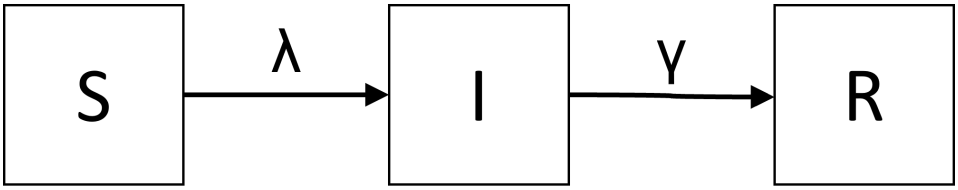

Figure 1.5: A basic compartments of the SIR model, with susceptible individuals proceeding to become infected at rate λ, and recover at rate γ.

nity to infection. These basic models can also be extended to include compartments for control strategies such as vaccination, or age-structured disease compartments to allow age-dependent transmission rates.

Once the specific formulation of the model has been determined, the system of ODEs which describe the rates individuals move between the compartments can be laid out. For the SIR system, the equations are laid out below in equations 1.1 to 1.3. These equations deal with proportions of the population in each compartment, so S is the proportion of the population under study which are susceptible to the disease. Additionally, it is enforced that $S + I + R = 1$, so that the entirety of the population is in one of the compartments.

$$\frac{dS}{dt} = -\beta SI \tag{1.1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I \tag{1.2}$$

$$\frac{dR}{dt} = \gamma I \tag{1.3}$$

If we examine equation 1.2, if the fraction of susceptible individuals in the population S is less than γ/β then $\frac{dI}{dt} < 0$ and the disease will die out. If however $S > \gamma/\beta$ then $\frac{dI}{dt} > 0$ and the proportion of the population infected will increase. This ratio, between the rate of infection and the rate of recovery, defines the reproductive ratio. $R_0 = \beta/\gamma$.

This formulation of the SIR model assumes a closed population, with no births, deaths, immigration or emigration ($S + I + R = 1$). This assumption may be close enough to reality if the time-scale in question is very small compared to a typical lifespan of a member of the population under study, but in endemic situations this assumption is less useful. The addition of demography to the SIR model may be done by adding a birth rate ν and a death rate μ, leading to the equations below.

$$\frac{dS}{dt} = \nu - \beta SI - \mu S \tag{1.4}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \tag{1.5}$$

$$\frac{dR}{dt} = \gamma I - \mu R \tag{1.6}$$

The death rate in this system acts to increase the rate of recovery and decrease R_0, so $R_0 = \beta/(\gamma + \mu)$.

Analysis of these systems for stable equilibria ($\frac{dI}{dt} = 0$) reveals two values of I where the system is stable. The first is $I = 0$, the disease-free state, or

$$S^* = \frac{\gamma + \mu}{\beta} = \frac{1}{R_0} \tag{1.7}$$

which leads to the conclusion that the proportion of the population which must be susceptible for an endemic equilibrium to emerge is the reciprocal to R_0. Once again, R_0 emerges as a threshold, in order for a disease to be endemic R_0 must be greater than 1.

Further exploration of this system shows that to prevent the circulation of a disease of a given R_0 within a population, we need only reduce the population of susceptible individuals below a certain threshold, defined by R_0. This can be done via vaccinating a certain proportion of the population p. If we modify ν so that $\nu' = \nu(1 - p)$ in equation 1.4 (balanced by addition of νp in eq. 1.6), R_0 emerges as

$$R_0' = (1 - p)R_0 \tag{1.8}$$

and the threshold proportion that must be vaccinated that results from this is obtained by setting $R_0' < 1$, resulting in the following equation.

$$p_c = 1 - \frac{1}{R_0} \tag{1.9}$$

This phenomenon is known as herd immunity, and the obvious implication is that the larger R_0 is the greater the proportion of the population which needs to be vaccinated to control spread of the disease. This critical threshold was first recognised in C. E. Smith (1970). However, one must take into account the assumptions made when formulating this model, such as random mixing of the population and random delivery of vaccination. For a good discussion of the complexities of this threshold, see Fine, Eames, and Heymann (2011).

1.3.2 Subcompartments

In the models considered so far, all disease status compartments have had only one subcompartment. When this is true, the probability that an individual is in the compartment at a time after entering it is an exponential distribution. However, by subdividing each compartment into n subcompartments, the distribution of the period of time spent in the disease compartment can be altered.

As an example, if we subdivide the infected compartment of the SIR model:

$$\frac{dS}{dt} = \nu - \beta S \sum_{i=1}^{n} I_i - \mu S \tag{1.10}$$

$$\frac{dI_1}{dt} = \beta S \sum_{i=1}^{n} I_i - \gamma n I_1 - \mu I_1 \tag{1.11}$$

$$\frac{dI_i}{dt} = \gamma n I_{i-1} - \gamma n I_i - \mu I_i \forall i = 2, ..., n \tag{1.12}$$

$$\frac{dR}{dt} = \gamma n I_n - \mu R \tag{1.13}$$

we see that to maintain a constant average time between infection and recovery, as the number of subcompartments increases the rate at which individuals move between subcompartments must also increase commensurately. The variance in the length of the infected period decreases as n increases. When $n = 1$, this distribution is exponential; when $1 < n < \infty$, this distribution is a gamma distribution; as $n \to \infty$ this becomes a constant period.

1.3.3 Stochasticity

All models considered thus far have been deterministic, given the same starting conditions exactly the same disease trajectory will be observed. This deterministic view does not actually apply to the real-world dynamics of pathogens; if we could "re-run" an epidemic we are unlikely to see exactly the same hosts becoming infected at exactly the same time. The specific individual hosts which become infected has a large element of chance, and models which take account of this probabilistic element are common. The importance of randomness is highest when populations are small, as population sizes increase random elements will begin to cancel each other out and the observed randomness will decrease.

There are three methods for approximating random processes in disease transmission and recovery. The first method is to introduce randomness directly

into population variables; the second is to randomly vary parameter values; the third is to explicitly model individual-level random events (Matt J. Keeling and Rohani 2008). For example, observational noise is the simplest type of noise, and acknowledges the uncertainty inherent in recorded data such as case numbers. The underlying epidemic dynamics remain deterministic. However, this does not impact the observational dynamics, and modifies only the reported data.

Event-driven approaches are a popular method for incorporating demographic stochasticity. These methods require explicit consideration of the possible events in a given system. A common method to implement this event-driven randomness is Gillespie's Algorithm, shown in algorithm 1 (Gillespie 1975).

Algorithm 1 Gillespie's Direct Algorithm

1: Label all possible events E_1,..., E_n.
2: For each event determine the rate at which it occurs, R_1,..., R_n
3: The rate at which any event occurs is $R_{total} = \sum_{m=1}^{n} R_m$
4: The time until the next event is $\delta t = \frac{-1}{R_total} log(RAND_1)$
5: Generate a new random number $RAND_2$. Set $P = RAND_2 \times R_{total}$
6: Event p occurs if

$$\sum_{m=1}^{p-1} R_m < P \leq \sum_{m=1}^{P} R_m$$

7: The time is now updated. $t \rightarrow t + \delta t$, and event p is performed.
8: Return to Step 2.

Using the common Gillespie algorithm for simulating a stochastic system, if we consider an SIS model with no demographics:

$$\frac{dS}{dt} = -\beta SI/N + \gamma I \tag{1.14}$$

$$\frac{dI}{dt} = \beta SI/N - \gamma I \tag{1.15}$$

where N is the size of the population ($N = S + I$). Note that S and I are now the number of individuals in the compartment, rather than the proportion of the population. This is introduced because the event-driven approach requires that we deal with individuals becoming infected, and so we can no longer deal with proportions of the population without accounting for the size of that population. For this system, there are only 2 possible events:

- Transmission occurs at rate $\beta SI/N$. Result: $S \rightarrow S - 1, I \rightarrow I + 1$
- Recovery occurs at rate γI. Result: $I \rightarrow I - 1, S \rightarrow S + 1$

Transmission occurs at rate $\beta SI/N$, recovery at rate γI, and so either event occurs at a total rate of $R_{total} = \beta SI/N + \gamma I$. $RAND_1$ denotes a uniform random number drawn from the interval $(0, 1)$.

The time δt until *an* event occurs, either transmission or recovery, is therefore:

$$\delta t = \frac{-log(RAND_1)}{\beta SI/N + \gamma I} \tag{1.16}$$

and we choose which event occurs randomly, weighted by the rates at which either event is occurring. In this example, the transmission event occurs if:

$$RAND_2 < \frac{\beta SI/N}{\beta SI/N + \gamma I} \tag{1.17}$$

otherwise the recovery event occurs. Finally time is updated ($t \rightarrow t + \delta t$), the appropriate changes are made to the population variables, and the process is repeated.

A serious drawback of the Gillespie algorithm is that the increase in the number of interaction terms that must be considered increases prohibitively as the population becomes large. Additionally, the time interval between events decreases as there are more events happening, so the number of iterations that must be computed in a given time period also increases. An algorithm to increase efficiency was presented by Gillespie in 2001, and is called the τ-leap algorithm (Gillespie 2001). This discretises time, allowing multiple events to happen in a single time step, and is justifiable as long as the probability of an individual undergoing multiple events in a single time-step is small. This algorithm is presented in Algorithm 2 for the SIS model, taken from Matt J. Keeling and Rohani (2008).

1.3.4 Spatial Heterogeneity

An important assumption of these models is that of homogeneous mixing within the population. Each individual is equally likely to mix with every other individual in the population, such that every individual population member is equally likely to become infected. As the size of the population increases however, this becomes a less reasonable assumption. Interactions between individuals is often primarily local in nature, and directly transmitted diseases are dependent on interactions between individual disease hosts. Intuitively, a person who lives in the West Midlands, UK, is not equally as likely to physically interact with someone living in Ohio, USA, as compared to mixing with someone who also lives in the West Midlands.

Algorithm 2 τ-leap algorithm

1: Let the time increment between steps, δt, be small and fixed.

2: Let $M_T(t)$ and $M_R(t)$ represent the number of transmission and recovery events by time t

3: Defining $\delta M_i = M_i(t + \delta t) - M_i(t)(i = T, R)$, then

$$P(\delta M_T = 1|S, I) = \frac{\beta SI}{N}\delta t + o(\delta t)$$

$$P(\delta M_R = 1|I) = \gamma I \delta t + o(\delta t)$$

defined the transition probabilities for transmission and recovery events occurring in the time interval δt.

4: For small δt, the increments δM_i are approximately Poisson, such that:

$$\delta M_T \approx Poisson(\frac{\beta SI}{N}\delta t)$$

$$\delta M_R \approx Poisson(\gamma I \delta t)$$

5: Now, the variables can be updated:

$$S(t + \delta t) = S(t) - \delta M_T + \delta M_R$$

$$I(t + \delta t) = I(t) + \delta M_T - \delta M_R$$

6: Time is updated, $t = t + \delta t$.

7: Return to Step 4.

Spatial hetereogeneity refers to differences between populations or individuals at different geographical locations, and can arise from two sources. One source is spatial differences in the underlying forces which govern the dynamics of a population, for example environmental conditions of light, soil fertility, or rainfall. These can have important effects on the spread and incidence of disease, although the modern supply of georeferenced strain sequence data in combination with environmental data is now allowing the exploration of which environmental variables are most important (Munsey, Mwiine, Ochwo, Velazquez-Salinas, Ahmed, F. Maree, et al. 2021; Munsey, Mwiine, Ochwo, Velazquez-Salinas, Ahmed, Luis L. Rodriguez, et al. 2022).

The other source of heterogeneity describes the observed differences in population structures over space, generally arising from processes such as movement restrictions or simple stochasticity (Matt J. Keeling and Rohani 2008). This heterogeneity can also lead to some striking patterns in the spread of disease (Bolker and Grenfell 1996). Capturing this usefully can be done by acknowledging the spatial structure of the population. The simplest model is the metapopulation model, subdividing the population into subpopulations, and modelling the dynamics of these subpopulations independently alongside limited interactions between subpopulations. Ideally, the level of subdivision used would produce subpopulations where the assumption of homogeneous mixing is as close to reality as possible, although this is not always possible. Regardless, these metapopulation models are a useful tool to simulate the spread of disease (including livestock disease) over larger areas and populations in a mathematically rigorous way.

The 2001 foot-and-mouth epidemic in the UK was a clear example of space playing a strong role in the dynamics of disease spread. Cases were predominantly within three regions: Cumbria, Devon, and the Welsh borders; most transmission occurred within 3 kilometres of the source farm (Matt J. Keeling and Rohani 2008). Two of the three main modelling efforts during the epidemic were spatially explicit. A deterministic and non-spatially-explicit model was put forward by the Imperial group of modellers (N. M. Ferguson 2001; Neil M. Ferguson, Donnelly, and Anderson 2001). Morris et al. (2001) used Interspread, a spatially-explicit and highly detailed model with 54 parameters, to assess alternative control strategies for the epidemic. Finally, M J Keeling et al. (2001) developed and used a simpler spatially explicit stochastic model to assess disease dynamics. A good discussion of these modelling frameworks is found in Kao (2002), as well as Matt J Keeling (2005).

The Keeling model treats the farm as the basic epidemiological unit, and models the spread of infection between farms based on the spatial location of the

farm, and the number and demographics of the livestock on the farm. Each farm has an associated susceptibility S and infectiousness I, determined by the demographics of the livestock on that farm, and the relative susceptibility and infectiousness of cattle and sheep.

$$S^j = \sum_s N_s^j S_s \tag{1.18}$$

$$I^i = \sum_s N_s^i T_s \tag{1.19}$$

Where N_s^j gives the number of livestock of species s on farm j or i, and S_s and T_s are species-specific susceptibility and transmission rates.

The transmission process is then stochastic, such that the probability of farm j becoming infected by infectious farms on any day is:

$$P(infect) = 1 - exp\left[-S^j \sum_{i \in infectious} I^i K(d_{ij})\right] \tag{1.20}$$

With $K(d_{ij})$ a spatial transmission kernel which defines how a farms infectiousness decreases with the distance d between susceptible farm j and infectious farm i. The sum over all infectious farms creates an infectious pressure on susceptible farms, rather than have any individual infectious explicitly infect another. K subsumes all transmission routes which exist in reality, which has the advantage of rapid parameterization.

1.3.5 Model Validation

Once a dynamic mathematical system has been decided upon to represent the system of interest, obtaining a solution to the problem is the next step. With complex models, this generally takes the form of fitting the model to available data. Parameterization of such models is vitally important, as the selection of more accurate parameters improves the robustness of the interpretation of the model results. There is likely to be uncertainty in prior estimates of parameters, and data available from which to estimate the parameters might be patchy, incomplete or unreliable.

If the required outputs are point estimates of the parameters of a statistical model, Maximum Likelihood Estimation (MLE) is a suitable approach, first developed by Fisher in the 1920s. Given that we have a model and some data, our model will provide a probability distribution which allows us to estimate the probability of observing our data, given our model and parameters. As we vary our parameters, the probability of observing the data we have collected will change. For example, if

we have observed a coin flip 10 times, and it has come up heads 8 times, the probability that our model would assign to this is we assumed a per-flip heads probability of 0.2 is much lower than if we assumed the per-flip heads probability of 0.5. This is the probability of our data given our model and parameters; we can then reverse this, and ask what is the probability of the parameters given our data. The MLE method attempts to estimate the parameters for which the sample data is most likely (Myung 2003).

Depending on the model specification and data available, and analytic MLE solution may be tractable, but in many cases a MLE is found numerically using optimization methods.

When the objective is to obtain predictions of model parameter distributions, Bayesian inference can be a fruitful approach. Bayesian inference treats the parameters as random variables that are drawn from a probabilistic distribution given the observed data and some prior beliefs about those (the prior distribution), and attempts to update the belief given the data and the prior belief. A Bayesian approach to parameter estimation can provide continuous estimations without specific assumptions.

The core part of Bayesian inference is Bayes' theorem, which allows us to establish a relationship between our prior belief distribution, $\pi(\theta)$, and the posterior distribution $f(\theta|D)$, where D is the observed data and θ is our parameters. Bayes' theorem is below:

$$f(\theta|D) \propto L(D|\theta)\pi(\theta) \tag{1.21}$$

which allows us to obtain an estimate of $f(\theta|D)$ when we only have a prior belief distribution $\pi(\theta)$, and a likelihood function $L(D|\theta)$ which gives us the probability of our data given our parameters. The prior $\pi(\theta)$ can incorporate expert belief and prior research on the parameter, though if there is no prior belief it is typical to use an uninformative "flat" prior such as a uniform distribution.

Bayesian inference is useful when the problem is tractable analytically, however many problems in epidemiological research are not. In those cases, we can resort to numerical estimation methods such as Markov Chain Monte Carlo (MCMC) and Approximate Bayesian Computation (ABC) (T. McKinley, Cook, and Robert Deardon 2009; T. J. McKinley et al. 2018; Toni et al. 2009).

1.4 Aims

The purpose of this thesis is to develop a stochastic mechanistic model capable of accommodating the complications of endemic FMD, and using it to analyse the spread of FMD within the context of a region where it is already endemic, with the goal of aiding authorities in endemic regions in their efforts to control and eventually eradicate the disease. Additionally, we explore the role of carrier animals as a potential driver for the disease remaining endemic in those areas, as it may be important whether such animals do indeed act as disease reservoirs.

Chapter 2 outlines a model framework which accounts for most of the specific complications of endemic FMD, and the verification of this model. This is important for the following work using this model to compare control policies, increasing the confidence we can feel in the salience of the results observed.

Chapter 3 uses this model to assess the non-culling control policies which might be implemented in endemic countries, using a range of different plausible parameter values. Sensitivity analysis of those policies helps to identify the most important aspects of their implementation. This work has relevance to deciding control policy implementations for endemic regions.

Chapter 4 explores the possible persistence drivers leading to those regions being endemic, comparing possible carrier-animal transmission to the movement of infected livestock (and contaminated vehicles). The work has relevance to the ongoing debate on the infectiousness of carrier animals, as well as raising the possibility of the relevance of such animals to control efforts.

Finally, Chapter 5 explores the impact of the identified hypothetical persistence drivers on potential control policies. Carrier transmission may or may not be an extant phenomenon, but from the perspective of policy it is the impact of this on control policy choices that is most relevant, and this chapter offers some clarity on this question.

I believe that this model represents endemic FMD in greater and better detail than previous models, considering demographics and the specifics of maternally-derived and waning immunity. Furthermore, the model structure offers an ideal framework for investigating the effects of carrier transmission, which if it occurs will be extremely localised. The development of this model and comparison of vaccination policies will aid in future control efforts in currently endemic areas and indicate what role if any carrier animals might play in the current maintenance of the disease.

Chapter 2

Developing and Fitting a Model of Endemic FMD to the Republic of Turkey

2.1 Introduction

There is a mismatch in the FMD modelling world, the areas where the disease is endemic and modelling is most needed are generally the areas where data are not easily available and modelling the spread of disease and control policies is therefore difficult. Additionally, there are many dynamics of the disease which are not necessarily relevant in the case of an epidemic of FMD where the stated policy is elimination of the disease, but are very relevant when the disease is endemic. These extra dynamics make modelling of the endemic scenario more complicated than doing so for the epidemic scenario. Finally, most epidemiological modellers are based in rich countries and are consequently most interested in and are funded for modelling the spread of disease in their own country.

As a result of these factors, the vast majority of the FMD modelling literature focuses on regions of the world that are free of the disease, such as the UK, the USA, New Zealand and Australia. For example, much modelling work was done after the 2001 outbreaks of FMD in the UK and the Netherlands (Kao 2002; M J Keeling et al. 2001). Several different modelling groups have developed simulation models of FMD spread for epidemics in developed nations, such as AusSpread for Australia (Garner and Beckett 2005), InterSpread Plus for New Zealand (M.A. Stevenson et al. 2013), the North American Disease Spread Model (Harvey et al. 2007), the Keeling

model in the UK (M J Keeling et al. 2001, 2003), and its adaptation the U.S. Animal Movement Model (USAMM) and Disease Outbreak Simulation (USDOS) (Michael J. Tildesley, G. Smith, and Matt J. Keeling 2012; Tsao et al. 2020).

Few spatially explicit and mechanistic modelling efforts have looked at endemic regions, despite the vast majority of FMD cases taking places in these regions (Zaheer, Mo D Salman, et al. 2020a). Ringa and Bauch (2014) developed a pair-approximation SEIRV model for an idealised population of 40,000 farms, which showed that prophylactic vaccination was more effective than ring vaccination. However, this model was not based on real-world agricultural data and focused on only some features of the endemic disease such as waning immunity and disease re-importation, while ignoring others such as population demography. Kim et al. (2016) developed a modelling framework to simulate pastoral herds in the endemic Far North of Cameroon. Schnell (2019) also used a farm-level framework for modelling the possible effect of carrier herds and mobile herds of cattle on the endemicity of the disease in Cameroon, finding that asymptomatic carriers may be contributing to disease persistence but not mobile herds.

The Republic of Turkey offers a significant opportunity to probe the dynamics of endemic FMD. In the present day, FMD has been eliminated from the European Thrace region of Turkey in the west, but remains present and endemic in Anatolia, with disease prevalence overall shifting east (Branscum et al. 2008). Efforts to control the disease are longstanding, between 2008 and 2018 the Turkish government reduced the prevalence of the disease from 45% to 5% as a result of their control policies. They aim to achieve OIE status of FMD Free with Vaccination by 2023, via improved clinical surveillance, improved vaccine effectiveness, and management of animal movements. This also involves an extra focus on border regions. (Ozturk, Kocak, and Vosough Ahmadi 2020).

As one of the higher income countries where the disease remains endemic, high quality data has been collected on the spread of FMD within their borders for at least 20 years. These data include outbreak records such as dates, locations and serotypes, as well as agricultural data such as farm locations, and cattle shipments. These records offer most things needed to be useful for a stochastic spatial model of disease spread in an endemic context.

We aim to use this high-quality data from an important endemic region to develop a spatial stochastic model of the spread of the disease, and estimate transmission parameters which take into account the more complicated endemic disease dynamics. We develop a model which uses the available data to simulate the spread of FMD within and between farms, as well as population demography, maternal an-

tibody derived immunity, the movements of infected cattle, and waning immunity. Following this, we identify which of the relevant parameters are identifiable from the data available using the ABC-SMC algorithm. Finally, we use this algorithm and the incidence data from Turkey to estimate values for the identifiable parameters.

This work will provide another estimate for the relevant transmission parameters of FMD taking into account the endemic disease dynamics, and so will aid work modelling the disease in this and other regions where the disease is endemic.

2.2 Methods & Materials

2.2.1 Data

The data available from the Republic of Turkey consisted of: Farm outbreak data covering 2001-2012; cattle shipment data covering 2007-2012; farm location data; and farm cattle headcount data from 2010. A description of this data has been published previously in Dawson (2016).

Figure 2.1 shows a summary of the recorded incidence of farm-level FMD outbreaks over the period that the data covered, although this is likely an underestimate of the true incidence given imperfect surveillance and reporting. Daily incidence was calculated using the recorded confirmation date of an outbreak, although this is likely an underestimate the data were not enough to reliably calculate prevalence. Three serotypes were present in the data, but the two most prevalent were serotypes O and A. Serotype Asia-1 was seen in 2001 but did not reappear until the end of the period in question in 2011. Several major outbreaks are visible in the data: an outbreak of Asia-1 in 2001; an outbreak of serotype A FMD in 2007 followed by serotype O in 2008; and larger outbreaks of O, then A, and then Asia-1 in 2010 to 2012. The apparent serotype switching is likely due to a combination of waning serotype-specific immunity (due to no cross-reaction) and the introduction of strains which had partially escaped the vaccine in use; comparing the number of recorded outbreaks to the number of farms shows most farms were likely not infected at all over this period and so should not have had natural immunity. Some proportion of outbreaks did not have a serotype identified, this proportion appears to be relatively constant over time. In total 9282 infected farms were recorded over this period, 2879 being of serotype O, 2651 of serotype A, 905 of serotype Asia-1, and 2847 for which the serotype was unidentified.

Figure 2.2 shows the spatial spread of these recorded outbreaks, colouring each province by the number of outbreaks recorded in their borders. There is very clear heterogeneity in farm-level incidence, with several provinces acting as clusters.

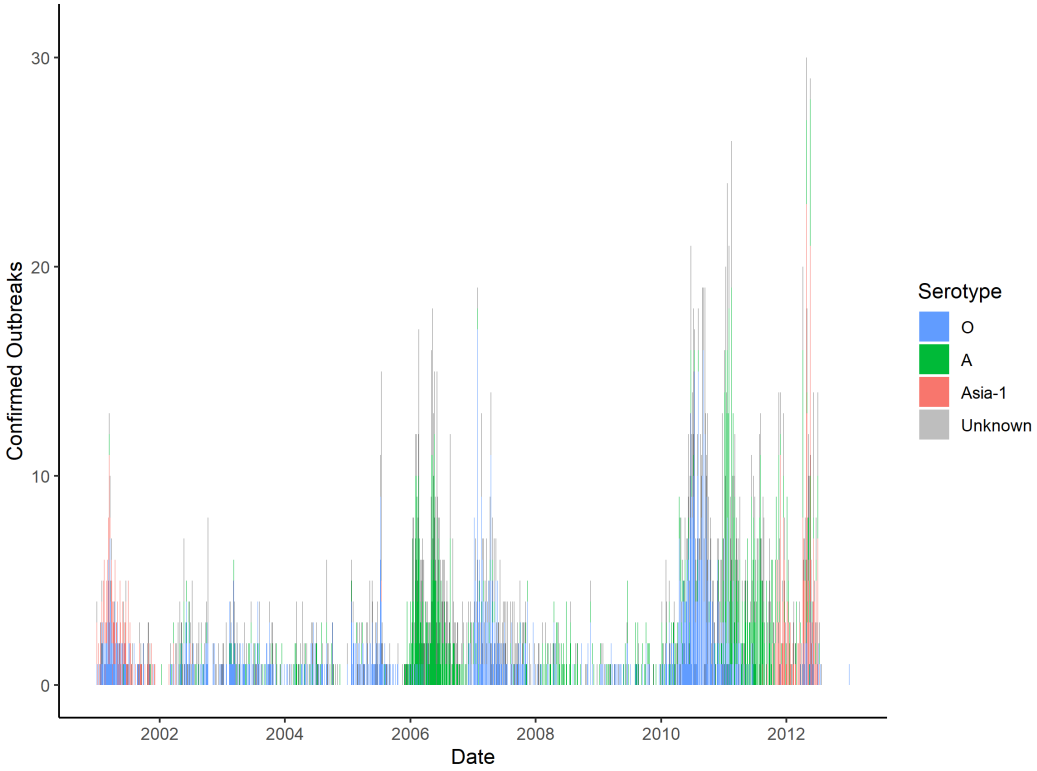

Figure 2.1: Farm level FMD incidence for the Republic of Turkey, over the period 2001 to 2012, coloured by serotype (Unknown indicating outbreaks where a serotype was not identified). The period begins with an outbreak of serotype Asia-1 concurrent with serotype O. O predominates during the next few years until 2005, when there is a major outbreak of serotype A, followed by another large wave of serotype O. There is decline in the number of cases after this, but another large outbreak of serotype O, then A, then Asia-1 return at the end of the period.

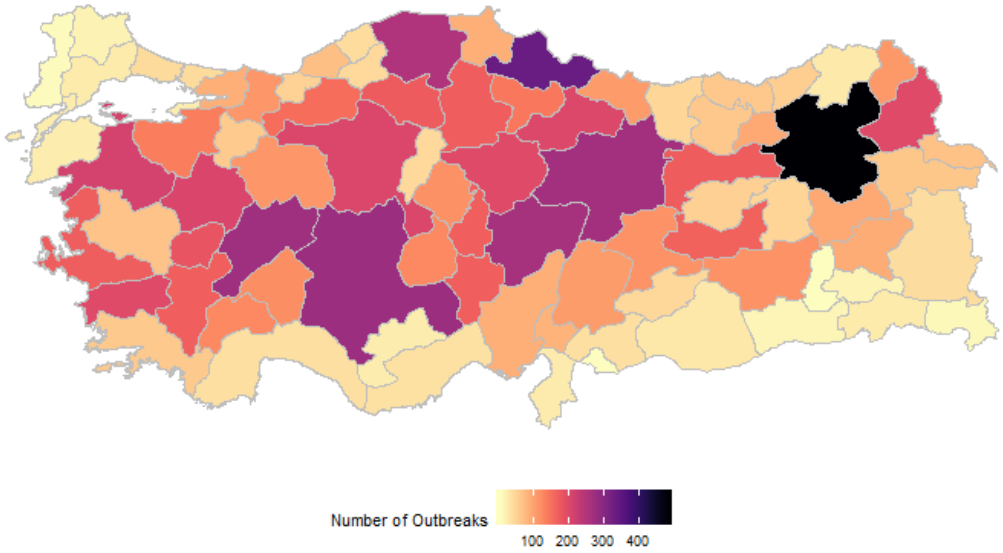

Figure 2.2: The number of recorded outbreaks by province in the Republic of Turkey over the period 2001 to 2012. Each province is coloured by the number of outbreaks associated with it, with darker colours indicating more outbreaks recorded. The province with the highest number of recorded outbreaks is Erzurum, in black in the east of the country. The other cluster of high-incidence provinces are clustered near the centre of the country, closer to Ankara.

Near the eastern edge of Turkey is the province of Erzurum, which is coloured black because of its much larger number of outbreaks compared to other provinces. In the centre of the country there is also a belt of provinces with relatively high disease incidence, including the province of Ankara, Afyon, Kayseri, and Silvas. Finally, on the northern border with the Black Sea are the provinces of Kastamonu and Samsun, also exhibiting high-incidence. In contrast, European Thrace has very low incidence during this period, and is one region of Turkey that is currently acknowledged as free of the disease. The southern border also demonstrated low incidence.

It is clear looking at Figure 2.3 that a lot of the incidence is concentrated in areas with many cattle. Two of the highest incidence provinces, Erzurum and Ankara, are also two of the provinces with the highest cattle population. To a large extent, the areas with high or low incidence are decided by the areas with high or low numbers of cattle.

The shipment data was available in relatively precise form, recording the number of cattle shipped between a source farm and destination farm, and on which day this occurred. 14,261,447 records of this type, spanning the entirety of Turkey and covering the years 2007 to 2012, and which contained the date of shipment,

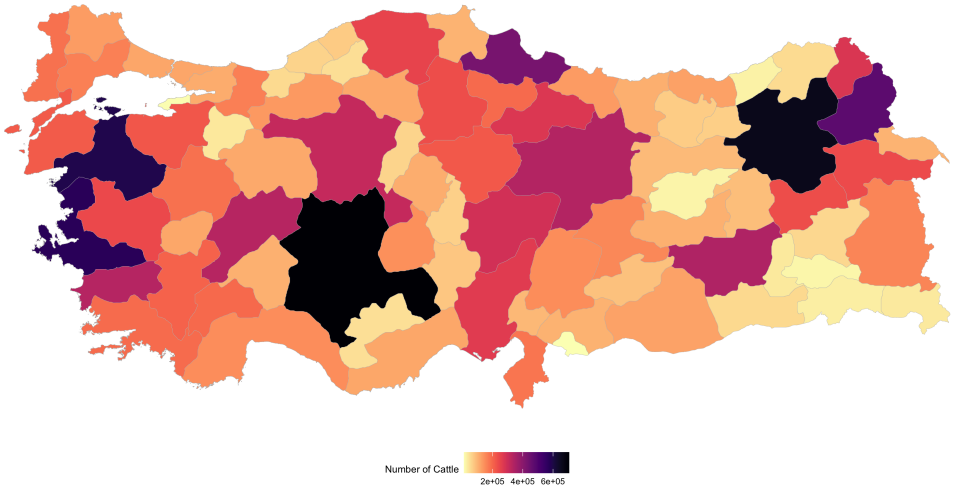

Figure 2.3: The cattle population of each province of Turkey, according to the data available. High concentrations of cattle are seen in Ankara province (the centre of Turkey), Erzurum Province in the East, and Izmir and Balikesir provinces in the West.

source and destination farms, and the number of animals moved, were graciously made available by the Turkish Ministry of Agriculture and Forestry. As an example of the detail of these shipment records, a subset of the records are displayed in Figure 2.5. Figure 2.4 demonstrates the high number of cattle shipments occurring every month in Turkey, as well as the clear seasonal pattern. In the Republic of Turkey Eid Al-Adha (Kurban Bayrami, the Festival of Sacrifice) occurs every year celebrating Abraham's willingness to sacrifice his son for God by sacrificing a cow or goat. Due to this there is a spike in movements every year, visible in the data. Incorporating these records allowed for the seasonality of such shipments to be explicitly modelled. The median shipment distance for the entirety of Turkey was 28.3 km, and the mean was 94.7 km due to the smaller number of very long distance shipments.

The data also make clear the local nature of most cattle movements, the majority of the recorded cattle shipments were between farms in the same district, with only a minority going further. The vast majority of these shipments moved only one animal, with a median of 1 and the 99th-percentile shipment size being 30 animals.

These data were made available as separate data-sets, and cross-referencing these data with each other was not straightforward. As they had been separate

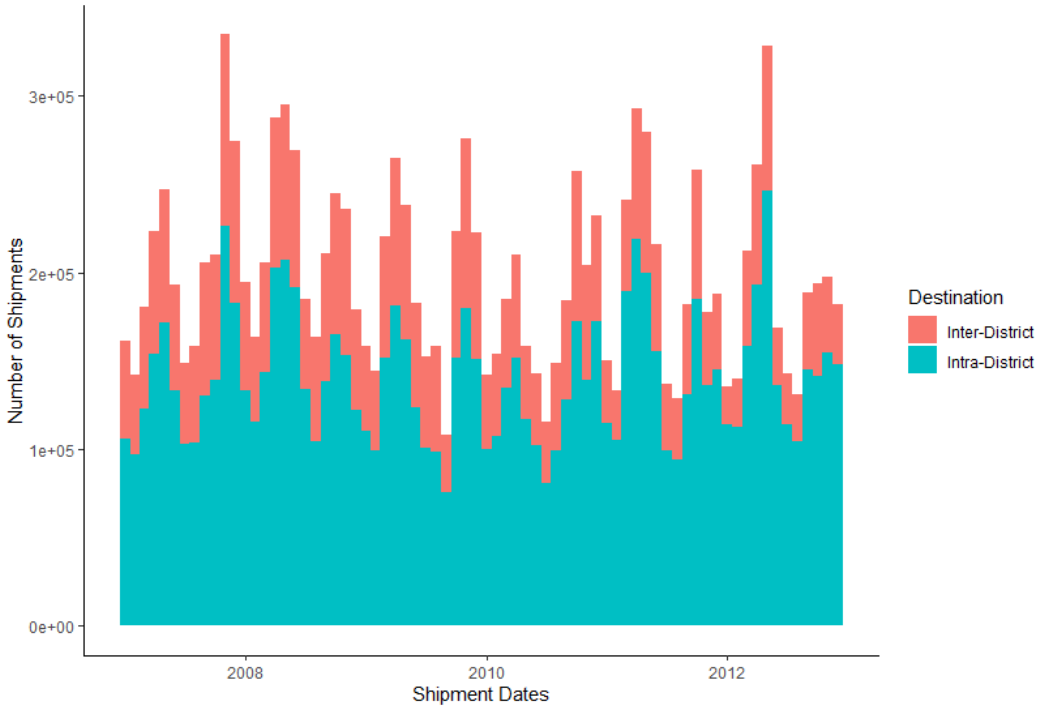

Figure 2.4: Monthly Cattle Shipments in the Republic of Turkey over the period 2007 to 2012, when data are available. Blue indicates the number of within district shipments, and red the number between districts. There is a clear seasonal pattern of shipments peaking every year for the festival Kurban Bayrami. Within-district shipments make up the clear majority of all cattle shipments recorded.

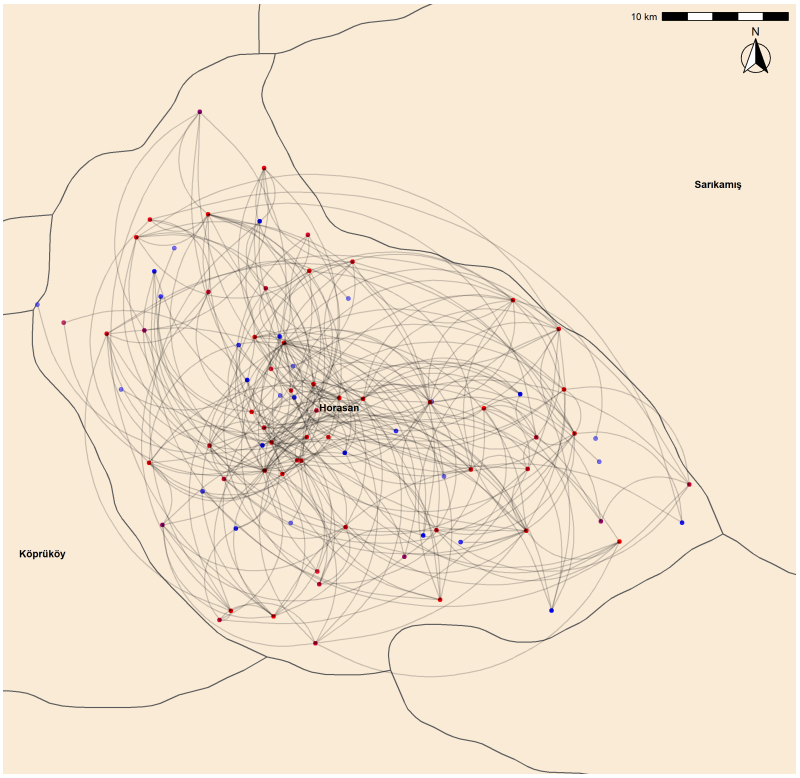

Figure 2.5: Individual cattle shipments within Horasan District, Erzurum Province, on the 1st of June 2012. Each point is a farm, with blue farms indicating source farms and red points destination farms. Purple farms are sources and destinations. Each line between points represents an individual cattle shipment.

data-sets, they did not always have a consistent key to allow this cross-referencing, and there were other inconsistencies. For example, the farm headcount dataset did not use exactly the same district naming scheme as the recorded outbreak data, so matching a farm where an outbreak was recorded with a specific farm headcount was not always straightforward.

A major discrepancy in the data received involved the farm location data. Of the 54,096 recorded farm locations, only 40,746 (75%) had a unique set of co-ordinates. 15445 farms shared a set of 2095 longitude and latitude coordinates, the vast majority shared their coordinates with at only one other record, but some shared them with up to 183 other farms, as shown in Figure 2.6. In many cases it was clear that farms had been recorded as at the centre of their district as their actual longitude and latitude were not known, and the duplicate coordinates only occurred within districts and not between them. The actual distance between farms sharing longitude and latitude coordinates could be as large as 20 kilometres. Manually checking a random sample of 20 duplicate farm addresses by searching their addresses in Google Maps demonstrated that the farms did exist. This presented a problem, duplicate farms "sitting on top of each other" would lead to falsely high spread of infection, as transmission would be calculated as if the farms were in the same place.

Several methods were used to attempt to resolve this. Cross-referencing the farm cattle headcount data could provide a correct location for only a small proportion of the duplicated locations, as only 56.2% of the headcount records had a separate longitude and latitude listed with it. Additionally, geocoding via the Google Maps Application Programming Interface could convert some of the addresses into a set of longitude and latitude coordinates. However, only a small number of addresses returned a useful set of longitude and latitude coordinates in this manner.

Finally, to avoid the problem of overlapping farms without discarding 13,000 farms, unique latitude and longitude coordinates were generated for the remaining duplicates by adding or subtracting a random number of degrees drawn from the uniform distribution $U(0.00, 0.05)$, which corresponds to approximately 0-6 km. The newly modified coordinate set was then reverse geocoded via Google Maps to check that the farm had not jumped to a different district than recorded (for example if it was near a border), and the coordinates accepted if this had not occurred.

Additionally, of the 47802 farm cattle headcounts provided, only 40208 of those could be matched with the provided farm location data. As the farm location is useless for our purposes without an associated number of cattle, those which could not be matched had to be discarded for ongoing work. Moving forward, we simulate

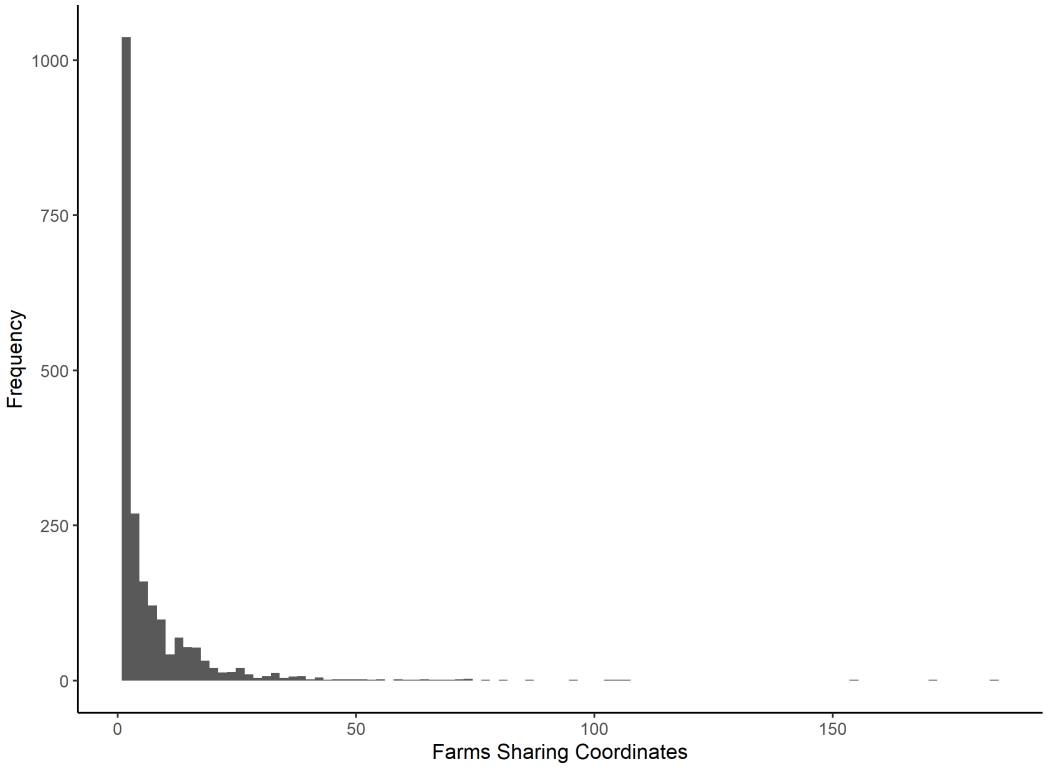

Figure 2.6: The distribution of the number of farms sharing a single set of longitude and latitude coordinates. Most farms with a duplicated location shared it with only one or two other farms, but some shared it with many other farms.

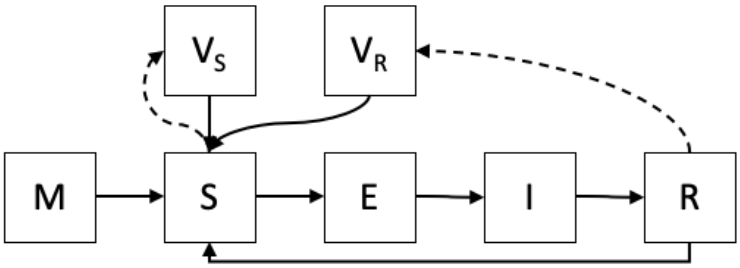

Figure 2.7: The basic disease compartments which animals in the model can be in and the progression between them. (**M**)aternal, (**S**)usceptible, (**E**)xposed, (**I**)nfectious, and (**R**)ecovered. V_S indicates susceptible individuals which were vaccinated, and V_R recovered individuals which were vaccinated. It was assumed that M, E, and I animals could not be successfully vaccinated. The dashed arrows pointing to the vaccinated compartments indicate that movement along this direction needs vaccination to be implement, which is a model parameter. The movement of individuals between these compartments is done at different rates, dependent on the population of each compartments as well as model parameter inputs. These rates are described in Eq. 2.1 and the parameters in Table 2.1. Note that arrows for natural birth rates, death rates, and sub-compartments are not included here for simplicity.

a single province (Erzurum province) with 1108 farms and 253 outbreaks between 2007 to 2012, for an average of 0.228 outbreaks per farm over the 5 year period.

2.2.2 Model Structure

We utilise a stochastic spatial metapopulation model, where each farm is considered a separate population and the within-farm and between-farm dynamics are modelled interdependently. Figure 2.7 describes the progression of disease states for each infected animal. At the beginning of the model timeline, it is assumed that all animals are in the susceptible compartment. Progression between these compartments is described by Ordinary Differential Equations (ODEs) outline in (2.1). Natural immunity is represented by the Recovered compartment, and the waning of

this immunity by the gradual transition of animals in this compartment back to the Susceptible compartment at rate λ_R. The Maternal compartment has 3 subcompartments, the Recovered and both Vaccinated compartment have 20, to provide an non-exponential distribution of time spent in each compartment as discussed in Chapter 1. The number of subcompartments was chosen to ensure animals would not immediately begin leaving a compartment as soon as they entered, balanced against the expected rate of transition through the compartment. Additionally, due to a lack of age data, there is no age-stratification of the compartments. The meaning of each term and the values used are described in Table 2.1. Stochastic simulation of these ODEs was done via the τ-leap approximation (Gillespie 2001). This offers large advantages in speed for minor sacrifices in accuracy, and also allows a fixed time increment for synchronising with the between-farm transmission.

$$
\begin{aligned}
\frac{dM}{dt} &= \alpha N \frac{(R + V_S + V_R)}{(N - M)} - \mu M - \Omega_n M, \\
\frac{dS}{dt} &= \alpha N (1 - \frac{(R + V_S + V_R)}{(N - M)}) + \mu M + \lambda_R R + \lambda_{V_R} V_R + \lambda_{V_S} V_S - \frac{\beta S I}{N} - \Omega_n S, \\
\frac{dE}{dt} &= \frac{\beta S I}{N} - \sigma E - \Omega_n E - \Omega_d E, \\
\frac{dI}{dt} &= \sigma E - \gamma I - \Omega_n I - \Omega_d I, \\
\frac{dR}{dt} &= \gamma I - \lambda_R R - \Omega_n R, \\
\frac{dV_R}{dt} &= -\lambda_{V_R} V_R - \Omega_n V_R \\
\frac{dV_S}{dt} &= -\lambda_{V_S} V_S - \Omega_n V_S
\end{aligned}
\tag{2.1}
$$

The virus is transmitted between farms either by local spread or the shipments of cattle. The probability of spread from an infected farm to a susceptible farm (defined as a farm where the number of susceptible animals is greater than or equal to 1) via local spread is calculated by equation 2.2. This depends on the number of infectious animals on the infecting farm, the number of susceptible animals on the susceptible farm, and the distance between them. Initial scale and shape parameters were chosen (prior to fitting) matching the dispersal kernel from Jewell, M. J. Keeling, and Roberts (2009), but the kernel has been used to flexibly describe the spread of FMD in many different regions such as the UK and Japan (Jewell, M. J. Keeling, and Roberts 2009; Probert et al. 2018). It has also been used in the USDOS model of disease spread in the USA, although the lack of FMD there prevents its validation (Tsao et al. 2020). For the purpose of computational

speed this is done in a grid, using the algorithm outlined in (Sellman et al. 2018). If infection is adjudged to happen, the susceptible farm has a number of susceptible animals proceed to the exposed/latent stage, drawn from a binomial distribution.

$$
\begin{aligned}
P(ls) &= 1 - e^{-TN_i^{inf} SN_j^{sus} K(d_{ij})}, \\
K(d_{ij}) &= \frac{1}{1 + (\frac{d}{scale})^{shape}}.
\end{aligned}
\tag{2.2}
$$

Livestock shipments are simulated on a daily basis and replay the animal movement records provided by the Republic of Turkey. This involves moving the number of cattle recorded between the recorded farms, on the day this occurred. Doing this allows the seasonality of those shipments to be accurately captured, but limits the period which can be modelled to 2007-2012, excluding 2001-2007. Shipments are modelled as a random sample without replacement from the animals at the source farm, hence the probability of selecting at least one infected animal is proportional to the shipment size and number of infected animals on the farm.

Vaccination occurs in the model only in response to a control policy option, either ring vaccination or mass vaccination. Farms are identified as requiring vaccination with probability equal to the input vaccine coverage, and for ring vaccination an additional requirement of being within a specified radius of a known infected farm. These farms are added to a queue and farms then vaccinated up to a daily vaccination capacity. For ring vaccination this queue is ordered such that the outer farms of the ring are queued first, an 'outside-in' strategy; there is no ordering for mass vaccination as all farms are targeted for vaccination. Should vaccination be scheduled for a simulated farm, vaccination leads to both susceptible and recovered individuals proceeding to their respective vaccinated compartments, in proportion to the efficacy of the vaccine. Maternally immune (M) are assumed not to be vaccinated, and currently infected animals (compartments E and I) are added to the count of vaccines used but do not proceed to the vaccinated compartment due to their current active infection. The realised vaccine efficacy fluctuates on each farm, being drawn from a normal distribution characterised by the provided mean and standard deviation of the vaccine efficacy. Compartment V_S wanes at rate λ_{V_S}, and compartment V_R at the longer duration of either λ_R or λ_{V_R}. This is to prevent the situation where naturally immune animals are simulated as having their immunity duration cut short by vaccination because the duration of vaccine-induced immunity is shorter.

The available control policies are ring vaccination, movement controls, and

Table 2.1: Relevant parameters of the ODEs and model, with their value(s)

Parameter	Description	Value(s)	Source(s)
α	Birth rate	2%/year	
β	Transmission rate	6 / 11	(Orsel, Dekker, et al. 2005; Orsel, Jong, et al. 2007; Tadesse et al. 2019)
γ	Recovery rate	1 / 11 days	(Yadav et al. 2019)
λ_R	Recovered waning rate	250 days	(T. R. Doel 2005; E. El-Sayed et al. 2012)
μ	Maternal waning rate	120 days	(Nicholls, Black, and M. M. Rweyemamu 1984)
σ	Symptomatic rate	1 / 1.5 days	(Yadav et al. 2019)
$\mathbf{\Omega}_d$	Infection mortality rate	2%	(Şentürk and Yalçin 2008)
$\mathbf{\Omega}_n$	Natural mortality rate	2%/year	
λ_{V_S}	Susceptible vaccinated waning rate	150 days	(Cox et al. 2010; T. R. Doel 2003; T J D Knight-Jones, Bulut, et al. 2015)
λ_{V_S}	Recovered vaccinated waning rate	$\max(\lambda_R, \lambda_{V_R})$	(Cox et al. 2010; T. R. Doel 2003; T J D Knight-Jones, Bulut, et al. 2015)
T	Inter-farm per-capita transmission	6.806e-6	(M J Keeling et al. 2001; Michael J Tildesley, Savill, et al. 2006)
S	Inter-farm per-capita susceptibility	1.0	
scale	Kernel Scale parameter	1	(Jewell, M. J. Keeling, and Roberts 2009)
shape	Kernel shape parameter	2	(Jewell, M. J. Keeling, and Roberts 2009)

mass vaccination. Both ring vaccination and movement controls are reactive, in response to a detected farm infection, and occur within a radius of the infected farm. Ring vaccination occurs 'outside-in', reactively vaccinating the farms furthest away but within the radius and working its way in towards the infected farm. Movement controls are implemented in a similar way to ring vaccination, with relevant farms identified within a radius of a known infected farm and marked as under a movement ban with probability equal to the input movement ban compliance. Movement ban simply prevents shipments of cattle both arriving or leaving these farms, mechanistically preventing the replay of a shipment record that would otherwise have occurred. Mass vaccination occurs on a defined interval, and vaccinates all of the farms in the region whenever that interval has been reached. All three of these policies can be toggled on or off, and their parameters can be changed. All three of the control policies are implemented in Turkey, and the specifics of their implementation is discussed in the Existing Control Policies subsection shortly.

Code for the model is available at https://github.com/gguyver/fmd-model-thesis.

2.2.3 ABC-SMC Algorithm

Model fitting was done using the ABC-SMC algorithm as described in (Toni et al. 2009), and later described in Minter and Retkute 2019. ABC-SMC is useful as it does not require knowing the likelihood function of the model as MCMC does, and is simpler to set up. Generally speaking, Sequential Monte Carlo Approximate Bayesian Computation (SMC ABC) involves sequential generations of ABC, where a distance metric $\rho(\cdot,\cdot)$ is defined which measures how different simulated data is from the observed data. A proposed particle (set of parameters drawn from a distribution) is accepted if $\rho(\cdot,\cdot) < \epsilon$, where ϵ is the tolerance for matching the observed data. The first generation samples and perturbs from the prior distribution $\pi(\theta)$, however later generations sample and perturb from the previously accepted particles, and ϵ_t is generated from these particle distances as well. In this manner, each generation therefore samples from an *approximate* posterior $\pi(\theta|\rho(y,\cdot) < \epsilon)$, and as $\epsilon \to 0$ the approximate posterior will tend to the true posterior at a greater computational cost. However, instead of setting the tolerance schedule at the beginning, I set the initial tolerance to ∞ and calculated the tolerance for following generations by using the bisection method outlined in the supplementary material of T. J. McKinley et al. 2018, with minimum, maximum, and mean quantiles of 45%, 55%, and 50%. This aids in the problem of setting the tolerance ϵ too low or too high, as this value is now based on the observed errors. The distance metric was the least squares of the

simulated incidence against the "true" or observed incidence, with incidence taken as the count of newly recorded infected farms on each day. Algorithm 3 outlines the SMC ABC algorithm.

Algorithm 3 SMC ABC algorithm

1: Set the number of generations T, the number of particles n_{part}, and the target acceptance rate p_t.
2: Set $\epsilon_t = \begin{cases} \infty & \text{if } t = 1 \\ B(p_t) & \text{if } t > 1 \end{cases}$ where $B(p_t)$ refers to McKinley *et al*'s bisection method for choosing tolerances at each generation (T. J. McKinley et al. 2018).
3: Set particle indicator $j = 1$
4: If $t = 1$, sample $\theta^{''}$ independently from $\pi(\theta)$. If $t > 1$, sample $\theta^{'}$ from the previous population $\{\theta_{t-1}\}$ with weights $\{W_{t-1}\}$, and perturb the particle to $\theta^{''} \sim Q_t(\cdot|\theta^{'})$ according to a Markov transition kernel $Q_t(\cdot)$.
5: If $\pi(\theta^{''}) = 0$, return to 4.
6: Generate n data sets $z_i^{''} \sim \pi(\cdot|\theta^{''})$, and calculate $\hat{\pi}(\boldsymbol{y}|z^{''}) = (1/n)\sum_{i=1}^{n} \mathbb{1}(\rho(\boldsymbol{y}, z^{''}) < \epsilon_t)$.
7: If $\hat{\pi}(y|z^{''}) = 0$, then return to 4.
8: Set $\theta_t^{(j)} = \theta^{''}$ and $W_t^{(j)} = \begin{cases} \hat{\pi}(\boldsymbol{y}|z^{''}) & \text{if } t = 1 \\ \frac{\hat{\pi}(\boldsymbol{y}|z^{''})\pi(\theta_t^{(j)})}{\sum_{j=1}^{n_{part}} W_{t-1}^{j} Q_t(\theta_t^{(j)}|\theta_{t-1}^{(j)})} & \text{if } t > 1 \end{cases}$
9: If $j < n_{part}$, increment $j = j + 1$ and go to step 4.
10: Normalise the weights so that $\sum_{j=1}^{n_{part}} W_t^{(j)} = 1$.
11: If $t < T$, increment $t = t + 1$ and go to step 2.

2.2.4 Identifiability Analysis

Identifiability analysis was performed to ascertain which parameters were recoverable from the data using algorithm 3, and which were not. For each set of parameters recovery was attempted for, prior distributions were generated and values drawn from these distributions, the set of these values being called a particle. This was done 5 times, generating 5 particles, to account for heterogeneity in identifiability at different areas of the prior distributions.

For each of the sampled particles a single simulation was run and the results taken as an "observed" outbreak. The ABC-SMC algorithm was then run for each of these particles until it either converged on a set of values or it became infeasible to proceed because it was not converging. This was done with 500 particles per generation ($n_{part} = 500$). $Q_t(\cdot)$ was a weighted multivariate normal distribution using weights W_{t-1}, and the distance metric was the least squares of the simulated incidence compared to the "true" incidence. The distance metric was calculated on

this time-series, it was not required that the specific farms recorded as infected also be the ones infected in the simulation. The intention was to match a general state of endemic FMD rather than the exact farms infected. The aim of this was to recover the original sampled parameter value for as many of the parameters as possible, and to find as large a set of parameters as possible that were identifiable in this manner.

Due to the limitations of the model and the computational resources available, only Erzurum Province of Turkey was simulated. This is the darkest province in Figure 2.2, as it is the province where the most outbreaks (496) were recorded in the 11-year period. The province covers 25066 km^2, contains 1108 farms, which themselves contain a total of 605,177 cattle. This was done because the computational complexity of the simulations scales exponentially with the number of farms being simulated, and larger areas therefore take much longer to model in the framework that has been adopted here.

Table 2.2: The prior distributions used to generate "true" values for parameter identifiability analysis.

Parameter	**Parameter Description**	**Distribution**
β	Acutely infectious transmission	$U(0.135, 1.8)$
λ	Average duration of recovered state	$U(150, 550)$
T	Inter-farm per capita transmission	$N(6.8e-6, 6.8e-6)$
scale	Kernel scale parameter	$N(1.0, 0.75)$
shape	Kernel shape parameter	$N(2.0, 0.75)$

This was first done for the parameters within-farm transmission β, the duration of immunity λ, the between-farm per-capita transmission parameter T, and the kernel scale and kernel shape parameters, this set of parameters is labelled **ID1**. Subsequent to the results of this, another attempt was made dropping the kernel shape parameters (labelled **ID2**), and then another attempt was made also dropping the kernel scale parameter (labelled **ID3**) to try and find the optimal combination of parameters that were identifiable. The prior distributions that were sampled from are described in Table 2.2. A summary of the parameters used for these attempts are laid out in Table 2.3, and the values used for the other fixed parameters are shown in Table 2.1.

Finally, each possible 2-parameter or 3-parameter combination of the parameters β, T, $scale$, and $shape$ were assessed in turn using the same procedure as described previously. λ was no longer assessed due to the results of the previous attempts, and reverted to the value described in Table 2.1. The specific parameter combinations are shown in Table 2.3.

Table 2.3: The parameter sets used for the attempts to assess parameter identifiability. Each one has a set label which identifies it for ease of analysis.

Set Label	Parameter Set
ID1	$\{\beta, \lambda, T, scale, shape\}$
ID2	$\{\beta, \lambda, T, scale\}$
ID3	$\{\beta, \lambda, T\}$
ID4-2-1	$\{\beta, T\}$
ID4-2-2	$\{\beta, scale\}$
ID4-2-3	$\{\beta, shape\}$
ID4-2-4	$\{scale, T\}$
ID4-2-5	$\{shape, T\}$
ID4-2-6	$\{scale, shape\}$
ID4-3-1	$\{\beta, scale, T\}$
ID4-3-2	$\{\beta, scale, shape\}$
ID4-3-3	$\{scale, shape, T\}$
ID4-3-4	$\{\beta, shape, T\}$

2.2.5 Parameter Estimation

Parameter estimation was carried out using algorithm 3 and the parameters T, $scale$, and $shape$. As before, 500 particles were used per generation and the prior distributions described in Table 2.2. Least squares of the incidence and the sum difference of the incidence were both used as the summary statistics.

For each ABC-SMC particle the model was simulated once and compared to the outbreak incidence data for Erzurum Province over the 5-year period 2007-2012. Due to the period under analysis being endemic for the disease, but lacking in data which might allow the model to begin with built-up immunity in the population already, the model was given a burn-in period of 365 days to allow the initial seeded infection to cause an outbreak and settle towards endemicity before comparing to the already endemic real-world data. This burn-in period data was discarded and not used for comparison or analysis. Subsequent to the burn-in period, the model was simulated for a 5-year period using the Erzurum farm location and headcount data as well as the relevant shipment data, and compared to the realised incidence according to the ABC-SMC algorithm.

2.2.6 Existing Control Policies

As there were control policies for FMD in place during this period, the fit attempt also needed to include control policies and surveillance. During this period surveillance for FMD in Turkey was almost entirely passive surveillance, relying on farmer

reporting (unpublished communication). An attempt to fit the parameters without including the extant control policies would return a parameter estimate which assumed the effect of the control policies to be the effect of the underlying parameters of the disease and would therefore be a dramatic underestimate of disease transmissibility. Vaccine efficacy was drawn from a normal distribution with mean 65 and standard deviation of 5 as the vaccine in use at the time was known to be approximately this effective (T. Knight-Jones et al. 2014). Mass vaccination was also in place during this period, occurring every 6 months (182 days), as were reactive ring vaccination and reactive movement bans within 10 km of a known infected farm. After discussion of the control policies implemented in Turkey during this period, these were assumed to occur in a 10 km radius with 90% coverage, and for the movement bans to last 7 days. Detection was assumed to catch 95% of infected farms. An average delay of 3 days between infection and detection was assumed, which was the average delay in the assumed start dates to confirmation dates for those outbreaks where this was provided. However, there are no data for vaccination or reporting coverage.

2.3 Results

2.3.1 Identifiability Analysis

Using the parameter set outlined in Table 2.3 for **ID1** for identifiability analysis, the most identifiable parameter analysed was transmission T, which was recovered 3 out 5 times. Recovery of a parameter was decided based on whether the highest peak of the posterior distribution was close to the "true" value, and whether the posterior probability distribution was significantly different to the prior distribution. The final density plots of each parameter are shown in Figure 2.8. In this figure parameter recovery is taken as when the peak (assuming there is one) of the density plot is at, or close to, the "true" value indicated by the vertical black lines.

The other parameters analysed were either recovered once out of the 5 attempts, in the case of β, $scale$, and $shape$, or not recovered at all in the case of λ. It was considered that perhaps there were too many parameters and the parameter space was too large.

Subsequent to this attempt, which of the parameters of the set identified by the label **ID2** were attempted, shown in Figure 2.17. Performance improved with this attempt, as β was recovered 3 out of 5 times, and $scale$ 2 out of 5 times. However, T was only recovered 2 out of 5 times, a reduction from the 3 seen previously. Additionally, λ was again not recovered, with the final distribution being similar to

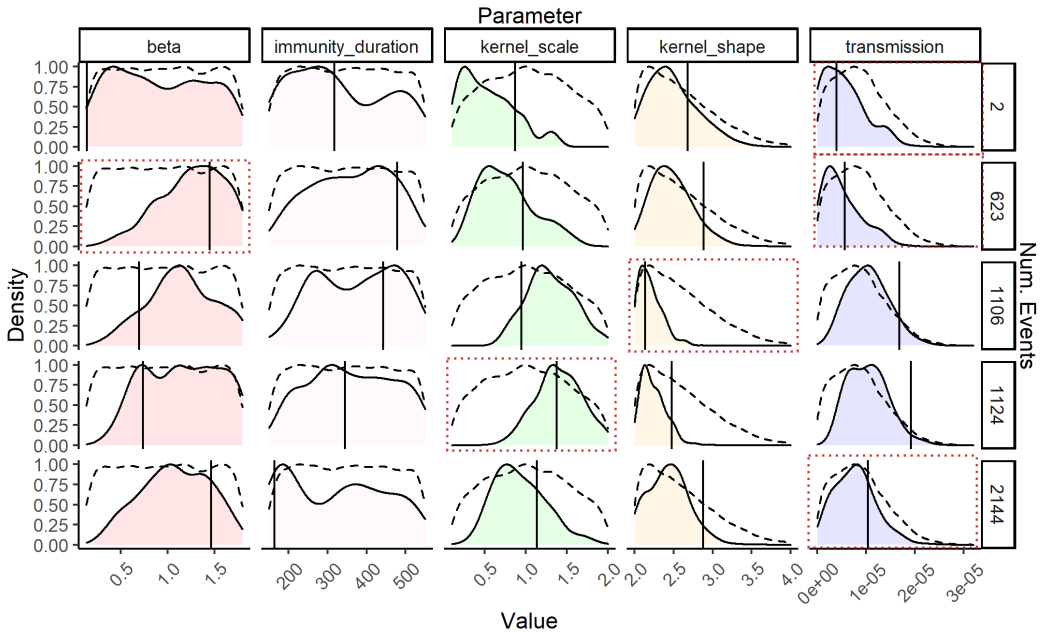

Figure 2.8: The density distributions of the parameter set $\{\beta, \lambda, T, scale, shape\}$ (**ID1**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 1 out of 5 times, λ was not recovered, $scale$ was recovered 1 out of 5 times, $shape$ was recovered 1 out of 5 times, and T was recovered 3 out of 5 times.

the prior uniform distribution in all five attempts.

The final parameter distributions of **ID3** are shown in Figure 2.10. This shows an improvement in the identifiability of β, with 4 out of 5 attempts succeeding and showing tighter distributions where recovery occurred. T improved back to being recovered 3 out of the 5 attempts. However, λ once again failed to be recovered, with posterior distributions similar to the prior.

As λ had failed to be identified on 3 separate occasions, this parameter was dropped from subsequent attempts and reverted to the value established in Table 2.1.

Figures 2.11, 2.12, 2.13, 2.14, 2.15, and 2.16 show the results of the 2-parameter combinations of β, T, $scale$, and $shape$ identified in Table 2.3.

For parameter set **ID4-2-1** (fig. 2.11), which looked at β and T, performance was poor. β was recovered three times, and T only recovered twice. Similar performance was observed for set **ID4-2-2** (fig. 2.12), where β was also only recovered once, and $scale$ was recovered 2 out of 5 times.

Parameter set **ID4-2-3** (fig. 2.13) assess β and $shape$ together, seeing poor performance also. β was recovered 3 out of 5 times, and $shape$ 3 out of 5.

For parameter set **ID4-2-4** (fig. 2.14), both $scale$ and T were recovered 4 out of 5 times. This parameter set performed the best out of the 2-parameter combinations assessed.

Worst performing was parameter set **ID4-2-5** (fig. 2.15), where $shape$ and T were both only recovered once out of 5 attempts. Finally, parameter set **ID4-2-6** (fig. 2.16), showed $scale$ recovered once and $shape$ recovered twice out of the 5 attempts with that set of parameters.

For the 3-parameter sets described in Table 2.3, set **ID4-3-1** (fig. 2.17) exhibited poor performance. Of the 5 fitting attempts, β was recovered 3 times, $scale$ once, and T twice.

The worst performance was seen with the set **ID4-3-2** (fig. 2.18), where β, $scale$, and $shape$ were all recovered once out of the 5 attempts.

Much better performance was seen with set **ID4-3-3** (fig. 2.19). This assessed $scale$, $shape$, and T together, and the least identifiable parameter with this set of parameters was $shape$, which was only recovered 3 out of the 5 attempts. Although no parameter was recovered every time, both $scale$ and T were recovered 4 out of the 5 attempts.

Finally, set **ID4-3-4** (fig. 2.20) demonstrated decent performance, with β, $shape$, and T all being recovered on 3 out of the 5 attempts.

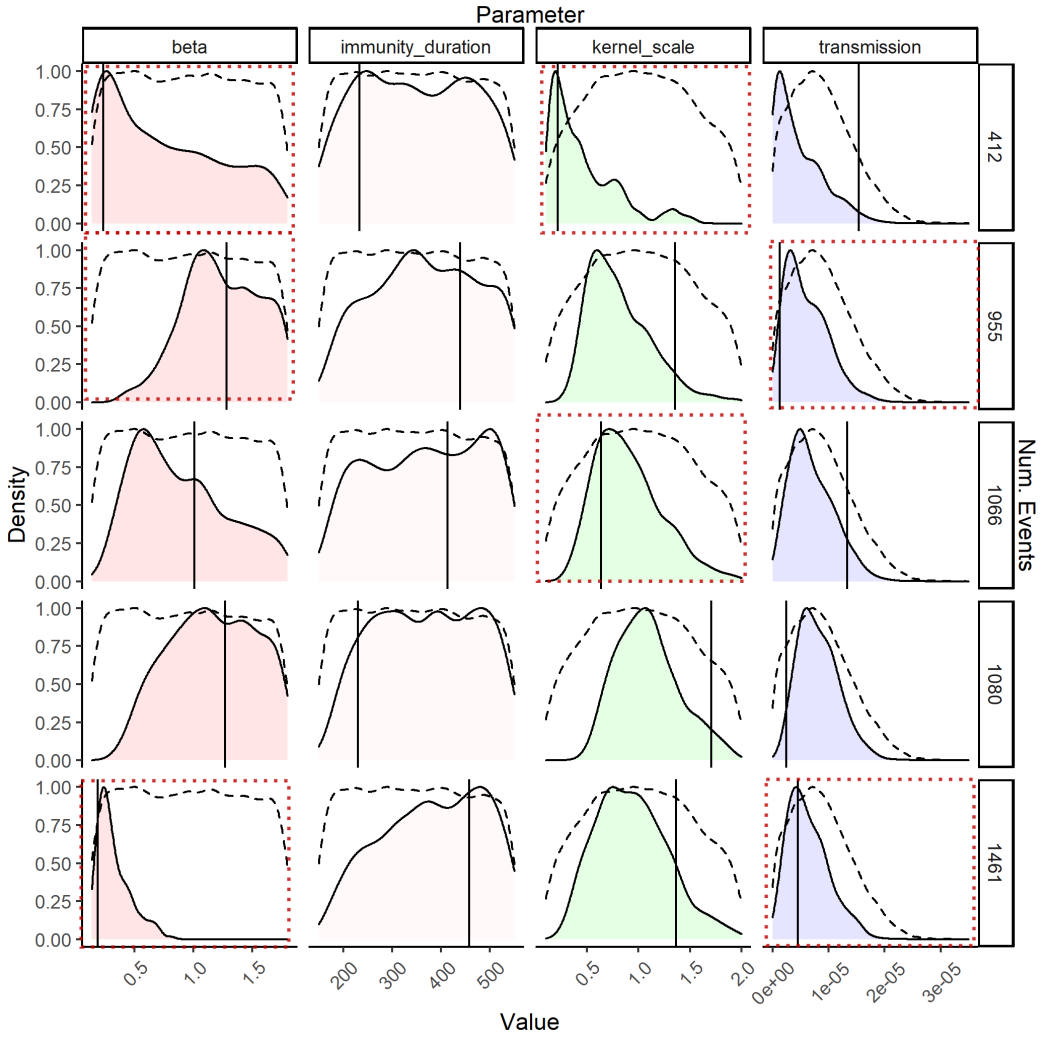

Figure 2.9: The density distributions of the parameter set $\{\beta, \lambda, T, scale\}$ (**ID2**) after 7 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to.Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 3 out of 5 times, λ was not recovered, $scale$ was recovered 2 out of 5 times, and T was recovered 2 out of 5 times.

The parameter set that demonstrated the greatest identifiability with the greatest number of parameters was parameter set **ID4-3-3**, which assessed dispersal kernel $scale$, $shape$, and T together. It was this set of parameters that were used for the parameter estimation using the real data.

For the 3-parameter sets described in Table 2.3, set **ID4-3-1** (fig. 2.17) exhibited poor performance. Of the 5 fitting attempts, β was recovered 3 times, $scale$ once, and T twice.

The worst performance was seen with the set **ID4-3-2** (fig. 2.18), where β, $scale$, and $shape$ were all recovered once out of the 5 attempts.

Much better performance was seen with set **ID4-3-3** (fig. 2.19). This assessed $scale$, $shape$, and T together, and the least identifiable parameter with this set of parameters was $shape$, which was only recovered 3 out of the 5 attempts. Although no parameter was recovered every time, both $scale$ and T were recovered 4 out of the 5 attempts.

Finally, set **ID4-3-4** (fig. 2.20) demonstrated decent performance, with β, $shape$, and T all being recovered on 3 out of the 5 attempts.

The parameter set that demonstrated the greatest identifiability with the greatest number of parameters was parameter set **ID4-3-3**, which assessed kernel $scale$, $shape$, and T together. It was this set of parameters that were used for the parameter estimation using the real data.

2.3.2 Parameter Estimates

Using the ABC-SMC algorithm with the identified parameters, the most likely parameter values were $scale$ = 1.23, $shape$ = 2.09, and $T = 4.98e-6$ to 4.98e-6. Weighted density distributions of these parameters are shown in Figure 2.21, demonstrating relatively tight and sharp peaks around these values.

Figures 2.22 and 2.23 compare the incidence of FMD in the simulations against the real recorded incidence in the province of Erzurum. Plots of both normal and cumulative incidence are provided for clarity. The real observed incidence is very sporadic and does not exceed 5 new farm-level infections in one day until almost 4 years in to the 5 year period under investigation. There are a total of only 253 infections recorded over this entire period. Most of the simulations are reasonably fit to the observed incidence until approximately 2011, when there is an increase in the observed incidence that the simulations are much less likely to follow.

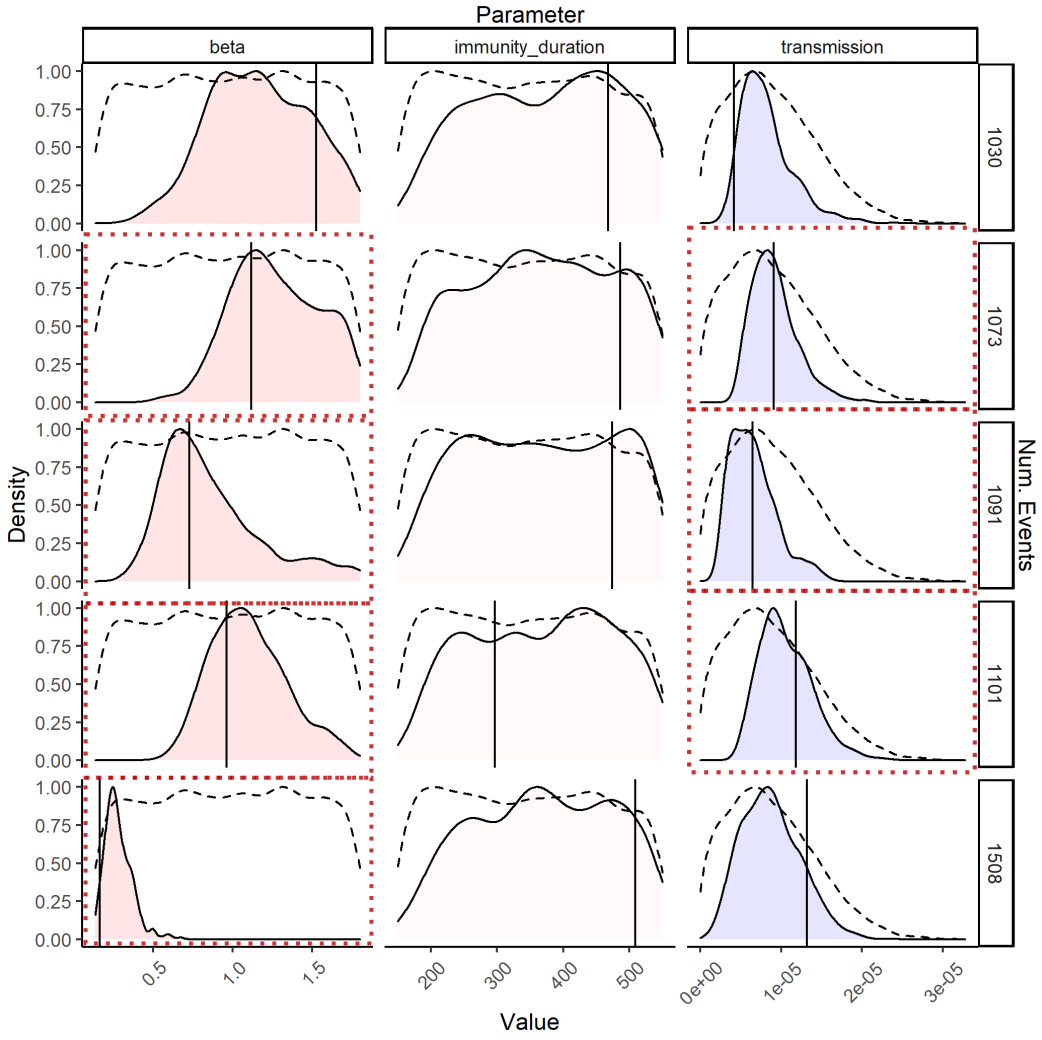

Figure 2.10: The density distributions of the parameter set $\{\beta, \lambda, T\}$ (**ID3**) after 7 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 4 out of 5 times, λ was not recovered, and T was recovered 3 out of 5 times.

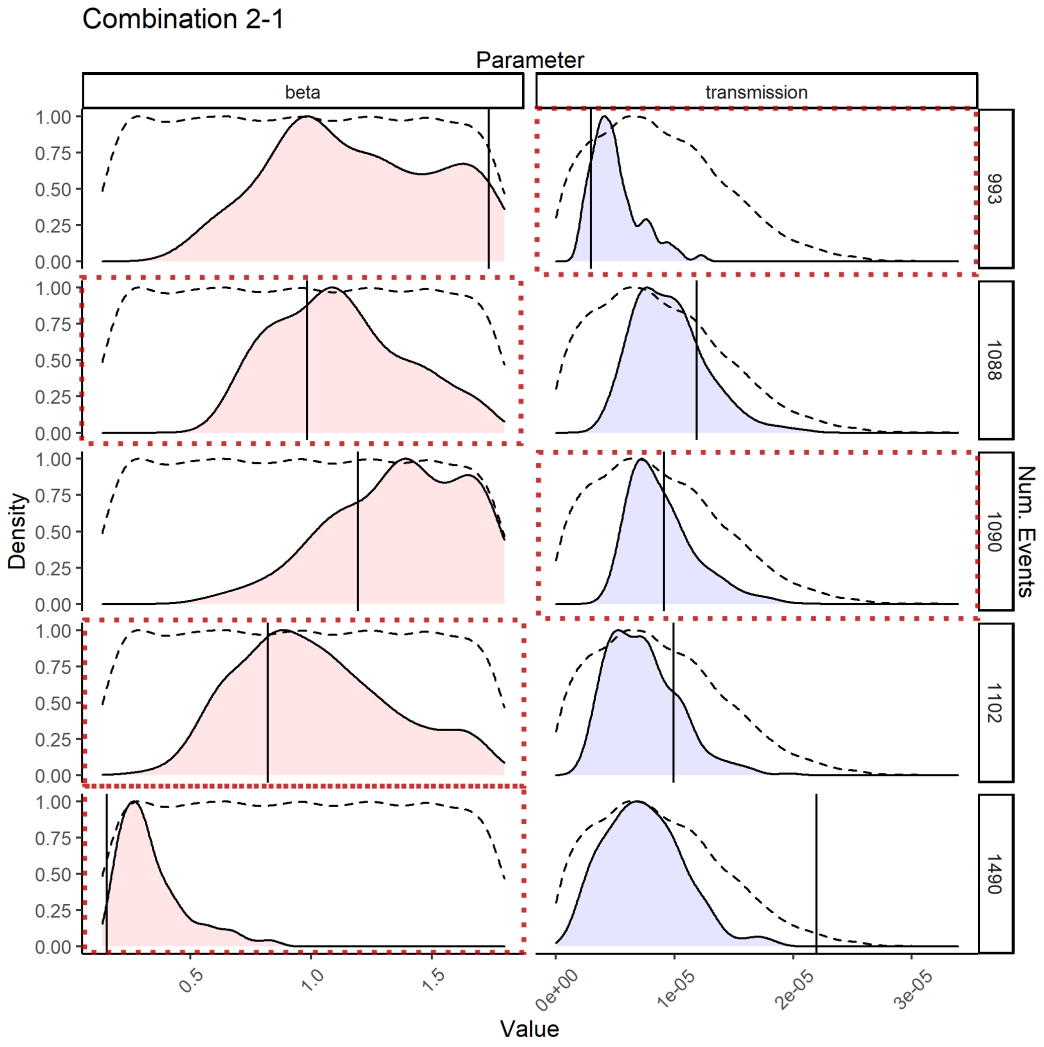

Figure 2.11: The density distributions of the parameters β and T (**ID4-2-1**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 3 out of 5 times, and T was recovered 2 out of 5 times.

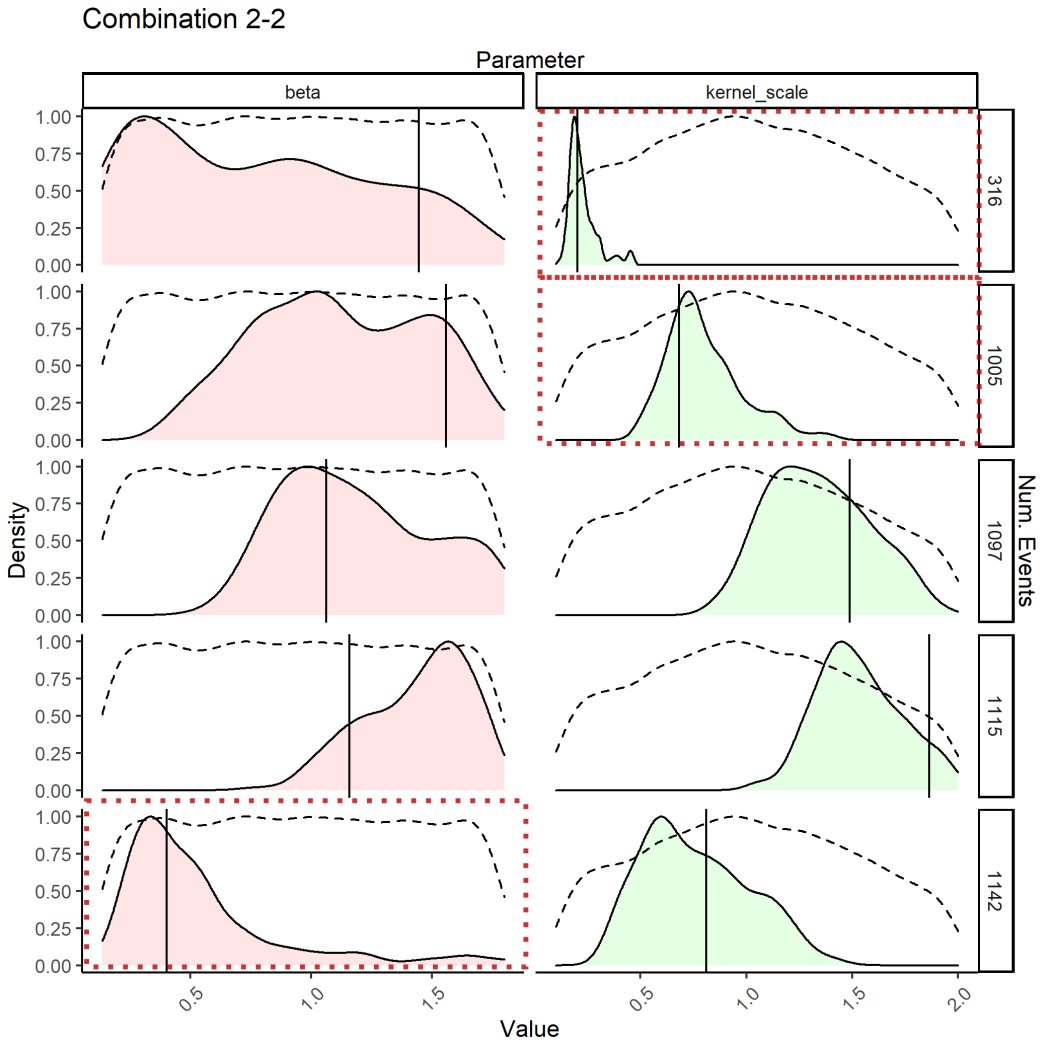

Figure 2.12: The density distributions of the parameters β and *scale* (**ID4-2-2**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 1 out of 5 times, and *scale* was recovered 2 out of 5 times.

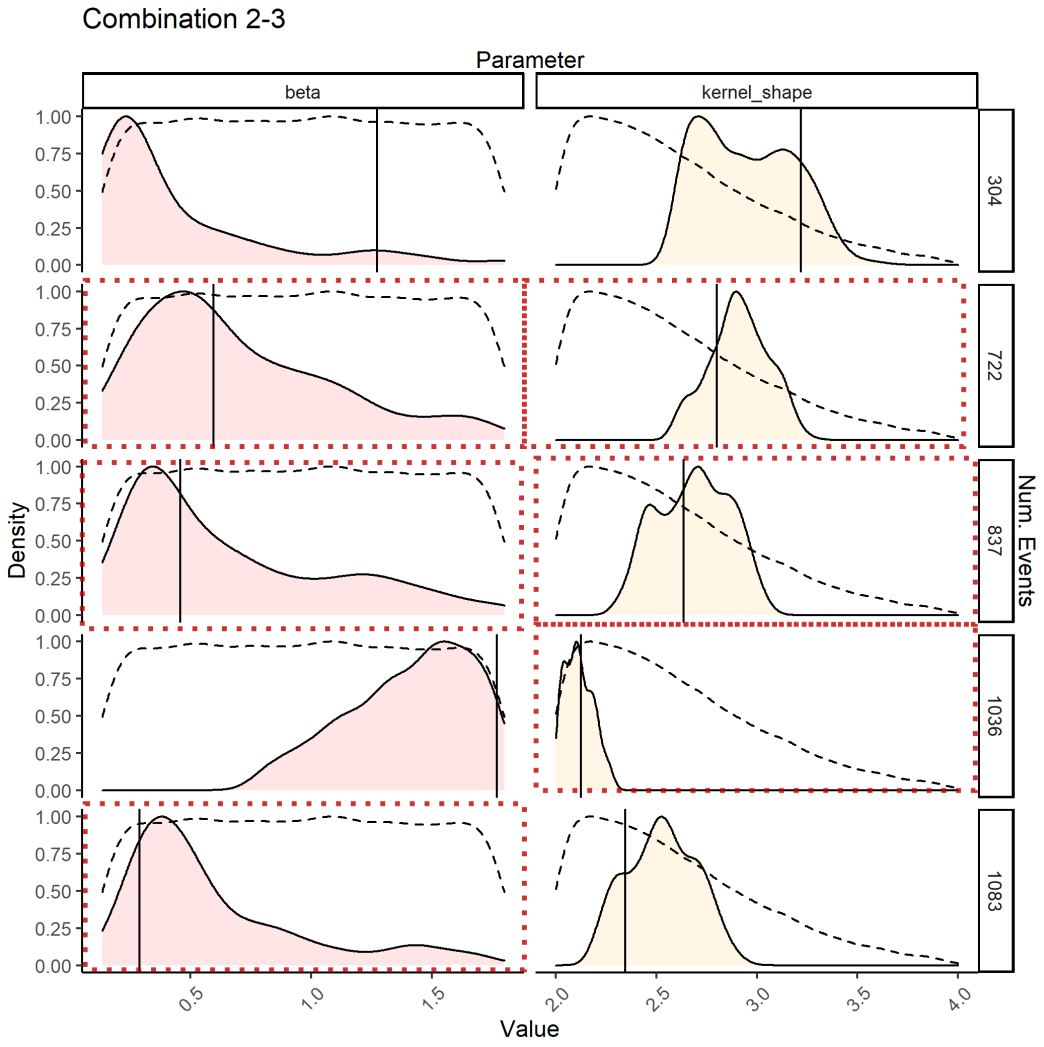

Figure 2.13: The density distributions of the parameters β and *shape* (**ID4-2-3**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 3 out of 5 times, and *shape* was recovered 3 out of 5 times.

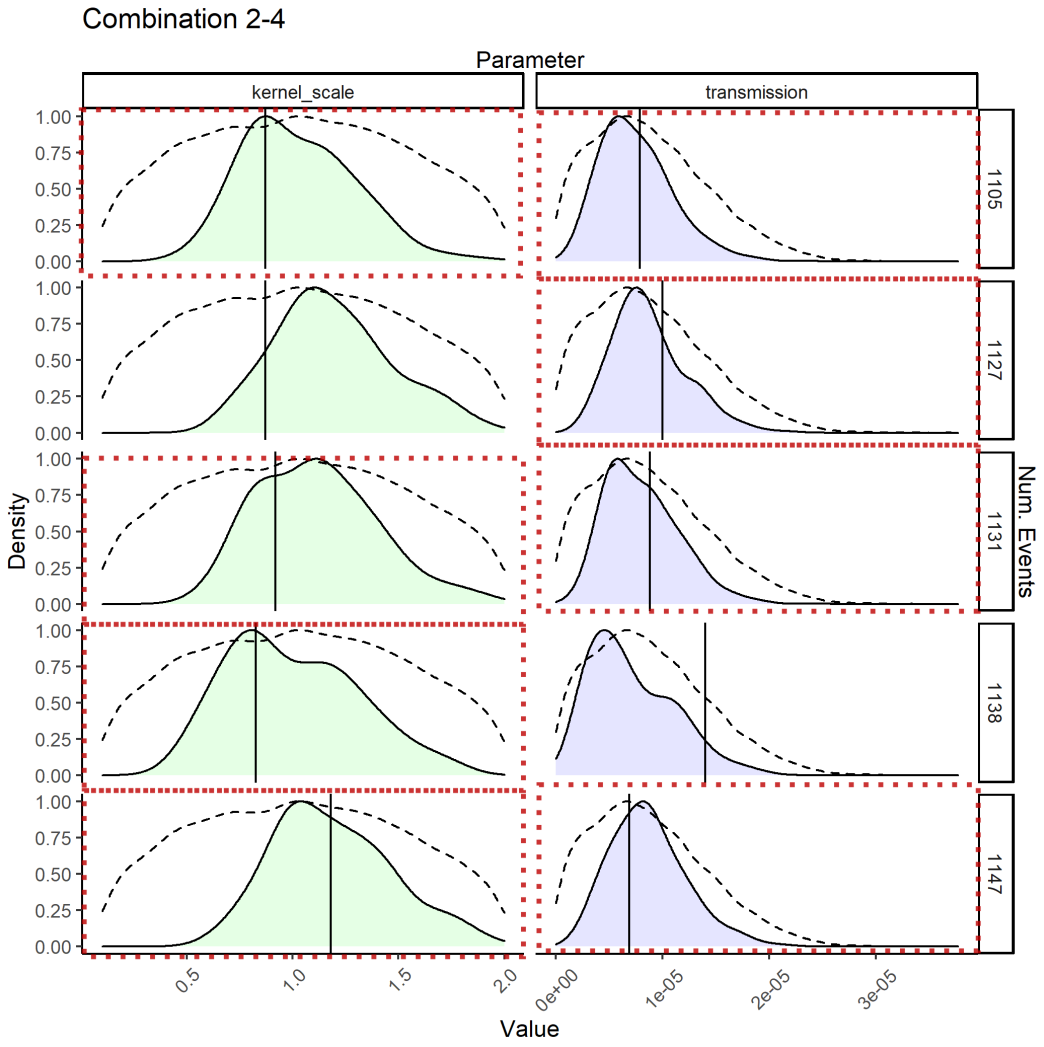

Figure 2.14: The density distributions of the parameters *scale* and T (**ID4-2-4**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, *scale* was recovered 4 out of 5 times, and T was recovered 4 out of 5 times.

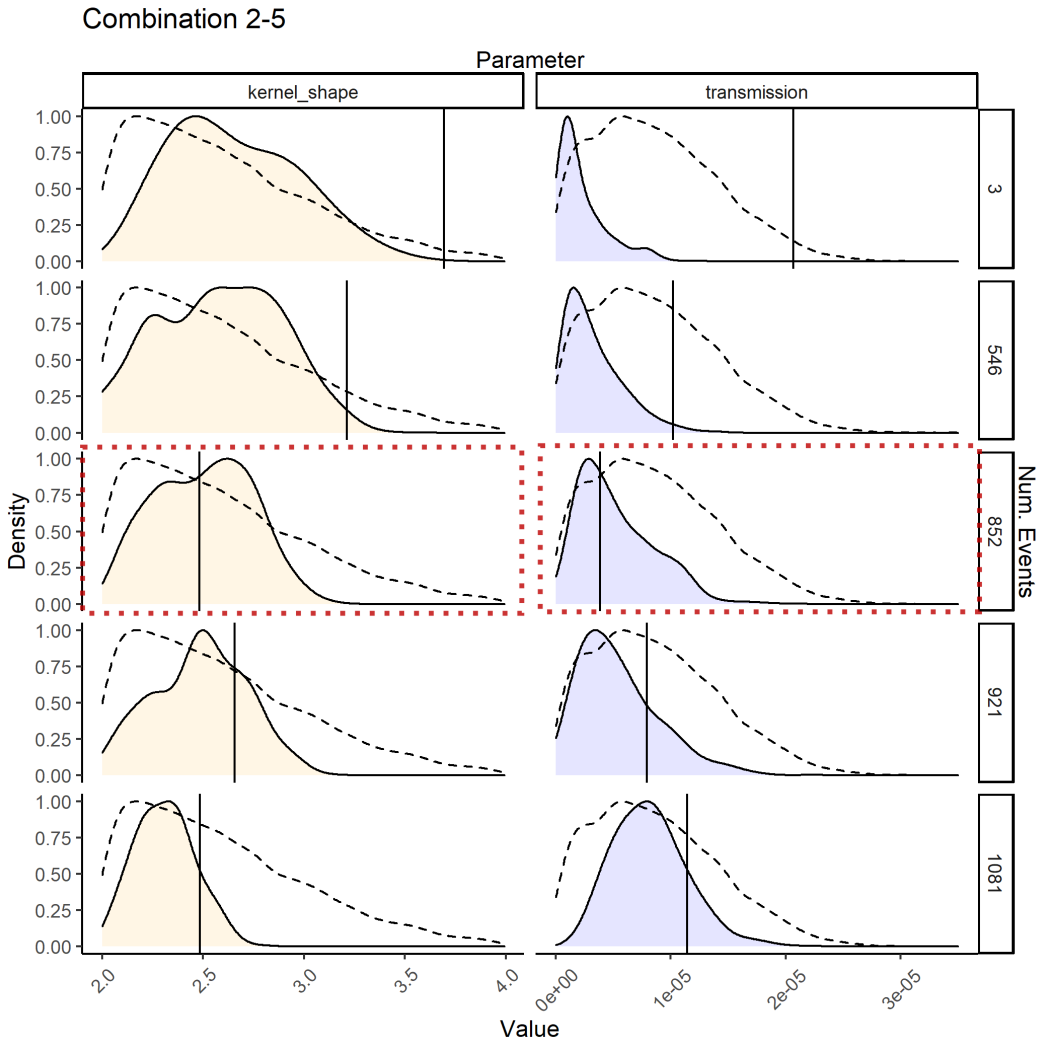

Figure 2.15: The density distributions of the parameters *shape* and T (**ID4-2-5**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, *shape* was recovered 1 out of 5 times, and T was recovered 1 out of 5 times.

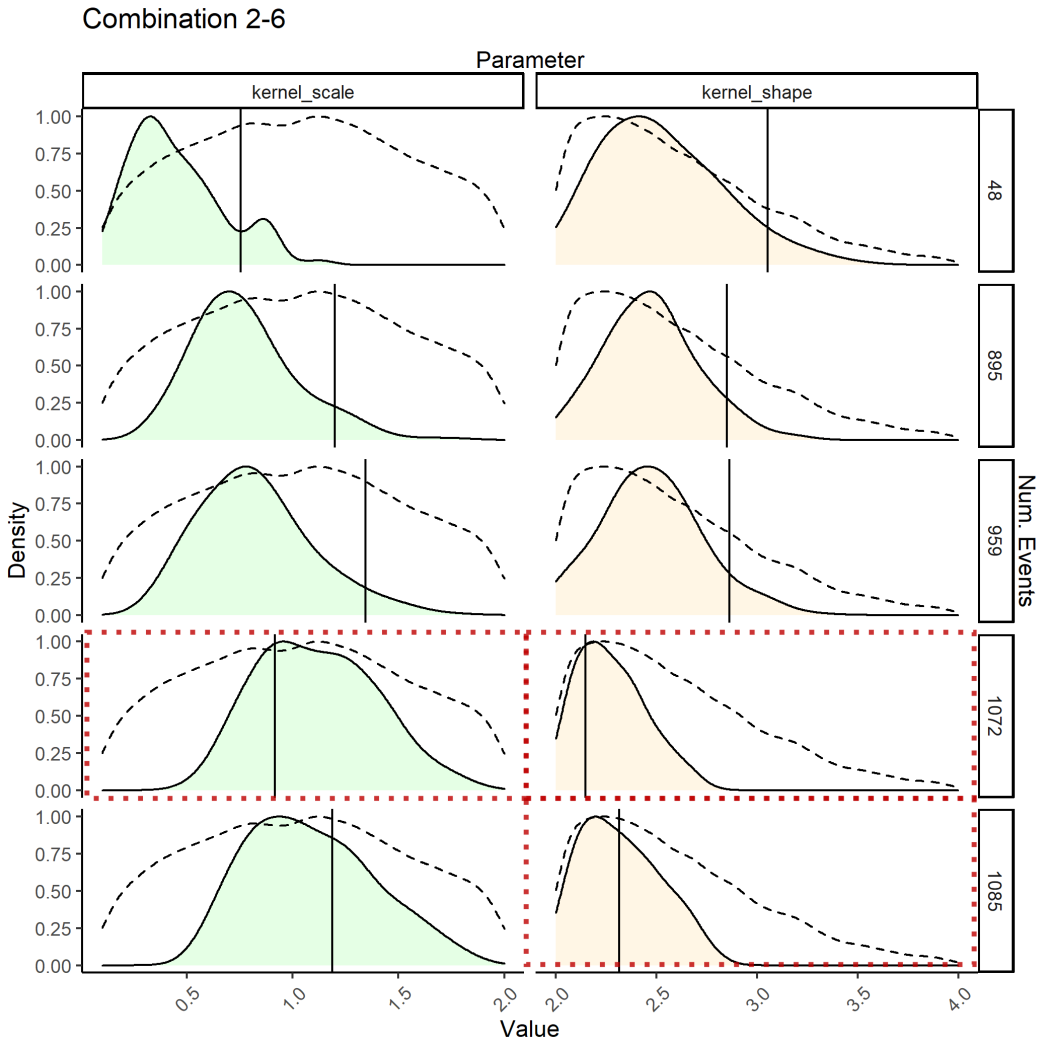

Figure 2.16: The density distributions of the parameters *scale* and *shape* (**ID4-2-6**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, *scale* was recovered 1 out of 5 times, and *shape* was recovered 2 out of 5 times.

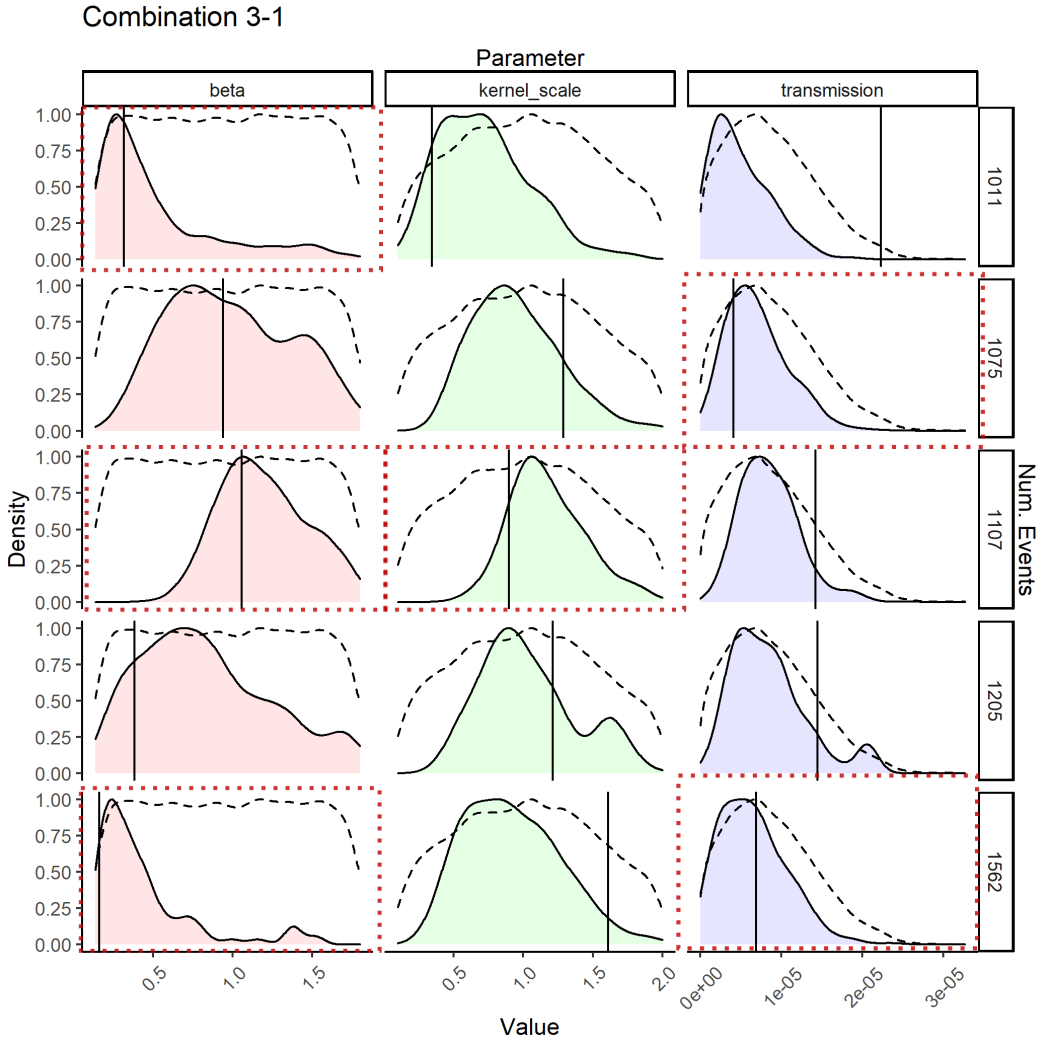

Figure 2.17: The density distributions of the parameters β, *scale*, and T (**ID4-3-1**), after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 3 out of 5 times, *scale* was recovered 1 out of 5 times, and T was recovered 2 out of 5 times.

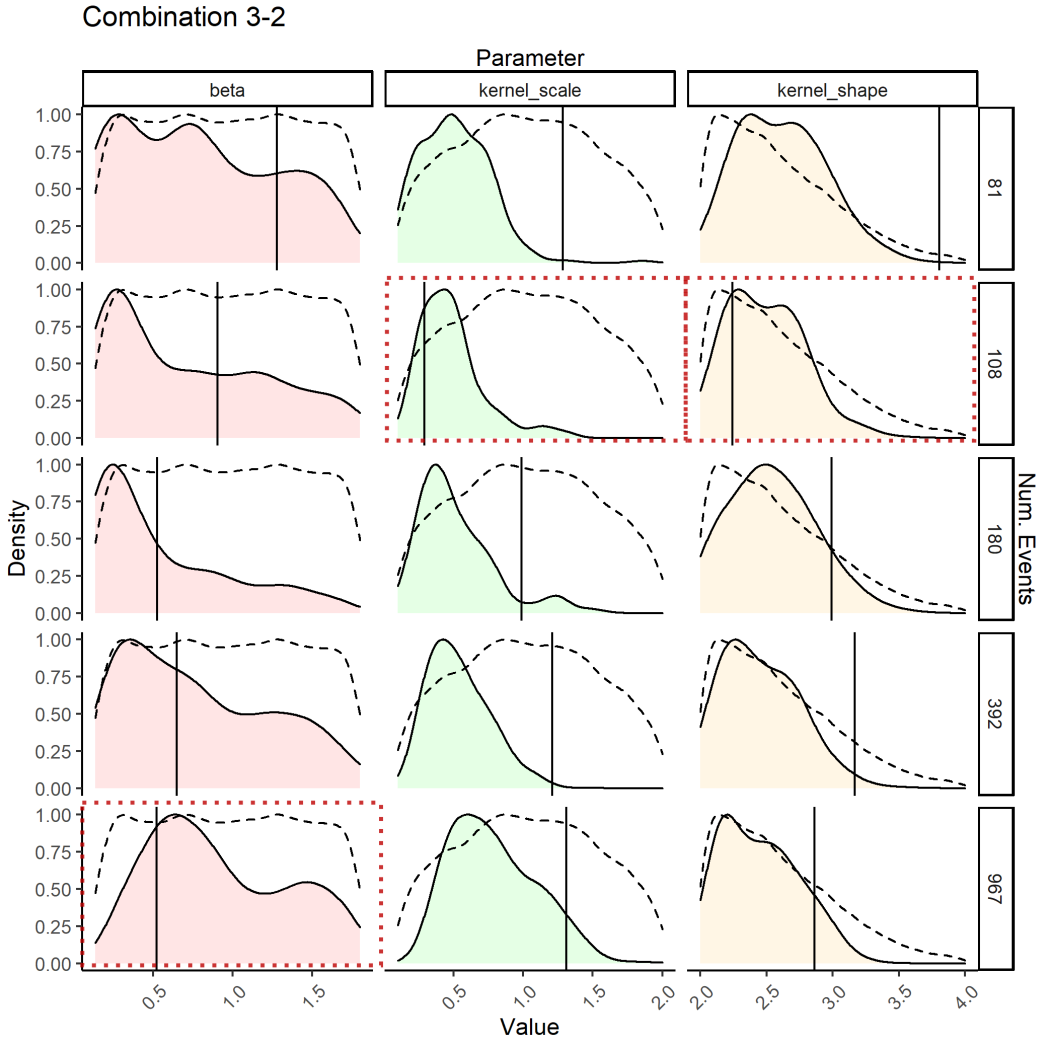

Figure 2.18: The density distributions of the parameters β, *scale*, and *shape* (**ID4-3-2**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 1 out of 5 times, *scale* was recovered 1 out of 5 times, and *shape* was recovered 1 out of 5 times.

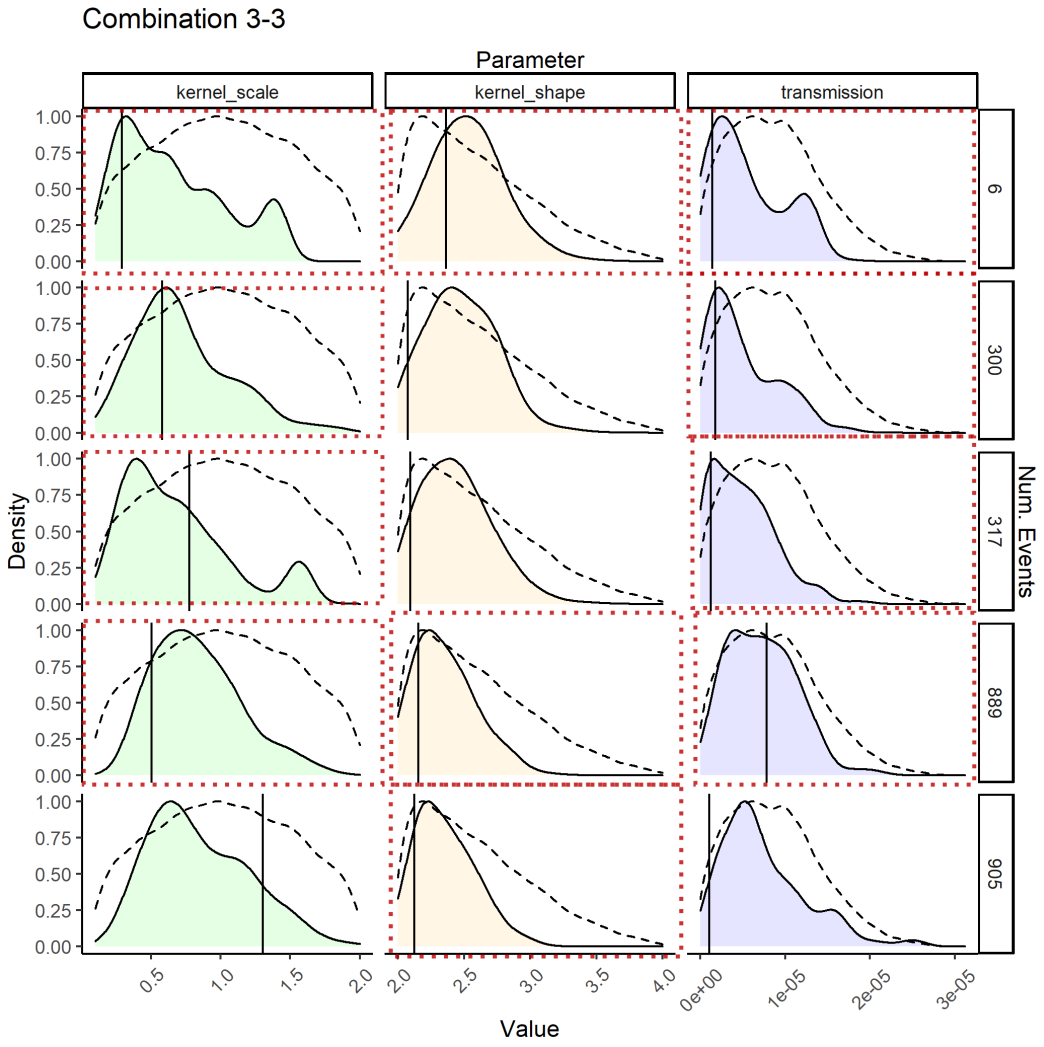

Figure 2.19: The density distributions of the parameters *scale*, *shape*, and T (**ID4-3-3**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, *scale* was recovered 4 out of 5 times, *shape* was recovered 3 out of 5 times, and T was recovered 4 out of 5 times.

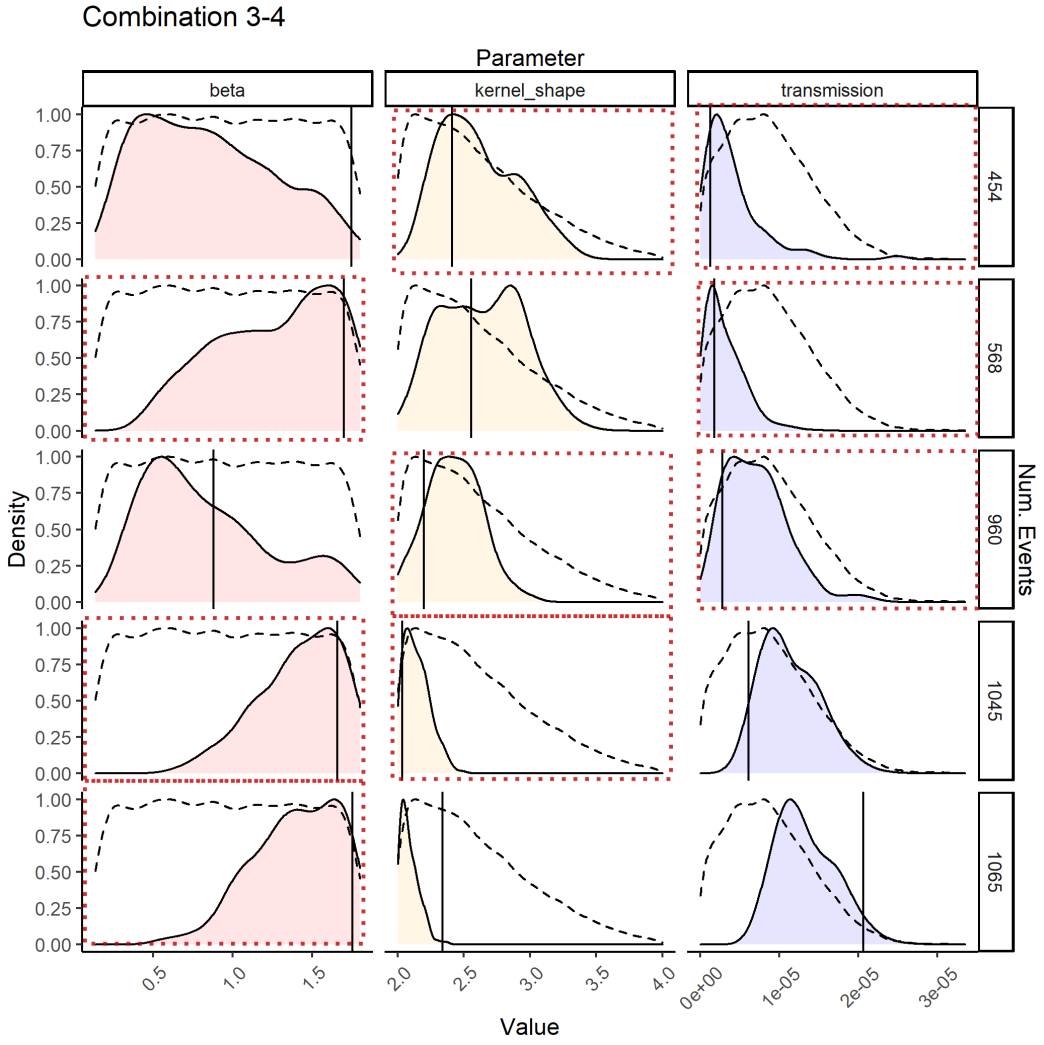

Figure 2.20: The density distributions of the parameters β, *shape*, and T (**ID4-3-4**) after 6 generations of ABC-SMC. Each column is a different parameter, with colour-coded density plots. Each row corresponds to a different "true" value sampled from the prior distribution and recovery attempted via ABC-SMC. The black dotted line on each plot indicates the prior distribution for that parameter, and the vertical solid black line indicates the "true" sampled value for that particular parameter and fit. On the right-hand axis, the number indicate how many events were seen in that "true" outbreak, calculated as the total incidence of infection over the simulation. Higher totals indicate more information to fit to. Attempts where a parameter was considered recovered are surrounded by a dotted red box. With this set of parameters, β was recovered 3 out of 5 times, *shape* was recovered 3 out of 5 times, and T was recovered 3 out of 5 times.

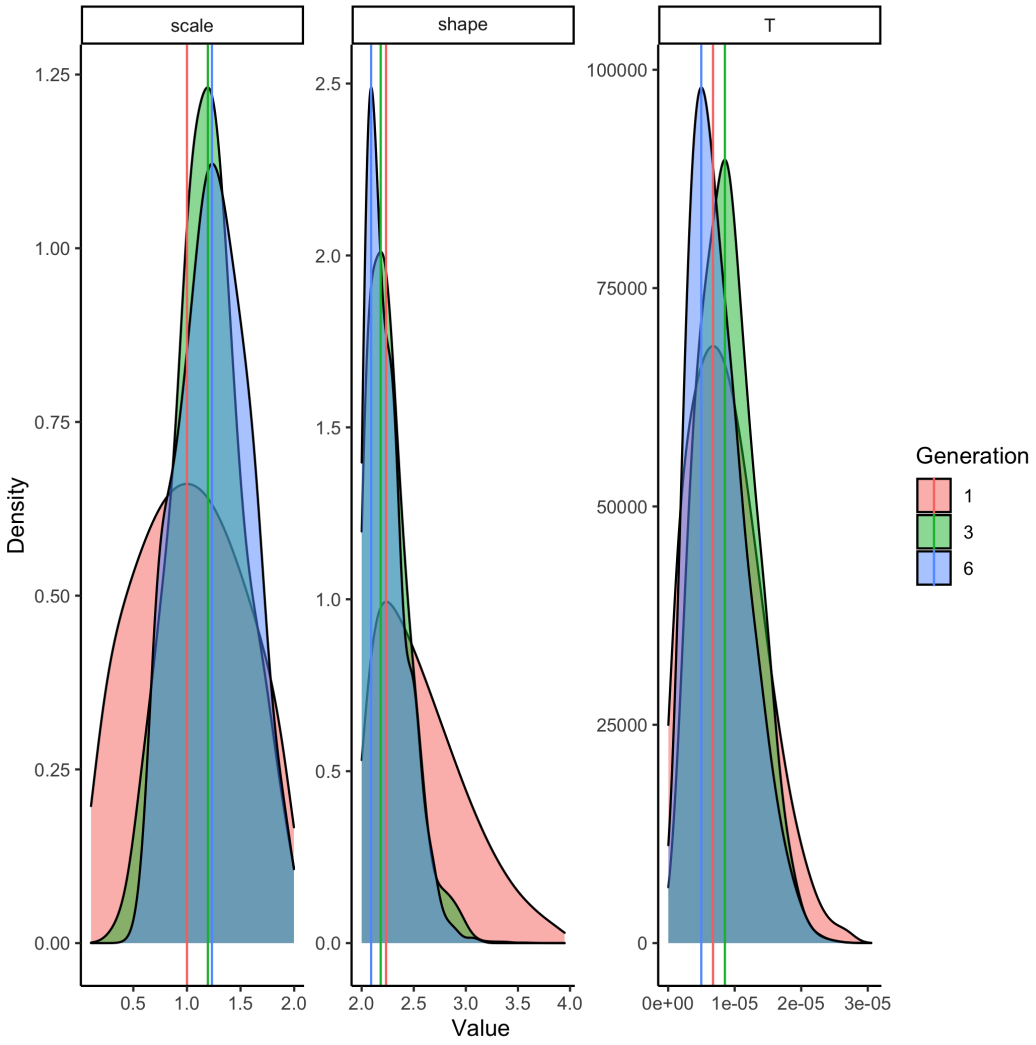

Figure 2.21: The weighted density distributions of the parameters *scale*, *shape*, and T after 6 generations of ABC-SMC with 500 particles per generation. Each parameter demonstrates a clearly defined peak, for *scale* this peak corresponds to a value of 1.23, for *shape* to 2.09, and for T to 4.98e-6. Each coloured line indicates this peak for its generation.

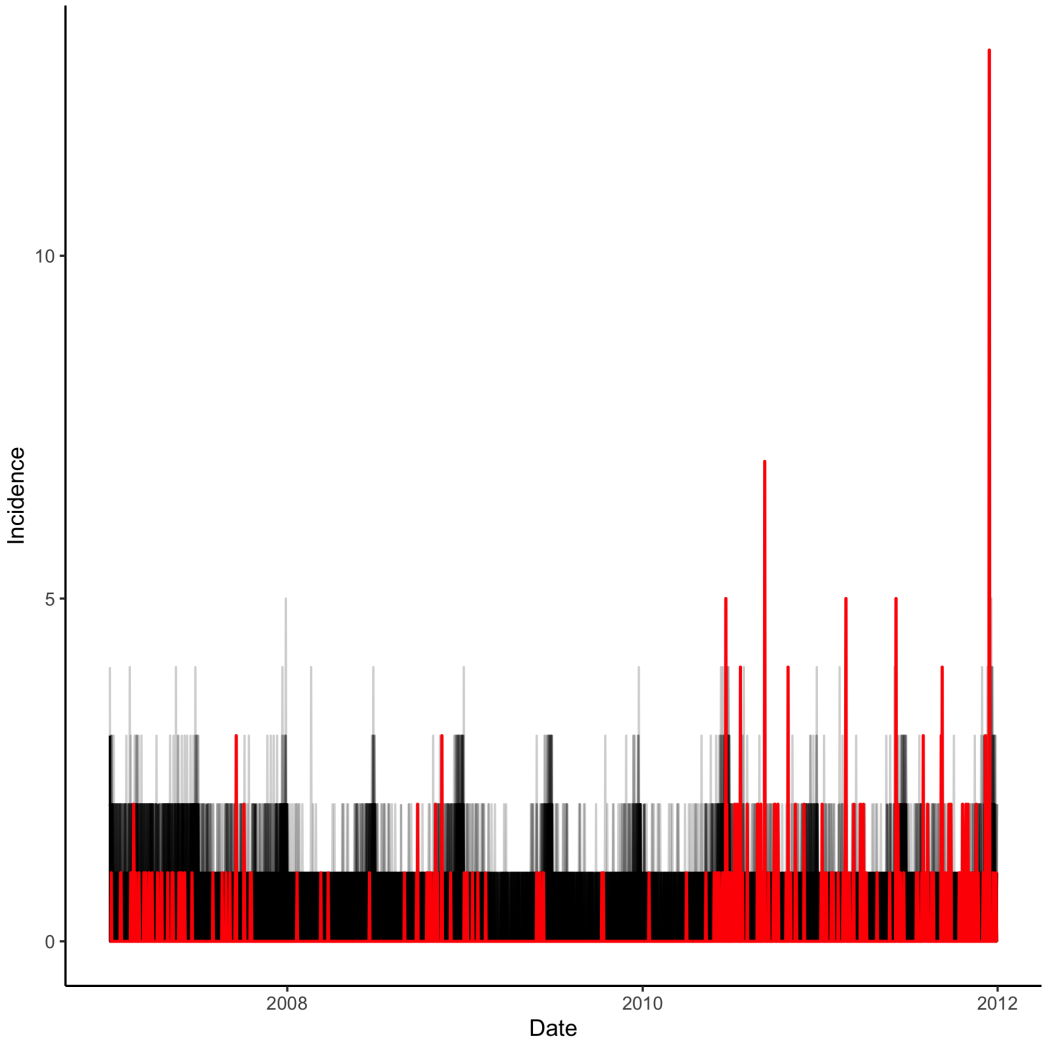

Figure 2.22: Incidence over time for the province of Erzurum. The real data is in red, and the simulated data of the final generation of fitting is in black. Dark black indicates incidence values that are common for the simulations, lighter grey areas uncommon values.

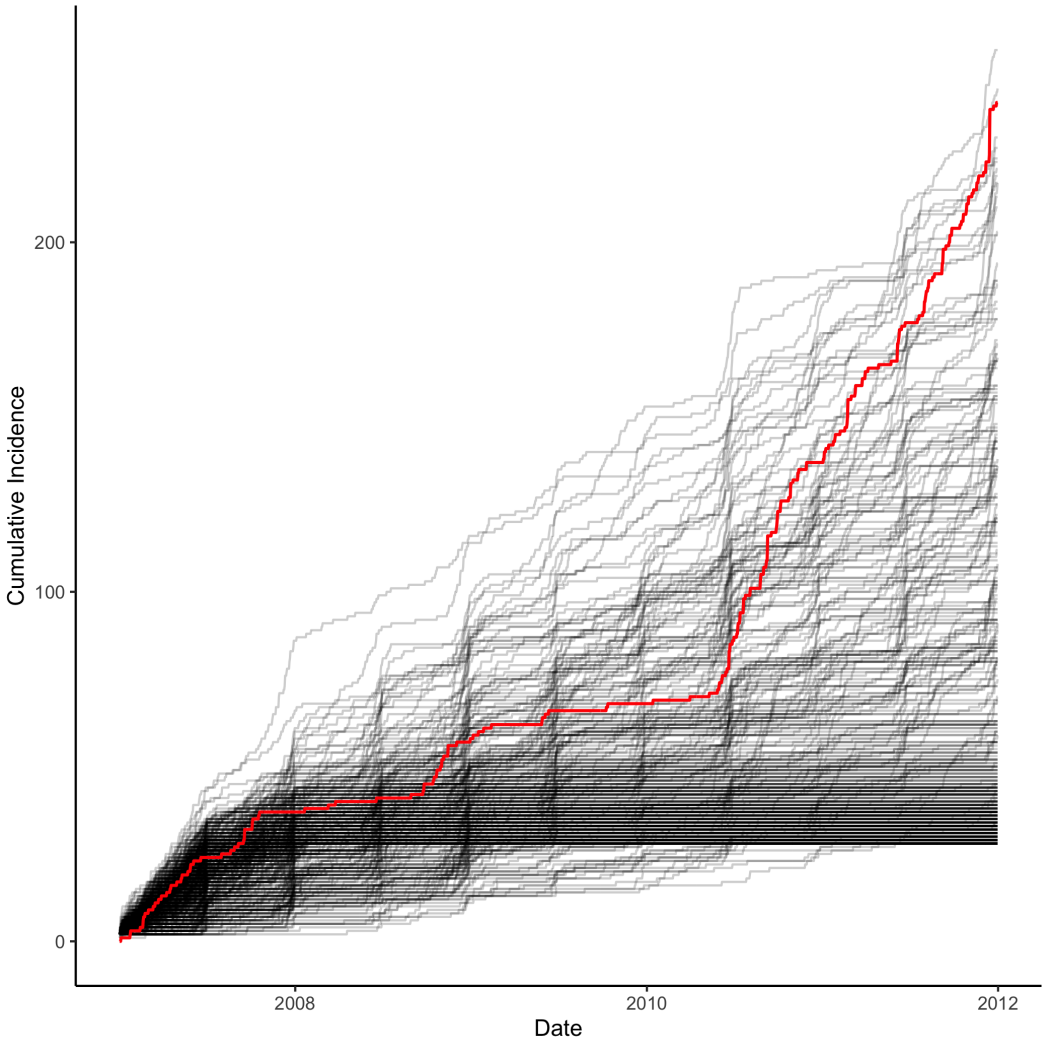

Figure 2.23: Cumulative incidence over time for the province of Erzurum. The red line indicates the real data from this province over this time period, light grey lines indicate the results of one simulation of the final generation. Most simulations are similar to the real data for the period 2007 to 2011, but fewer also match the rise in incidence at the tail end of this period in 2012.

2.4 Discussion

This work has developed a model to describe the dynamics of FMD spread in the endemic region of Turkey, and used this model and the available data to fit a dispersal kernel and transmission parameters. Not all of the parameters that might have been desirable to identify from the data were in fact identifiable, and so I undertook work to establish which combination of parameters was both large enough to be worth while and identifiable from incidence data.

The results indicated that the parameters $scale$, $shape$, and T best fit this combination of desiderata. The parameter λ was eliminated from consideration as it did not appear to be identifiable from the data. Additionally the parameter β was eliminated from the final combination of parameters; though it was identifiable in combination with some parameters, it was not identifiable well enough or consistently enough to be included.

This accords with my intuitions. All of the parameters that were considered identifiable are part of the dispersal kernel, whereas the two originally included parameters were both within-farm parameters. The kernel has a large effect on how well the disease spreads from farm to farm, and farm-level incidence is the data being fit to, whereas β and λ both mainly affect the within-farm dynamics and so the effect of varying them would lead to only minor variations in farm-level incidence which would be difficult to detect.

After deciding on a parameter combination that was relevant and identifiable, I followed up with an attempt to fit to the farm-level incidence data of Erzurum province, which returned estimates of $T = 4.98e-6, shape = 2.09$, and $scale = 1.23$ for the three parameters. The transmission (T) parameter was similar to the estimates from the literature I had sourced my prior distribution from (Table 2.1), which were from the 2001 UK FMD epidemic (ranging from 5.4e-6 to 1.3e-5), and it was useful for the kernel to be validated on data from an endemic region. The lower value of transmission was expected as the shipment transmission route has been separated out from the kernel.

Viewing Figure 2.22 demonstrates the reasonably close fit to the observed incidence data, as well as making it clearer the difficulty in fitting a model to such sporadic data. It was sometimes a challenge to find parameter values which did not either lead to too many infections or lead to infections dying out completely. Figure 2.23 makes this clearer, there were only 253 recorded infections for the province over the entire 5 year period of 1,108 farms being fit to, a rate of approximately 0.1386 infections/day and 0.228 infections/farm. Most farms (median and mode) were not

recorded as infected at all during this period. The dynamics of the disease were also difficult to fit, many proposed particles fit the period of quiet endemic disease circulation of the first 3.5 years but were less able to predict the small outbreak that took place in the final year and a half.

An assumptions made in the development of this model are the assumption that all of the real incidence was observed and recorded in the data available to us. It is very likely that the recorded incidence is not all of the true incidence due to some infections not being recorded or detected. Because the recorded infections might have been seeded by unobserved infections, this would have the effect of reducing the correspondence between my parameter estimates and the "real" parameters. Accounting for this could be done by including detection and surveillance parameters in the parameter inference scheme, however this was not considered feasible given the large parameter space this opened up and so the estimate of detection from Turkey was used.

Some limitations of this work arose from limitations of the data, the quality of which was not everything to be desired. As discussed in the methods, there was limited overlap between data sources to allow cross-referencing which results in uncertainty about the extent of the correspondence between the farms simulated and the real farms present in reality. This also adds uncertainty about the resulting parameter estimates, excluded farms may have impacted the real dynamics we are attempting to simulate and their exclusion from the simulations would result in skewed estimates of the most likely course of infection. Additionally, there was no data available on non-cattle species such as goats, sheep, or pigs. Although the number of swine in Turkey is very low for religious reasons, there are millions of sheep and goats which may act as reservoirs for the disease and reinfect cattle repeatedly. The lack of data on these animals is disappointing, and it would be useful in future if such data were available, as they may allow more accurate model simulations of disease spread.

Other limitations arose from decisions made, often due to limitations of the data or computational complexity, that nevertheless could have been otherwise. One of these is the limited geographic area covered, which also limits the number of recorded infections and provides less information for parameter inference. This decision was due to the computational limitations of the model, as greater areas are simulated the number of interactions between farms increases exponentially resulting in large increases in running time. In light of the available computational resources, simulating Erzurum Province was a reasonable decision to balance accurate inference with the time available, yet simulating a greater area may have allowed tighter or

more parameter estimates.

Another limitation which arose out of this decision was the aggregation of serotype-specific infection data into a pan-serotype incidence time-series for the purposes of model fitting. This increased the information available for fitting and reduced the computational complexity of the simulations, allowing for a better and faster model fit. Although little data was available for serotypes A and Asia-1 in Erzurum over this period, it did preclude the possibility of serotype-specific parameter estimates, as there is evidence they can differ in transmission dynamics (Pacheco, Lee, et al. 2016; Pacheco, Tucker, et al. 2012).

In developing this model, I have endeavoured to portray the more complicated dynamics that can and do occur in the spread of the disease in the endemic regions, both in the Republic of Turkey and other areas. Unlike epidemics of FMD in regions otherwise free of the disease, multiple serotypes exist and there is already a reservoir of population immunity from prior infections. Additionally, the dynamics of endemic diseases play out over a longer period of time, which necessitates population demography and which itself adds complications due to the existence maternally derived antibodies. Not all of these could be included in this work, such as the multiple co-circulating serotypes already discussed. There are also other dynamics which were not included in the model which may also be relevant to the spread of the virus in regions endemic for FMD, such as culture-specific agricultural practices (e.g. pastoralism) or climate.

One of these dynamics, and a limitation of the model, is that spread via shipments is assumed to happen only via the movement of infected animals. Although difficult to parameterise and limited by the lack of data on vehicles, this could be extended to allow simulation of fomite spread, where virus particles contaminate the vehicles and people moving between farms. It is known that fomites can last up to several months in the right conditions, and research indicates that environmental contamination can sustain R above 1 by itself, so this might be one method that the disease could be so sporadic in this region (Bravo de Rueda et al. 2015; Colenutt et al. 2020). The environmental transmission investigated here encompasses more than just vehicle contamination however, and such a route alone might not support $R > 1$. Another possibility is the addition of carrier animals, which is explored in later chapters.

Another limitation of the model is the lack of simulation of the effect of multiple recurrent infections on the immune status of individual cattle. As discussed by T. R. Doel (2005), the duration of the protective immunity generated by infection (and vaccination) can vary depending on prior infection status, with those

animals infected (and surviving) the most also ending up with the most robust immune responses. In endemic regions this preexisting immunity could complicate the immunological landscape that we are attempting to fit to, but it is very difficult to know whether this is relevant without data on pre-existing immunity. This also makes it very difficult to develop prior distributions for the parameters, so it is perhaps beyond reach for the moment.

This chapter has developed a simulation model of Foot-and-Mouth Disease which takes into account several of the important and under-studies dynamics of the disease when endemic, including: waning immunity; the effect of maternally derived antibodies on newborn calves; and demographics. Using this model, we have explored which parameters were identifiable from the data available and fit those parameters using an approximate Bayesian inference scheme, providing a novel estimate of these parameters from an endemic system. This model is a good platform to begin to explore the effect of different control strategies on endemic dynamics.

Chapter 3

Assessing The Performance of Control Policies In Endemic Regions Of The Republic of Turkey

3.1 Introduction

FMD is a highly economically important livestock disease, in both areas that are currently free of the disease and areas where it is endemic. In free countries, control programs and bio-security measures create large costs. Epidemics in these regions can cause tremendous losses and lead to the culling of millions of animals however, as seen in the 2001 epidemics in the UK and the Netherlands. They also lead to restrictions on access to international livestock markets, which has additional enormous costs (Bouma, A. R. W. Elbers, et al. 2003; Bourn et al. 2002; T. J. D. Knight-Jones and J. Rushton 2013).

However the burden of the disease is not equally distributed globally, with poorer countries both more dependent on livestock and less able to control the disease. Although costs in endemic regions are hard to estimate reliably, FMDV directly reduces herd fertility via symptoms such as milk drop and lameness, in addition to preventing the use of high-productivity but more susceptible livestock. The long-standing presence of the disease also prevents international livestock market access, especially to the developed free countries (T. J. D. Knight-Jones, McLaws, and J. Rushton 2017; T. J. D. Knight-Jones and J. Rushton 2013).

Control of this disease therefore offers significant opportunities to assist in the development of many economies. Attempts to control FMD date back several

centuries. Prior to the development of effective mass-producible vaccines in the 1950's, control efforts focused on isolation of known infected animals from the rest of the herd, passive immunization where possible, and elsewise culling them. Mass Vaccination (MV) of animals with FMD vaccines was instituted in Europe in this period until the early 1990's, when elimination of the disease allowed a bio-security-based strategy to become feasible (Blancou 2002; David J. Paton, K. J. Sumption, and Charleston 2009).

The fundamental concepts for the control of animal diseases such as FMD are: (i) to prevent access of the virus to susceptible hosts; to control contact between infected and susceptible animals; (ii) to reduce the number of infected animals; (iii) to reduce the number of susceptible animals (Premashthira et al. 2011). Applying these concepts practically transforms these concepts to: movement controls such as quarantine, or zoning; planned culling of infected animals or herds; vaccination of susceptible animals.

In free-without-vaccination countries such as the USA or European countries, this status is maintained via bio-security efforts, and control of an epidemic is often achieved by some combination of culling of infected or at risk animals, with vaccination sometimes used as a temporary measure to arrest the spread of the disease, and movement controls of livestock also implemented (Premashthira et al. 2011; Michael J Tildesley, Savill, et al. 2006). Countries which are free-with-vaccination maintain this status via widespread prophylactic vaccination campaigns, South American countries have pursued this strategy since the 1960's with a large degree of success (Premashthira et al. 2011). One major difference with endemic regions is willingness to cull, endemic regions are generally Low and Middle Income Countries (LMIC)s, the economic importance of livestock and commonness of FMD means that culling of animals after detecting infection with FMDV is rare.

Regions where FMD is endemic face a number of challenges in their attempts to control disease circulation. In many such areas political attention for FMD is limited by the circulation of other animal diseases, limited funds, as well as other pressing political problems such as human development, or in some cases civil unrest or military conflict (F. F. Maree et al. 2014). The presence of multiple serotype of FMD complicates vaccination efforts, assuming the LMIC in question even has access to high-quality vaccines, and there must also be an effort to match the vaccine used to the strains actually circulating. Circulating strains may also change rapidly, due to mutation or introduction from elsewhere, which may render vaccines ineffective and require reformulation (David J. Paton, K. J. Sumption, and Charleston 2009). Additionally, farming practices in LMICs may make it easier for

the virus to circulate, with cattle grazed on communal land or transhumant herds allowing rapid spread of FMDV (Laura W Pomeroy et al. 2015; Sinkala et al. 2014). For these reasons and more, efforts to control FMD in endemic regions take large amounts of funding and political will to be seen through to control of the disease.

The Republic of Turkey, from which our data originates, has used all of these policies other than culling. Ring Vaccination (RV) and Movement Ban (MB)s within a 10 km radius, which involve vaccinating farms and preventing the movement of animals within a ring around a newly detected infected premises, are regularly implemented. Since at least 2009 they have also commenced prophylactic biannual mass vaccination with a trivalent vaccine with an efficacy of 65%, and in 2015 this was upgraded to a double-dose $6\times$ PD_{50} regime which greatly increased the efficacy (T J D Knight-Jones, Bulut, et al. 2015; T. J. D. Knight-Jones, S. Gubbins, et al. 2016; T. Knight-Jones et al. 2014). Over this time period, they have reduced the number of FMD outbreaks they experience significantly, experiencing only 6 outbreaks in the last quarter of 2021 (FAO 2022).

We aim to use the stochastic spatial metapopulation model developed in a previous chapter, as well as the estimates of the dispersal kernel parameters, and the high-quality data available from the Republic of Turkey, to investigate the efficacy of these different control strategies in a region where the disease is already endemic. We simulate these policies alone and in combination with each other, and assess which policy combinations are most efficacious in reducing the circulation of the disease, as well as their likelihood of elimination of the disease from the region and speed at doing so. Finally, we perform sensitivity analysis to estimate which parameters are most important to these policy combination outputs.

This work has implications for policy choice in regions of the world which are currently experiencing endemic FMD.

3.2 Methods

To investigate the efficacy of different control strategies in the Republic of Turkey from an endemic situation, the model outlined in the previous chapter was used, with the fit parameters values used for the dispersal kernel, and within-farm transmission model parameterised as described in Table 2.1.

To generate an endemic situation, the model was simulated for 5 years with no controls in effect, and the output of this saved. This endemic situation was then used as the starting point for all of the different control policies that were assessed. This allowed an endemic starting point for the imposition of controls to be simulated,

and also meant that differences in outcomes with different policies could be isolated to the effect of the control policies rather than a different starting situation.

These simulations were simulated on the province of Erzurum for computational reasons.

81 unique control policy scenarios were assessed in this manner, varying the control strategy parameters amongst the values given in Table 3.1. For example, a strategy might be a combination of parameter values such that Vaccine Efficacy (VE) is 65%, the ring vaccination radius is 5 km, and there are no movement bans or mass vaccination as their respective values are 0 km and ∞, which was interpreted as not implementing those control policies. In this manner, each possible control policy was assessed on its own and in combination with the other control policies.

Each control policy combination was simulated 100 times for 5 years, beginning from the simulated endemic starting situation previously discussed. Simplifying assumptions were that detection of infected premises was complete and that coverage was total. The outcomes of interest were the total numbers of infected farms, the Probability of Elimination (P(E)) (taken to be the proportion of simulations where the disease was eliminated), and the Time To Elimination (TTE). These were compared to a scenario where no control policies were implemented.

Table 3.1: The different control strategy parameter values which were assessed in combination, for example VE of 65% in combination with ring vaccination at 5 km. For ring vaccination and movement bans, a radius of 0 km indicates that the policy was not implemented. For mass vaccination, an interval of ∞ indicates that the policy was not implemented.

Parameter	**Parameter Values (unit)**
Vaccine Efficacy	{65, 80, 90} %
Ring Vaccination Radius	{0, 5, 10} km
Movement Ban Radius	{0, 5, 10} km
Mass Vaccination Interval	{∞, 365, 182} days

3.2.1 Sensitivity Analysis

To test which parameters were most important to different control policies, sensitivity analysis was performed for different control policy combinations. Of these there were seven: Ring Vaccination; Movement Bans; Mass Vaccination; Ring Vaccination + Movement Bans; Ring Vaccination + Mass Vaccination; Movement Bans + Mass Vaccination; and all three policies in concert.

To reduce the dimensions of the problem whilst still exploring each parameter distribution thoroughly, Latin Hypercube Sampling (LHS) was used to generate

500 samples from the relevant parameter distributions (Table 3.2), and each set of parameter values (particle) was simulated 100 times for 5 years in Erzurum Province.

Each control policy combination varied the detection and vaccine parameters, grouped as the Surveillance parameters in Table 3.2, as well as the relevant control policy parameters. For example, when analysing the combination of RV and MB policies, the Surveillance parameter group as well as the Ring and Movement parameter groups were varied, but not the Mass parameter group as MV policies were not being assessed.

Detection Probability was the probability that an infected farm would be detected and reported for reactive control policies, with Detection Delay outlining the time between infection and detection. Vaccine Efficacy was the average efficacy of the vaccine, drawn from a normal distribution with this as the mean for each farm vaccinated, as described in Chapter 2. Vaccine Duration is λ_{V_S}, the average duration of the vaccine immunity state. Vaccine Capacity was defined as the percentage of the total number of farms that could be vaccinated in a day. For both Ring Vaccination and Movement Bans, the Radius parameter defined the ring around a known infected farm that would have the control policy implemented. Coverage (for Ring and Mass Vaccination) controlled the probability that a farm identified for vaccination would actually be vaccinated, and for Movement Bans Compliance this controlled whether a farm would comply with movement restrictions. Movement Ban Duration controlled the time period of a given movement restriction order, and Mass Vaccination Interval defined the time period between vaccination campaigns. Model code is available at https://github.com/gguyver/fmd-model-thesis.

After simulation of the parameters, outputs were calculated and analysed. The inputs assessed are outlined in Table 3.2 and are random samples of the parameter distributions selected according to the LHS method. The outputs assessed were: (i) the average total incidence over the 5 year period simulated; (ii) the probability of disease elimination (P(E)); (iii) and the average time to elimination conditional on elimination occurring (TTE). For each of these outputs Partial Rank Correlation Coefficient (PRCC) sensitivity analysis was performed to assess the importance of each parameter to the outcomes. PRCC analysis is a standard, efficient, and robust sensitivity measure for non-linear but monotonic relationships between inputs and outputs (Marino et al. 2008). For a good overview of different sensitivity analysis techniques useful in infectious disease modelling, see Wu et al. (2013).

PRCC sensitivity analysis was done using R 4.0.5, and the epiR package version 1.0-2 (R Core Team 2020; Mark Stevenson et al. 2021).

Table 3.2: A summary of the parameter ranges used for sensitivity analysis. Related parameters are grouped with each other and given a descriptive name for ease of reference. All parameters are drawn from a uniform distribution between the minimum and maximum value. Whether they are continuous (C) or discrete (D) is indicated in the Type column.

Parameter	**Value Min, Max**	**Group**	**Type**
Detection Probability	0, 100 %	Surveillance	C
Detection Delay	1, 14 days	Surveillance	C
Vaccine Efficacy	50, 100 %	Surveillance	C
Vaccine Duration	30, 730 days	Surveillance	D
Vaccine Capacity	0,100 %	Surveillance	C
Ring Vaccination Radius	1,10 km	Ring	C
Ring Vaccination Coverage	1,100 %	Ring	C
Movement Ban Radius	1, 10 km	Movement	C
Movement Ban Duration	1, 14 days	Movement	D
Movement Ban Compliance	1, 100 %	Movement	C
Mass Vaccination Interval	30, 730 days	Mass	D
Mass Vaccination Coverage	1, 100 %	Mass	C

3.3 Results

3.3.1 No Controls

All control policies were compared to the scenario of no controls and each other. When no controls were implemented, the disease continued the classic damped oscillations toward an endemic equilibrium, seen in Figure 3.1.

When no controls were implemented, an average of 7845.77 (standard deviation 93.13) newly infected farms occurred over the 5 year period simulated.

3.3.2 Ring Vaccination

The RV policy was able to produce a strong reduction in the circulation of the disease as a policy on its own, reducing the average total incidence of infected premises by 54.17% with the smallest radius and lowest efficacy vaccine (Table 3.3). Figure 3.2 shows the reduction in prevalence associated with this, with prevalence at less than 200 infected premises with a 5 km vaccination radius, and less than 100 infected premises with a 10 km vaccination radius.

Table 3.3 shows that increasing VE was associated with lower incidence, but that the largest reduction came from increasing the radius of vaccination. Increasing the radius at least halved the incidence again, however increasing VE from 65% to 90% reduced incidence by approximately 500 infected premises over the 5-year

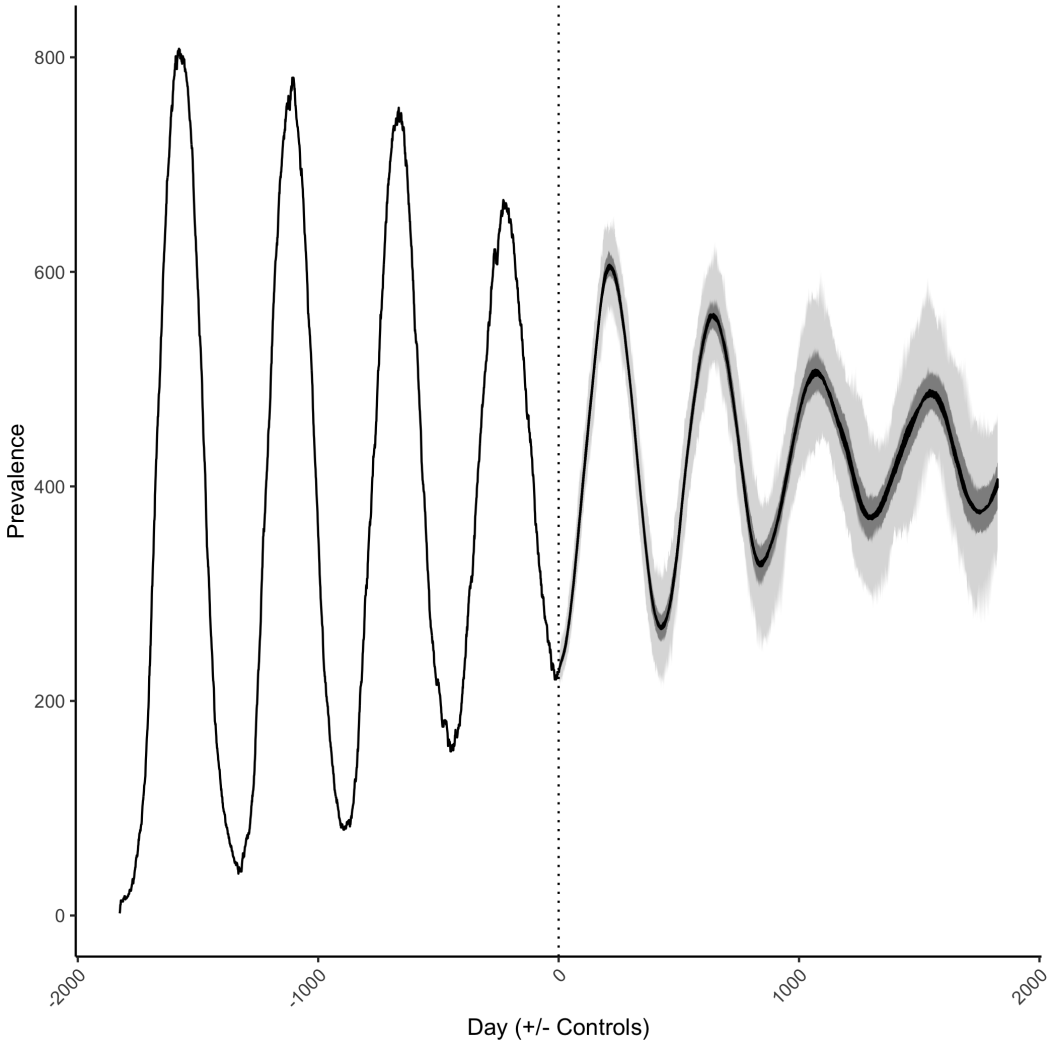

Figure 3.1: Average Prevalence of FMD with no implementation of control policies simulated. The vertical dotted line indicates the when the simulated implementation of the control policy would have begun, on day 0. The line to the right of this indicates the average prevalence over time, with a darker coloured area around indicating the Interquartile Range (IQR) of values, and the lighter coloured ribbon indicating the full range of values.

Table 3.3: Statistics of the standalone Ring Vaccination (RV) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Radius	VE	Incidence		P(E)	TTE	Vaccinated
5 km	65%	3,595.72	(-54.17%)	0	-	15,633.41
	80%	3,181.36	(-59.45%)	0	-	15,293.05
	90%	3,007.57	(-61.67%)	0	-	15,178.34
10 km	65%	1,483.99	(-81.09%)	0	-	19,564.26
	80%	1,165.63	(-85.14%)	0	-	18,811.46
	90%	1,049.26	(-86.63%)	0	-	18,450.66

Table 3.4: Statistics of the standalone Movement Ban (MB) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination (P(E)), the average time to elimination (TTE), and the average total number of days farms spent under a movement ban (Ban-days).

Radius	Incidence		P(E)	TTE	Ban-days
5 km	7,839.32	(-0.08%)	0	-	1,507,224
10 km	7,848.71	(0.04%)	0	-	1,860,761

simulated period.

3.3.3 Movement Bans

The MB policy on its own does not appear to have any effect on the prevalence of FMD, as shown in Figure 3.3. After the implementation of controls, the disease continues damped oscillation towards the endemic equilibrium. Table 3.4 shows that the total incidence for all combinations of MB policies was almost identical to the scenario where no controls were implemented.

3.3.4 Mass Vaccination

Implementing MV as a stand-alone policy leads to a large reduction in the prevalence of FMD. Both intervals simulated lead to a reduction, however biannual vaccination led to a larger reduction and constant control of the disease (Figure 3.4). Additionally, mass vaccination also lead to elimination of the disease in the majority of simulations. When annual vaccination was implemented, a greater VE reduced the

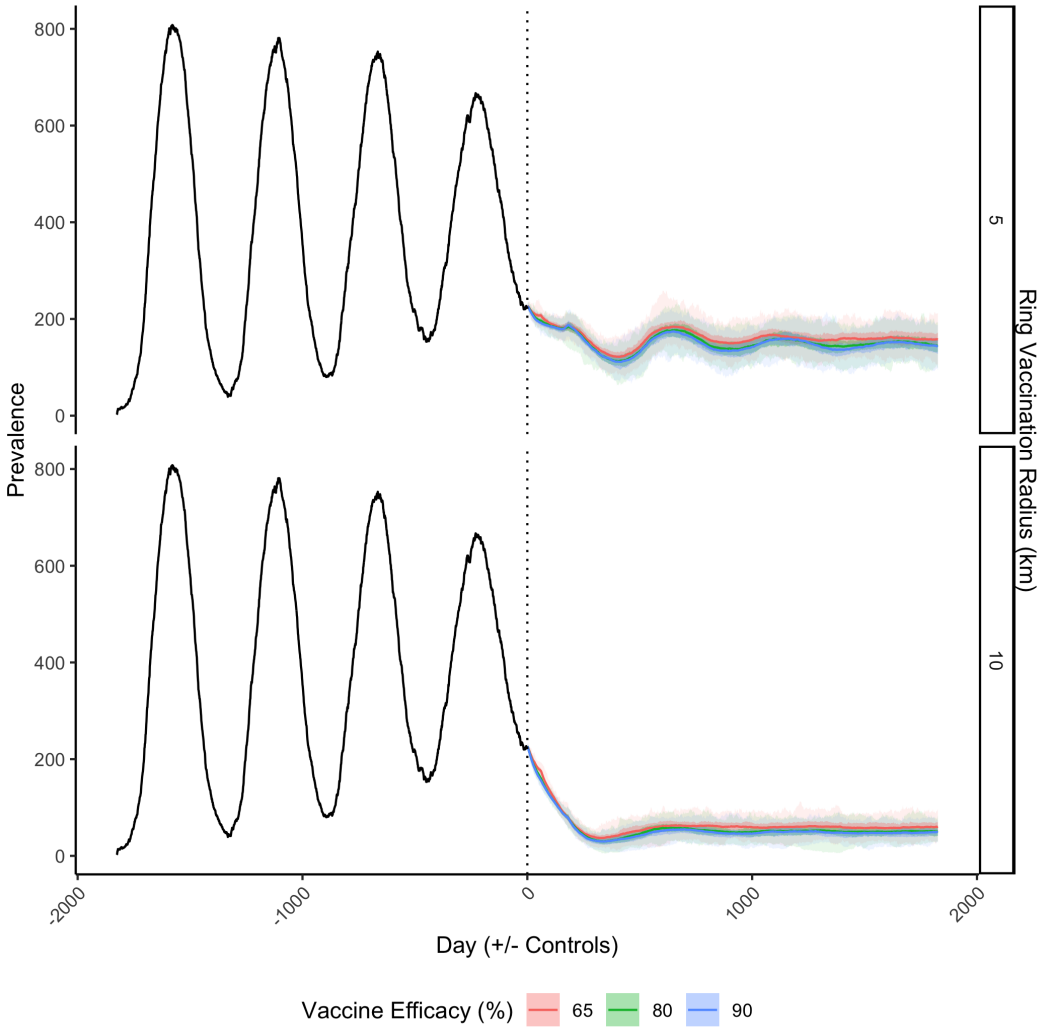

Figure 3.2: Average Prevalence of FMD after implementation of **ring vaccination** alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Both radii lead to a large reduction in prevalence compared to the prior endemic state, with the larger radius leading to a larger decrease. There is a large overlap between different VE values. Elimination is not observed.

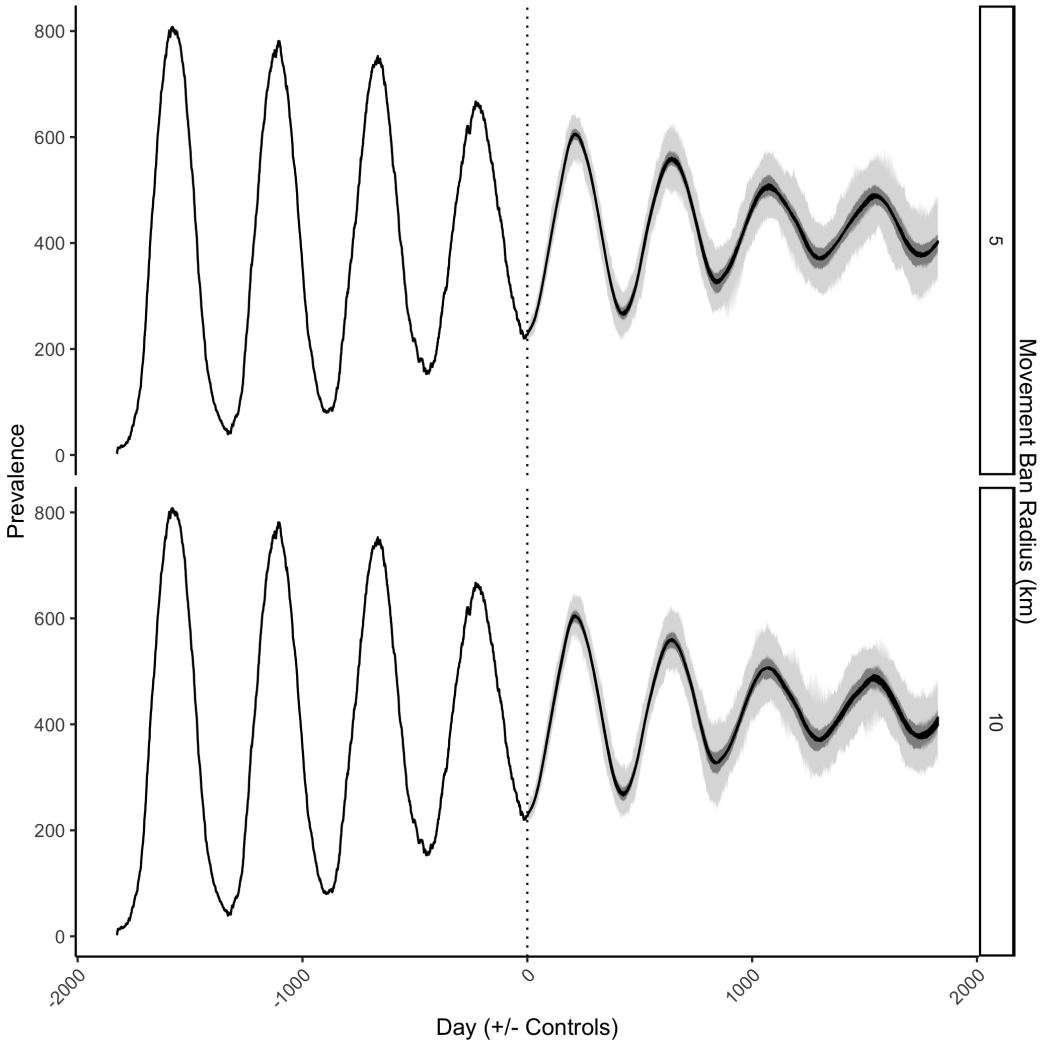

Figure 3.3: Average Prevalence of FMD after implementation of movement bans alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. The line indicates the average prevalence for the given movement ban radius, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Movement bans on their own do not lead to a reduction in prevalence of FMD when simulated for an already endemic state.

Table 3.5: Statistics of the standalone Mass Vaccination (MV) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination (P(E)), the average time to elimination (TTE), and the average number of farms vaccinated.

Interval	VE	Incidence		P(E)	TTE	Vaccinated
182 days	65%	1,010.24	(-87.12%)	0.97	540.57	10,968.66
	80%	982.12	(-87.48%)	1.00	406.80	10,969.96
	90%	977.13	(-87.55%)	1.00	372.59	10,970.20
365 days	65%	4,394.37	(-43.99%)	0.17	623.35	5,484.05
	80%	1,886.39	(-75.96%)	0.90	614.31	5,484.97
	90%	1,731.57	(-77.93%)	0.99	634.33	5,484.89

resurgences seen, with the greatest resurgences observed when VE was only 65%.

Table 3.5 shows that Mass Vaccination alone could lead to reductions in total incidence of 43.99 - 87.55% compared to a no control scenario. The least effective policy, of annual vaccination with a VE of 65%, averaged 4394.37 infected premises over a 5 year period, vaccinating 5484 farms. However, increasing the VE from 65% to 80% reduced this incidence still further to 1886.39 infected premises. A further increase from 80% to 90% did not see a commensurate reduction in incidence, averaging 1731.57 infected premises.

Biannual vaccination did not exhibit the same dependence on vaccine efficacy, with only minor decreases in incidence observed for the same increases in VE. Despite twice as many farms vaccinated, the biannual vaccination policy achieved much lower incidence than annual vaccination.

3.3.5 Ring Vaccination and Movement Bans

When implementing ring vaccination in concert with movement bans, a similar pattern to using ring vaccination alone is observed. A significant decrease in the prevalence of FMD is observed compared to no controls, with a larger decrease in prevalence when using a larger radius. The addition of movement bans does not appear to lead to an additional decrease in prevalence (Figure 3.5).

This is seen in Table 3.6, where the reduction in total incidence is almost identical to the reduction seen for ring vaccination alone (Table 3.3). The number of vaccinated farms is also almost identical. However, the total number of farm ban-days is between 484,201 to 1,701,312 ban-days.

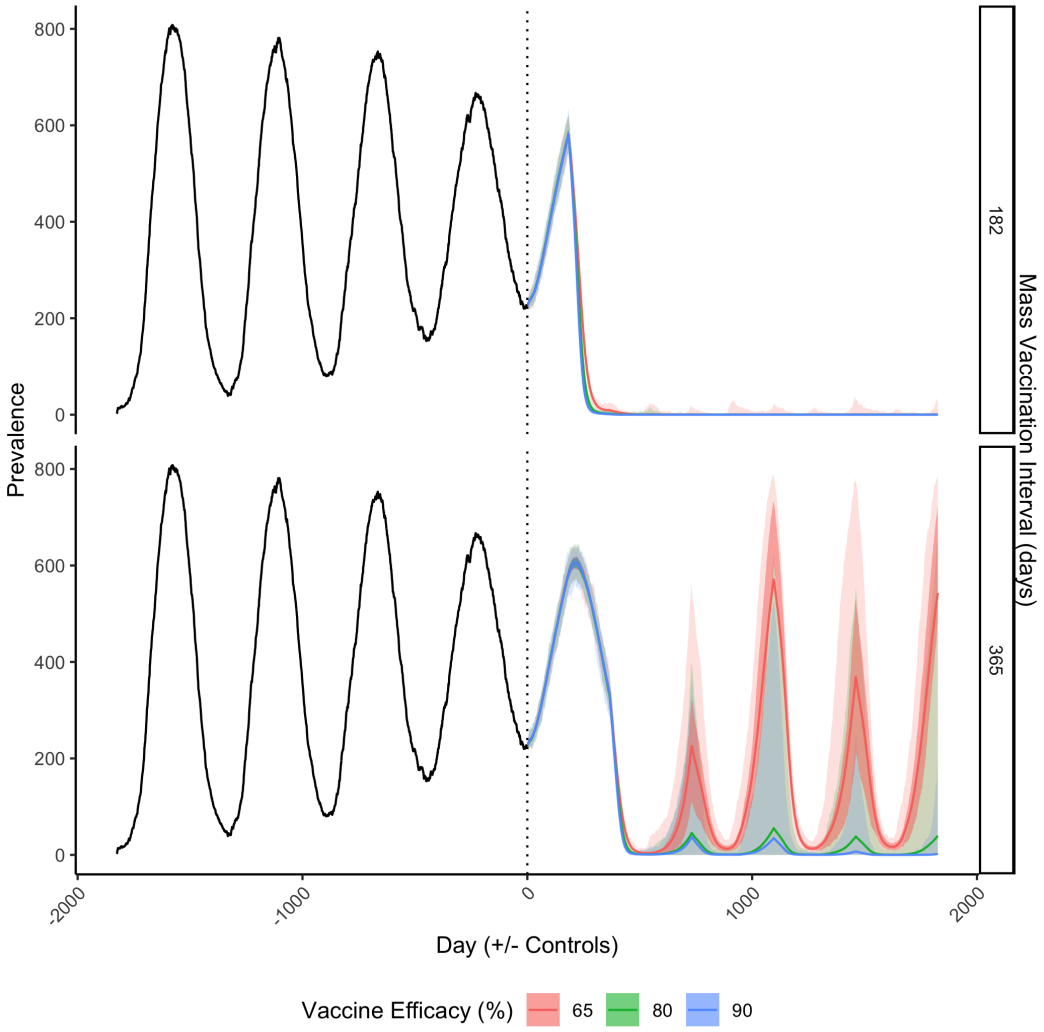

Figure 3.4: Average Prevalence of FMD after implementation of mass vaccination alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 182 day (6 month) mass vaccination interval, and the bottom facet for a 365 day interval. Mass vaccination can lead to a large reduction in the prevalence of FMD compared to the prior endemic state, although the wrong interval can blunt this effect as the reduction is much smaller for yearly mass vaccination compared to biannual vaccination. Greater VE leads to a greater reduction in prevalence, especially in the annual mass vaccination scenario.

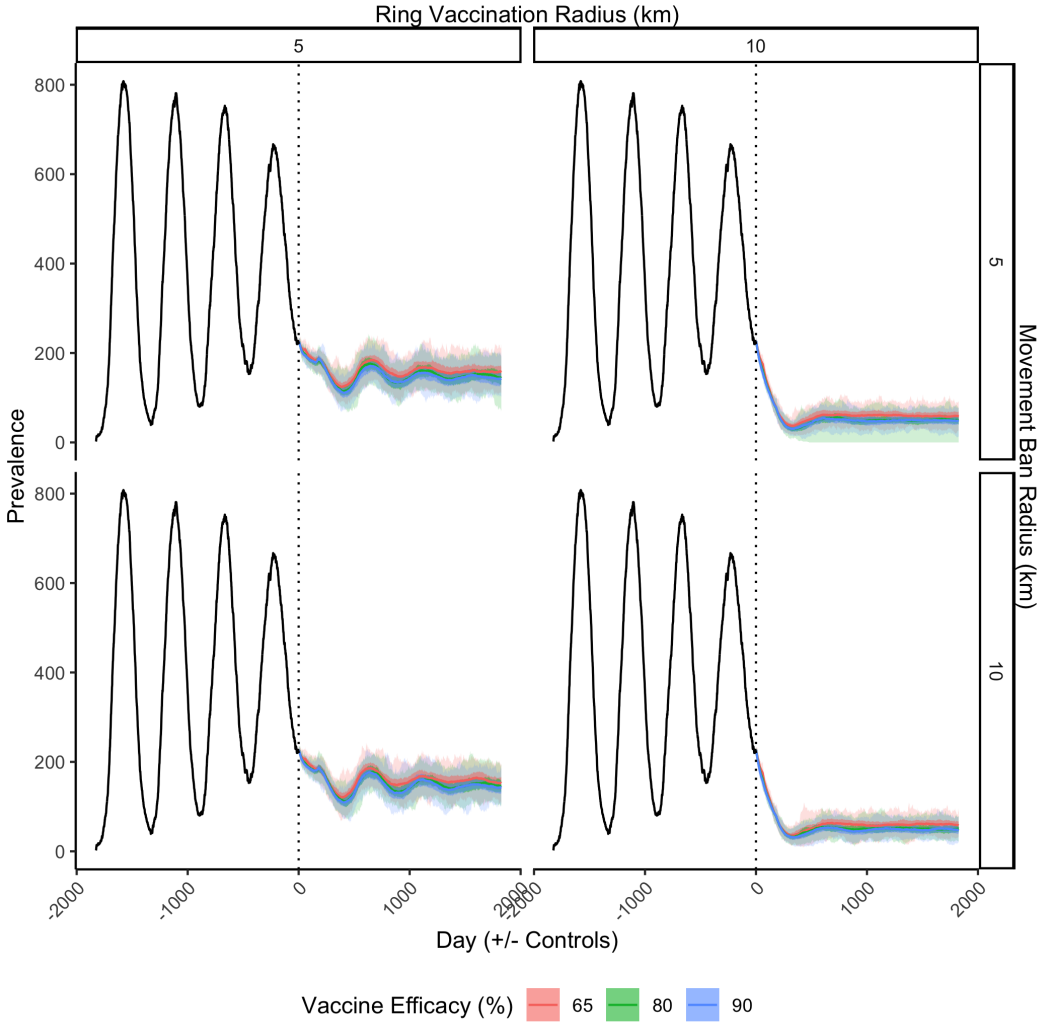

Figure 3.5: Prevalence of FMD after implementation of both ring vaccination and movement bans. Each column indicates either 5 or 10 km radius for ring vaccination, and each row a 5 or 10 km radius for movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. Ring vaccination leads to a reduction in prevalence, however even in concert with this movement bans do not lead to a further reduction.

Table 3.6: Statistics of the combined Ring Vaccination (RV) and Movement Ban (MB) policie. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

RV Radius	MB Radius	VE	Incidence		P(E)	TTE	Vaccinated	Ban-days
5 km	5 km	65%	3,587.71	(-54.27%)	0.00	-	15,625.88	1,066,567.0
		80%	3,175.60	(-59.52%)	0.00	-	15,266.29	1,036,471.1
		90%	3,003.88	(-61.71%)	0.00	-	15,131.99	1,028,079.2
	10 km	65%	3,578.97	(-54.38%)	0.00	-	15,611.27	1,667,237.4
		80%	3,172.62	(-59.56%)	0.00	-	15,310.92	1,654,611.2
		90%	3,011.98	(-61.61%)	0.00	-	15,155.84	1,647,136.9
10 km	5 km	65%	1,483.21	(-81.1%)	0.00	-	19,660.96	538,681.8
		80%	1,142.88	(-85.43%)	0.01	477	18,578.55	486,889.3
		90%	1,060.12	(-86.49%)	0.00	-	18,661.09	486,194.7
	10 km	65%	1,479.73	(-81.14%)	0.00	-	19,587.75	1,103,800.9
		80%	1,165.08	(-85.15%)	0.00	-	18,817.77	1,048,205.9
		90%	1,053.94	(-86.57%)	0.00	-	18,578.28	1,034,113.9

3.3.6 Ring Vaccination and Mass Vaccination

Combining Mass Vaccination and Ring Vaccination leads to a much reduced prevalence of FMD (Figure 3.6). When biannual MV is combined with any radius of RV, prevalence is reduced to a minimum within a year, with elimination of the disease likely. This appears to be invariant to the vaccine efficacy used. An RV policy in combination with annual MV also reduces the prevalence resurgences associated with VE, reducing prevalence more with a larger radius.

The two policies in concert reduced total incidence by between 73.88 - 98.66% compared to a baseline scenario of no controls, registering between 77 - 2569 total incidence depending on policy (Table 3.7). Between 8257 - 18521 farms were vaccinated, also depending on policy, more than MV as a stand-alone policy but less than RV as a stand-alone policy.

3.3.7 Movement Bans and Mass Vaccination

Using MV and MB together lead to a larger reduction in prevalence and incidence, but a very similar reduction to MV alone, and less of a reduction compared to using RV instead of MB policy options (Table 3.8). Farms vaccinated ranged from 5,464 to 11,000, similar to MV alone, and farm ban-days ranged from 179,719 to 944,365.

As seen in Figure 3.7, biannual vaccination led to sharp reductions of prevalence to a manageable level or elimination, whereas annual vaccination could lead to resurgences, the strength of which depended on the VE assumed.

3.3.8 Ring Vaccination, Movement Bans, and Mass Vaccination

Combining all of the control policies together, prevalence can be reduced to elimination of FMD with biannual mass vaccination, and a large reduction with annual mass vaccination (Figure 3.8). Ring vaccination at a 10 km radius reduces prevalence further in the case of annual vaccination. In agreement with the previous policy combinations, movement bans had no effect on prevalence or incidence.

The total number of farms vaccinated over the course of the simulations is similar in each scenario, with most biannual mass vaccination policies ranging between 12,570 to 15,434 farms (Table 3.9). Annual vaccination had a greater range, between 8285 to 19,166 farms vaccinated.

Movement ban-days ranged from 81,433 ban-days with biannual mass vaccination, ring vaccination at 10 km, and 5 km movement bans, to 1,141,609 ban-days with annual mass vaccination, 5 km ring vaccination, and 10 km movement bans.

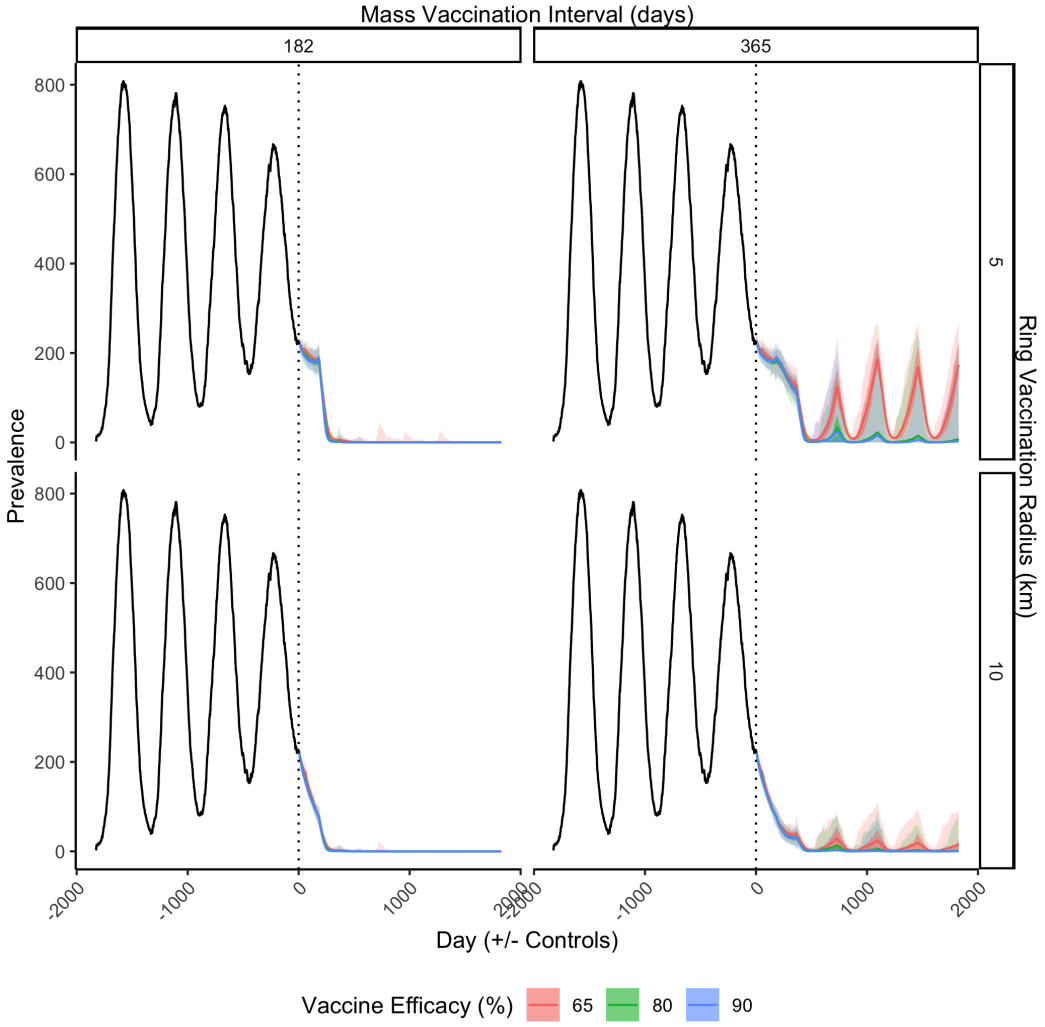

Figure 3.6: Prevalence of FMD after implementation of both reactive ring vaccination and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive ring vaccination. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination is clearly better than annual mass vaccination, though both lead to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. A larger ring vaccination radius leads to an additional reduction in virus circulation.

Table 3.7: Statistics of the combined Ring Vaccination (RV) and Mass Vaccination (MV) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Interval	Radius	VE	Incidence		P(E)	TTE	Vaccinated
182 days	5 km	65%	389.40	(-95.04%)	1.00	541.51	12,924.53
		80%	329.13	(-95.81%)	1.00	386.72	12,748.26
		90%	312.45	(-96.02%)	1.00	360.51	12,715.04
	10 km	65%	172.35	(-97.8%)	1.00	463.52	13,796.88
		80%	119.70	(-98.47%)	1.00	353.77	13,602.30
		90%	104.83	(-98.66%)	1.00	312.29	13,534.95
365 days	5 km	65%	2,049.70	(-73.88%)	0.08	765.13	13,656.72
		80%	719.03	(-90.84%)	0.94	712.43	9,172.00
		90%	646.42	(-91.76%)	0.98	653.28	8,934.63
	10 km	65%	478.26	(-93.9%)	0.69	803.23	12,373.75
		80%	241.26	(-96.92%)	0.99	632.66	10,096.36
		90%	178.88	(-97.72%)	1.00	506.88	9,517.39

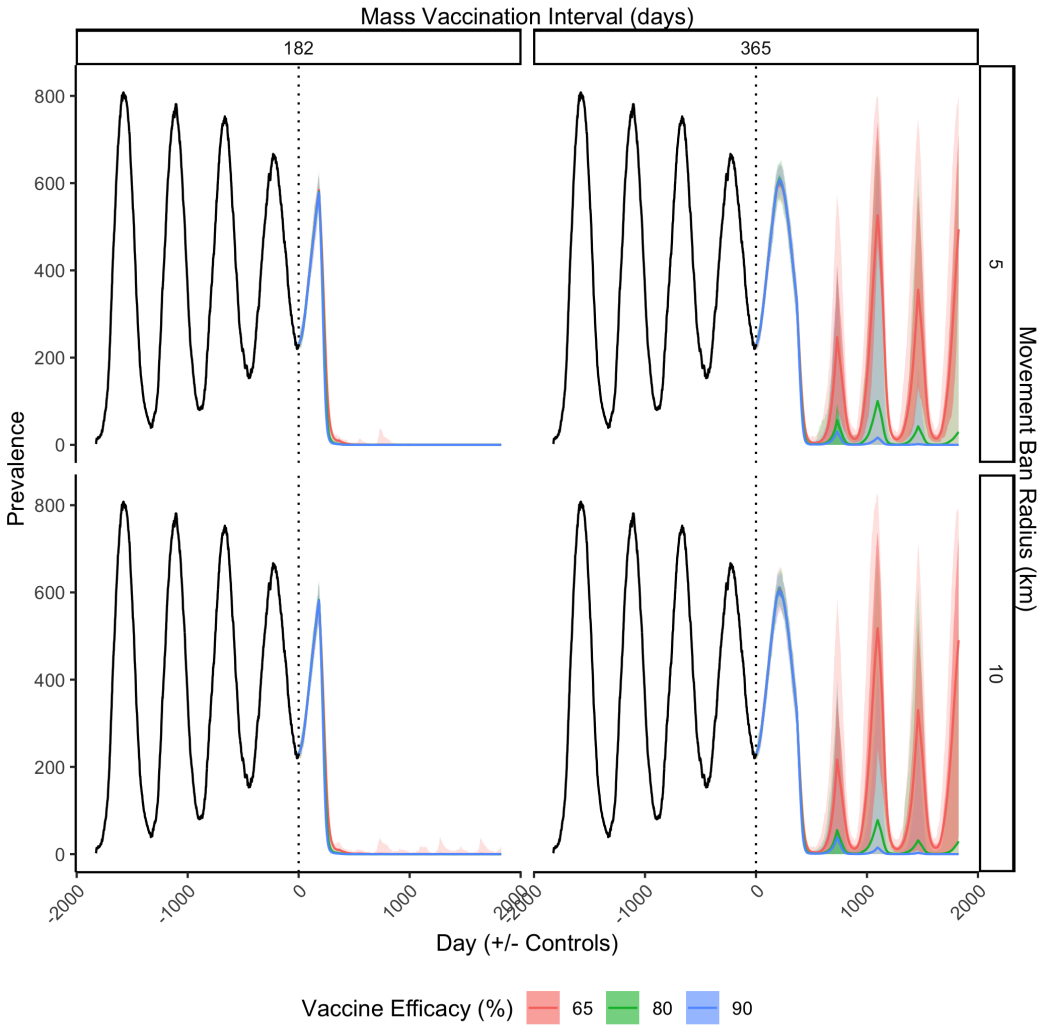

Figure 3.7: Prevalence of FMD after implementation of both reactive movement bans and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Movement bans appear to make no difference to the prevalence, regardless of which mass vaccination policy they are combined with.

Table 3.8: Statistics of the combined Movement Ban (MB) and Mass Vaccination (MV) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	Radius	VE	Incidence		P(E)	TTE	Vaccinated	Ban-days
182 days	5 km	65%	1,007.92	(-87.15%)	1.00	522.06	10,970.17	211,045.6
		80%	982.93	(-87.47%)	1.00	401.7	10,970.27	194,210.5
		90%	975.03	(-87.57%)	1.00	377.54	10,969.40	187,463.4
	10 km	65%	1,009.93	(-87.13%)	0.98	549.36	10,969.13	297,080.7
		80%	985.63	(-87.44%)	1.00	403.18	10,969.30	264,606.1
		90%	979.42	(-87.52%)	1.00	371.1	10,970.91	253,995.1
365 days	5 km	65%	4,262.94	(-45.67%)	0.23	621	5,484.14	732,364.2
		80%	1,969.70	(-74.89%)	0.92	745.34	5,484.10	391,732.7
		90%	1,693.05	(-78.42%)	1.00	607.74	5,484.94	346,906.4
	10 km	65%	4,145.75	(-47.16%)	0.25	647	5,484.31	992,394.7
		80%	1,919.25	(-75.54%)	0.92	673.25	5,486.41	503,077.7
		90%	1,703.10	(-78.29%)	1.00	626.5	5,485.32	448,691.4

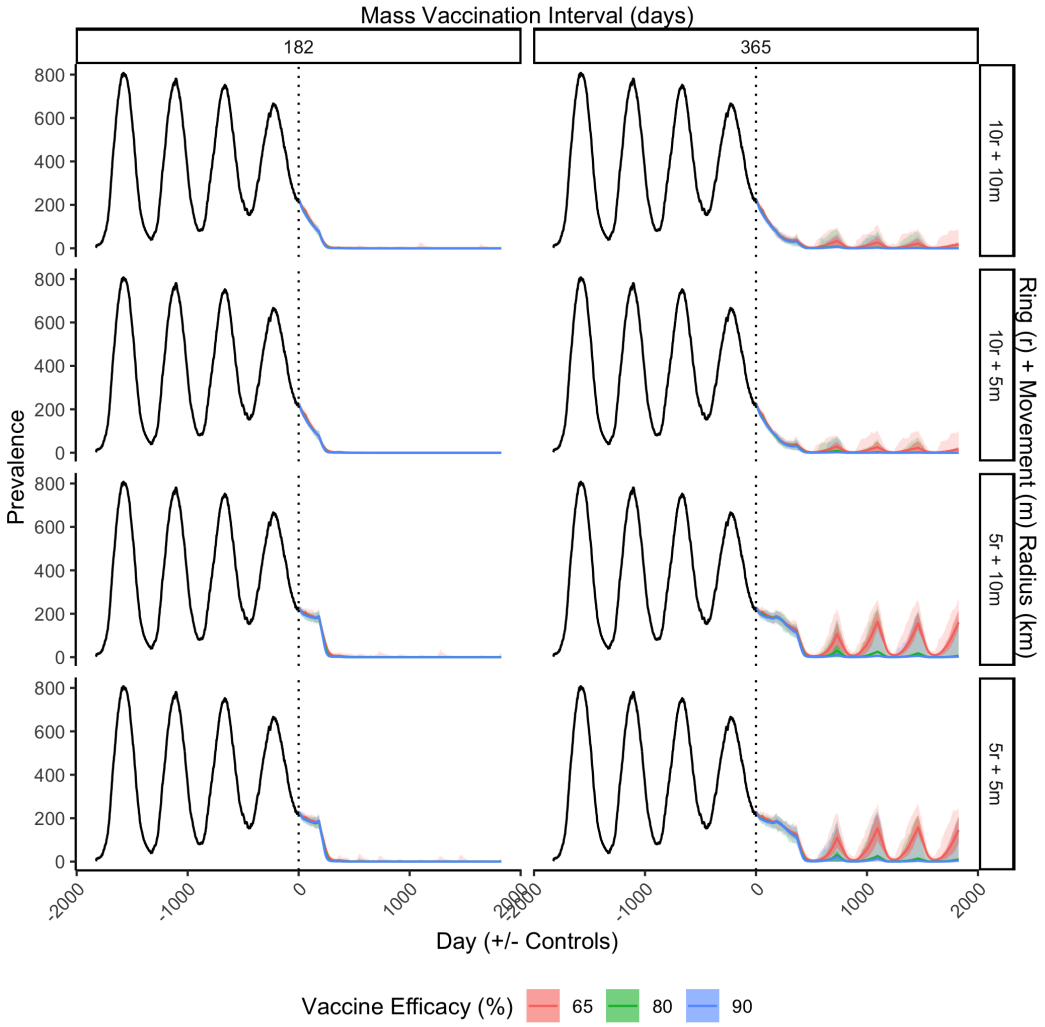

Figure 3.8: Prevalence of FMD after implementation of all three of reactive ring vaccination, reactive movement bans, and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a combination of a 5 or 10 km radius for reactive ring vaccination (indicated by r) and movement bans (indicated by m). The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Ring vaccination additionally reduces the prevalence of disease, however movement bans appear to make no difference to the prevalence, regardless of which policy they are combined with.

Table 3.9: Statistics of the combined Ring Vaccination (RV), Movement Ban (MB), and Mass Vaccination (MV) policies. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	RV Radius	MB Radius	VE	Incidence		P(E)	TTE	Vaccinated	Ban-days
182 days	5 km	5 km	65%	393.11	(-94.99%)	0.97	587.69	12,926.04	148,034.43
			80%	326.16	(-95.84%)	1.00	398.77	12,751.90	135,554.62
			90%	311.26	(-96.03%)	1.00	359.31	12,703.89	133,329.89
		10 km	65%	392.65	(-95.00%)	0.99	535.24	12,925.03	242,722.79
			80%	326.24	(-95.84%)	1.00	384.04	12,751.72	216,595.53
			90%	313.78	(-96.00%)	1.00	365.26	12,709.81	211,379.92
	10 km	5 km	65%	170.59	(-97.83%)	1.00	474.31	13,791.01	102,212.67
			80%	121.01	(-98.46%)	1.00	341.94	13,602.96	95,754.84
			90%	102.41	(-98.69%)	1.00	309.42	13,530.37	93,589.97
		10 km	65%	171.83	(-97.81%)	0.99	471.35	13,833.03	180,520.46
			80%	119.02	(-98.48%)	1.00	346.52	13,581.52	165,273.27
			90%	103.99	(-98.67%)	1.00	309.12	13,541.82	163,235.87
365 days	5 km	5 km	65%	1,856.26	(-76.34%)	0.17	910.53	13,015.82	523,067.53
			80%	735.01	(-90.63%)	0.92	696.80	9,210.16	266,455.92
			90%	636.44	(-91.89%)	0.98	613.36	8,896.03	246,258.24
		10 km	65%	1,895.80	(-75.84%)	0.14	831.79	13,143.11	911,527.86
			80%	734.56	(-90.64%)	0.93	715.46	9,213.51	443,347.84
			90%	600.59	(-92.35%)	0.98	588.80	8,763.51	388,015.67
	10 km	5 km	65%	497.10	(-93.66%)	0.69	856.46	12,575.10	205,807.88
			80%	220.37	(-97.19%)	1.00	604.3	9,842.19	135,054.17
			90%	173.83	(-97.78%)	1.00	482.02	9,444.26	126,189.21
		10 km	65%	517.91	(-93.4%)	0.68	859.10	12,789.02	429,147.91
			80%	223.22	(-97.15%)	0.98	569.11	9,896.13	263,291.56
			90%	190.56	(-97.57%)	1.00	557.64	9,710.11	253,201.26

3.3.9 Sensitivity Analysis

Sensitivity analysis focused on three different outputs, average total incidence (Figure 3.9), the probability of elimination (P(E)) (Figure 3.10), and the time to elimination (TTE) in simulations where elimination was achieved (Figure 3.11).

Detection delays and vaccination capacity were not associated with decreased total incidence in any of the control policy combinations that were assessed (Figure 3.9). Nor was MB compliance, duration, or radius significant when that policy was assessed, due to the lack of effect that was seen for that policy in prior analyses. RV coverage was also not significantly different from a correlation of 0 with total incidence.

The probability of detection was significantly negatively correlated with total incidence when assessing RV policies and when RV was used in concert with MV. The coefficient for this parameter was not significantly different from 0 when using MB policies without RV policies.

Additionally, MV coverage was significantly negatively correlated with incidence when the relevant policies were assessed, as was RV radius, and vaccine duration. VE was also weakly negatively correlated with incidence when a policy used vaccines. MV interval was significantly positively correlated with incidence, with longer intervals leading to more incidence.

A similar pattern is seen with the probability of, and time to, elimination (Figures 3.10, 3.11). Detection delay and vaccine capacity remained uncorrelated with the probability of elimination and time to elimination, as were MB compliance, duration, and radius. The most correlated parameters were MV coverage and interval, RV radius, and vaccine duration.

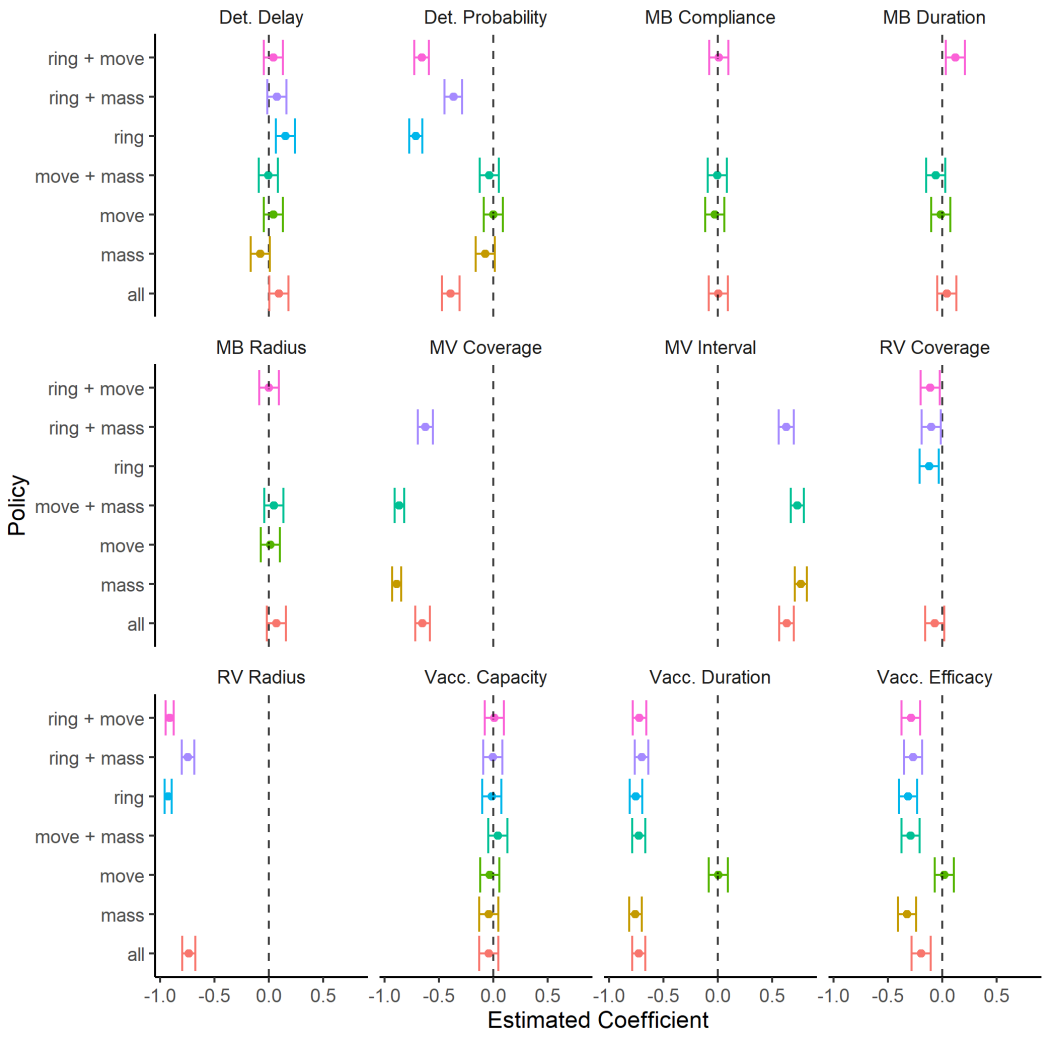

Figure 3.9: Estimated correlation coefficients of control policy parameters with the average total incidence, for each control policy combination. Each panel corresponds to correlation coefficient estimates for different parameters, each row in each panel a different control policy combination. Points indicate the point estimates, error bars denote the 95% confidence interval. A dotted line is shown at 0.0 for ease of interpretation. Parameters which were not relevant for a particular policy do not have a coefficient estimate for that policy on that panel. Detection Probability, Mass Vaccination Coverage and Interval, Ring Vaccination Radius, Vaccine Duration, and Vaccine Efficacy are the parameters most consistently associated with a reduction in total incidence.

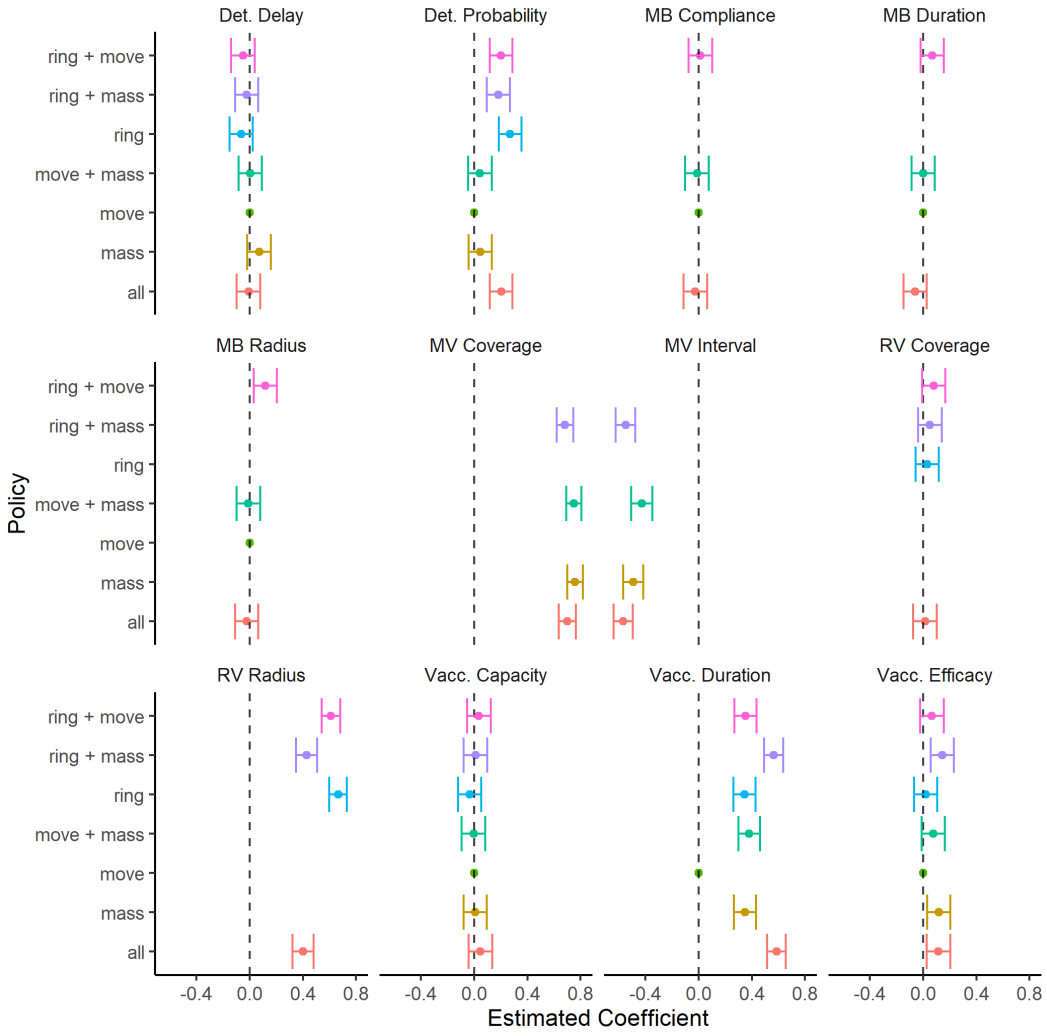

Figure 3.10: Estimated correlation coefficients of control policy parameters with the estimated probability of disease elimination, for each control policy combination. Each panel corresponds to correlation coefficient estimates for different parameters, each row in each panel a different control policy combination. Points indicate the point estimates, error bars denote the 95% confidence interval. A dotted line is shown at 0.0 for ease of interpretation. Parameters which were not relevant for a particular policy do not have a coefficient estimate for that policy on that panel, additionally policies where disease elimination did not occur are also not shown as a coefficient could not be calculated. Mass Vaccination Coverage and Interval, Ring Vaccination Radius, and Vaccine Duration, are the parameters most consistently associated with an increase in the probability of disease elimination.

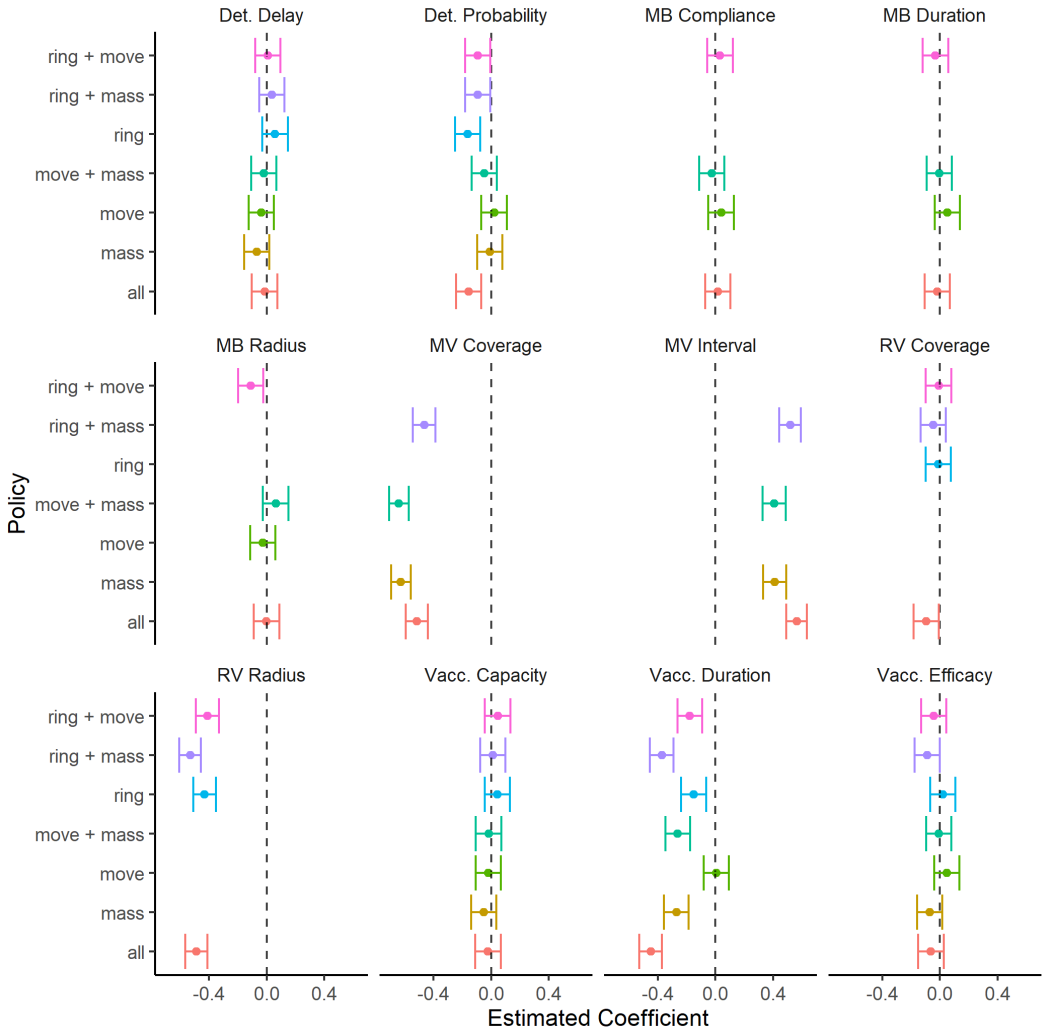

Figure 3.11: Estimated correlation coefficients of control policy parameters with the time to elimination, for each control policy combination. Each panel corresponds to correlation coefficient estimates for different parameters, each row in each panel a different control policy combination. Points indicate the point estimates, error bars denote the 95% confidence interval. A dotted line is shown at 0.0 for ease of interpretation. Parameters which were not relevant for a particular policy do not have a coefficient estimate for that policy on that panel, additionally policies where disease elimination did not occur are also not shown as a coefficient could not be calculated. Mass Vaccination Coverage and Interval, Ring Vaccination Radius, and Vaccine Duration, are the parameters most consistently associated with an decrease in the time to disease elimination.

3.4 Discussion

These results demonstrate that of the 3 control policies investigated, only 2 of them are observed to be effective in controlling the spread of FMD in a region where the disease is already endemic. Reactive ring vaccination is an effective method of controlling the spread of FMD in these simulations, as is proactive mass vaccination, however reactive movement bans within a radius of a detected infected premises do not appear to have any effect on the circulation of FMD when the disease is already endemic. This is observed even when the policy is combined with the other policies tested, MB policies do not lead to a greater reduction in incidence in combination with RV or MV policies in comparison to using those policies without movement bans. This ineffectiveness is also seen in the sensitivity analysis, where none of MB policy parameters were practically different from a correlation of 0, for all outputs assessed. The ineffectiveness of MB policies is surprising in light of their acknowledged effectiveness in controlling FMD epidemics (M. J. Tildesley et al. 2019), although their role in endemic regions is less clear. The potential importance of the movement of infected livestock to contribute to the spread of FMD is clear, yet at least one study has found that the movement of infected herds of cattle in Cameroon was not enough for the disease to persist as endemic in the area (A, N.J, and D.J 2011; Schnell 2019).

One possible reason for the failure of MB policies in these simulations is that the disease, already endemic, does not need to be spread to new areas of the simulated region as the disease is likely already present nearby and can spread via local transmission (e.g. aerosol transmission). In an epidemic outbreak in a country free of the disease, preventing the movement of animals between farms is part of an effort to prevent spread to new farms, in a region where the disease is already endemic this is more likely to be ineffective. However, this hypothesis is damaged by the fact that MB policies remain ineffective even when used with effective policies which greatly reduce the disease burden. This could also be tested by simulating epidemics with or without movement ban policies in effect and observing whether there is a difference in the epidemic trajectory, if it has an effect we would expect a slower growth of the epidemic.

Another possible reason for the failed MB policies is that the region, simulated for reasons of computational complexity, is too small for cattle shipments to play a large role in the spread of the disease. Animal movements present a risk not just of spread to presently-uninfected areas, but of long jumps to uninfected areas which are not at risk of aerosol spread due to the distance between them (M. J.

Tildesley et al. 2019). The median travel distance of shipments originating within Erzurum is 30.5 km, with a mean of 177.0 km, both larger than the median of 28.3 km and mean of 94.7 km for the entirety of Turkey. Erzurum itself is approximately 190 x 170 km, close to the mean distance of shipments originating in the province. If long distance jumps is the major role that animal movements play, yet the simulated region is too small for this effect to occur, then the role of movement bans in preventing the spread of disease may be underestimated. Simulating a larger region to see whether movement bans become more efficacious would be a reasonable extension of this work.

Ring vaccination is an effective reactive control policy, reducing the incidence of FMD by up to 86% as a stand-alone policy choice. A surprising result of this analysis was the small effect of the coverage of this policy, what percentage of farms within an infected premises radius were successfully vaccinated. By comparison, the radius of the policy was important in every analysis, with a larger policy leading to a greater reduction in incidence and a greater probability of disease elimination. It may be that there is a threshold effect, above which coverage is sufficient for a sharp drop in disease spread.

Mass vaccination was the most effective policy assessed, capable of reducing incidence up to 87% compared to no controls as a stand-alone policy, and up to 98% reduction in incidence when combined with ring vaccination. Because of this efficacy, the two parameters aligned with it (Interval and Coverage) are strongly correlated with the total incidence observed, as well as the probability of elimination and time to elimination. It is also the only policy assessed which could reliably eliminate the disease. This accords with the observed reality that elimination in both Europe and South America have depended on large mass vaccination campaigns, although such campaigns required decades of implementation before elimination could be declared (Leforban 1999; Parida 2009; David J. Paton, K. J. Sumption, and Charleston 2009). The discrepancy between real-world results and the model outputs are likely due to the much smaller area simulated and the lack of outside re-introductions of disease. The assumed perfect detection is less relevant for mass vaccination, which is a proactive policy.

Of the parameters that were not specific to individual control policies, the delay to detection was surprisingly little correlated with any of the three outputs, regardless of which control policy was in place. Although it is expected that this would not be relevant when implementing mass vaccination (which does not rely on detecting infected premises), it was expected that adding up to a 14 day delay to detection would severely reduce the efficacy of the reactive policies. However,

despite the small correlation coefficients, the overall pattern accords with the other results for total incidence. Detection delay is most correlated when RV policies are implemented stand-alone, and also when these are implemented in concert with MV policies. No correlation is seen with MB policies due to the ineffectiveness of those policies. For the probability of elimination and time to elimination, no correlation was found, likely due to such results depending heavily on MV policies.

Vaccine capacity was also uncorrelated for all control policies assessed. Vaccination capacity is most relevant when a lack of capacity prevents a needed vaccination of a farm, and all capacity values which are over this threshold are equally useful. It does not matter if capacity is 100 farms per day, or 500 farms, if you only ever need to vaccinate 50 farms at once. This threshold appears to be low. It is likely that the range of values assessed was too broad, with too many values above the threshold, for any correlation to be found.

The probability of detection exhibited strong negative correlations with total incidence whenever RV policies were implemented, but not when MB policies were. As a reactive policy, detecting infected premises is critically important to the efficacy of RV policies, but MB policies were not efficacious for other reasons.

Vaccine duration was strongly correlated with all three outputs. Although most FMD vaccines induce immunity that last approximately 6 months, it has long been recognised that a longer duration of vaccine-induced immunity could much reduce the difficulty of controlling the disease, and research efforts into different vaccine formulations is ongoing (Kamel, A. El-Sayed, and Castañeda Vazquez 2019; Singh et al. 2019). This sensitivity analysis calculates the sensitivity of the results to vaccine immunity duration controlling for other parameters, and demonstrates how important for control efforts it could be if vaccine duration could be extended.

Vaccine efficacy is also significantly negatively correlated with incidence, although it is less correlated with elimination. This accords with initial expectations, but is likely to be an underestimate of the correlation without range restriction (e.g. 0-100% efficacy rather than 50-100%). Although the range chosen was based off realistic expectations of the minimum VE required for a vaccine to be used in the field, it should not be forgotten that this minimum threshold is chosen because of the known effects of using an ineffective vaccine.

This work has demonstrated that MV in combination with RV policies are likely to be the most effective at reducing the circulation of FMD in regions already endemic for the disease. It has also demonstrated that MB policies are less likely to have a negative effect on circulation. However, a weakness of the work is the assumption of perfect detection of infected premises for the individual control pol-

icy combinations. The sensitivity analysis shows that the probability of detecting infected premises is an important variable for the effectiveness of RV policies, the assumption of perfect detection therefore likely overestimates for the efficacy of RV policies in a real-world setting.

An extension of this work would be to broaden the surveillance strategies simulated and compare their effect on optimal policies. This work has used passive surveillance, with infected premises being reported at some fixed probability (detection probability) and fixed delay (detection delay). A more sophisticated approach to the probability of detection might vary this probability and delay depending on local conditions, perhaps reporting is more likely when the disease is known to be in the area, or with a larger farm, although more research would have to be done to outline the form of this reporting function. Additionally, assessing proactive surveillance strategies used in reality, such as random proactive surveys of farms or monitoring sentinel farms, might also offer additional insights into the benefit of these in an already endemic situation (Caporale, Giovannini, and Zepeda 2012).

Another possibility for extension is the simulation and surveillance of strains of multiple serotypes, which are known to co-circulate in Turkey and many other areas. There is evidence that different strains of different serotypes can be more or less transmissible along different transmission routes (Pacheco, Lee, et al. 2016; Pacheco, Tucker, et al. 2012). Other work has found that different serotypes might induce different immunity profiles (Laura W Pomeroy et al. 2015). Does the optimal policy change, or do the most important parameters change, when there are more strains circulating? Similar questions could be asked with more detailed assumptions about the mechanisms of transmission which might contribute to the disease remaining endemic, such as fomite contamination of the environment, or the hypothesis of 'carrier' transmission.

In summary, ring vaccination and mass vaccination are the most effective control policies for regions where FMD is endemic, however reactive movement bans are not effective at all in our results despite being implemented in Turkey. Ring vaccination at a radius of 10 km, in combination with biannual mass vaccination, emerged as the clear optimal policy for reducing the circulation of disease and maximising the probability of elimination. When considering these policies, it was most important to maximise the radius of ring radius and mass vaccination coverage, and minimise the interval mass vaccination was implemented on. However, all of these conclusions must take into account the optimistic bias of the results seen because of the assumption of perfect detection of infected premises, perfect coverage in control policy implementation, and no outside re-introductions of disease. More research to

bound the effects of these assumptions on policy effectiveness should be undertaken.

Chapter 4

Carrier and Shipment mediated persistence of FMD

4.1 Introduction

FMDV is highly diverse, capable of infecting many different wild and domesticated species, with up to 7 immunologically distinct serotypes circulating globally and multiple lineages within those serotypes. Despite similarities in FMD clinical symptoms across species, the severity of those symptoms varies with species infected and the strain characteristics. This complexity makes efforts to control the disease difficult, however the picture may be further complicated by the phenomenon of persistent infection in ruminants, as the virus may remain cryptically present in otherwise symptom-free populations (Carolina Stenfeldt and Jonathan Arzt 2020).

Infection of ruminants with FMDV leads to several distinct phases of infection. Upon infection with FMDV, animals will enter a latent phase while the virus replicates within the host animal. At this point the animal is not infectious and no symptoms are exhibited. In cattle, approximately 1-2 days before symptoms are shown the animal will begin shedding infectious virus, becoming sub-clinically infectious (Yadav et al. 2019). The vast majority of naïve cattle exhibit clinical symptoms: most commonly lesions around the mouth, tongue and feet (for which the disease is named), but also fever, milk drop, and possible lameness, during which they are clinically infectious (Carolina Stenfeldt and Jonathan Arzt 2020). Approximately 10 days after the appearance of clinical symptoms, a proportion of the cattle will recover fully and generate protective immunity against the infecting strain. The remainder however, become persistently infected with no symptoms -

also referred to as as carrier animals. Cattle are generally acknowledged as carriers if live virus can be recovered from the Oro-pharyngeal Fluid (OPF) 28 days or more after infection, although recent efforts have been made to define this status based on a probability function of persistence instead (Bronsvoort et al. 2016). This period of sub-clinical infection can potentially last up to 3 years, although most evidence suggests around 6 months to 1 year is likely (Carolina Stenfeldt and Jonathan Arzt 2020; Tenzin et al. 2008). Experimental evidence suggests that close to 50% of cattle become carriers; although field studies generally find lower proportions, these studies are not typically undertaken at the time of infection and hence natural attrition of carrier animals should be taken into account (C. Stenfeldt et al. 2016; Carolina Stenfeldt and Jonathan Arzt 2020; Carolina Stenfeldt, Heegaard, et al. 2011; Paul Sutmoller, McVicar, and Cottral 1968). Vaccination does not prevent an animal from becoming a carrier (C. Stenfeldt et al. 2016).

Sheep, similar to other ruminant animals, may also become persistently infected with FMDV regardless of the occurrence of clinical disease (S. Alexandersen, Z. Zhang, et al. 2002; Carolina Stenfeldt, Pacheco, et al. 2020). Swine, despite experiencing severe clinical symptoms with most strains of FMDV, clear the virus within 4 weeks and do not appear capable of maintaining persistent FMDV infection; no live virus is recoverable from tissues 28-100 days post infection, though specific biological reasons for this are not known (Carolina Stenfeldt and Jonathan Arzt 2020).

Infectious persistently-infected cattle have been proposed as a mechanism supporting the persistence of the disease in areas where the disease is currently endemic (Jonathan Arzt et al. 2018; Condy et al. 1985; P. Moonen and Schrijver 2000; Tenzin et al. 2008). Infectious carrier animals would act as a disease reservoir, allowing reinfection of the population once immunity from prior waves of infection has waned. It is, however, unclear whether persistently-infected cattle are capable of transmitting infectious virus to other susceptible animals (Soren Alexandersen, Zhidong Zhang, and Alex I. Donaldson 2002; Carolina Stenfeldt and Jonathan Arzt 2020). Outbreaks in Zimbabwe in 1989 and 1991 were blamed on initial carrier transmission events, however the situation was unclear (Soren Alexandersen, Zhidong Zhang, and Alex I. Donaldson 2002). More recently, research has demonstrated that the virus taken from the OPF can be infectious (Jonathan Arzt et al. 2018). A summary of the research by Tenzin et al. (2008) noted that after calculating a rate of transmission following a synthesis of multiple studies, transmission from carriers could still not be entirely ruled out. The possibility of carrier animals triggering a new outbreak after a contained outbreak is one of the reasons why the OIE

mandated trade ban lasts for 6 months if a vaccinate-to-live policy (retaining vaccinated animals after the end of the epidemic) is used rather than the 3 months for a vaccinate-to-kill policy (culling vaccinated animals after the outbreak), as vaccination does not prevent sub-clinical infection. However, multiple experimental studies housing susceptible cattle with carrier animals have failed to find evidence of transmission or viral shedding from carrier cattle, and it has never been observed in the field (Soren Alexandersen, Zhidong Zhang, and Alex I. Donaldson 2002; Moonen et al. 2004; Tenzin et al. 2008). Additionally, recent field experiments observing animals in Vietnam and India observed no transmission from carriers (Bertram, Vu, et al. 2018; Bertram, Yadav, et al. 2020; Hayer et al. 2018). If "carrier" animals are capable of infecting naive animals, it is clear that the per-capita probability of such an event must be very low.

An alternate explanations for the persistence of FMD in endemic areas involves the movement of infected animals into proximity with herds containing susceptible animals. After an initial wave of infection in an area, the local population of susceptible animals replenishes after an outbreak via births, movements, or waning immunity. The time delays between spatially separated outbreaks in a large area can, therefore, allow the infection to persist in the larger region as there is always a sub-region where a proportion of the population immunity has waned to act as new hosts for the disease. The movement of infectious animals, by livestock shipments or transhumance, between these partially connected and newly susceptible populations therefore offers a clear mechanism for this to occur (A, N.J, and D.J 2011; Fèvre et al. 2006; M. Rweyemamu et al. 2008). Supporting this interpretation is the known effectiveness of movement bans in reducing the spread of the disease during ongoing outbreaks (M. J. Tildesley et al. 2019), although movement alone does not appear to be sufficient to maintain FMDV transmission in regions such as Cameroon (Kim et al. 2016).

A third explanation is fomite contamination of the environment. The shedding of infectious virus particles by infected animals is known to contaminate nearby surfaces, and the virus is known to be stable for a time in the environment. The survival time of the fomites are highly variable, explicitly depending on the surface it is on and local environmental conditions: the laboratory-investigated optimal survival conditions for FMDV are pH of 7-7.5, a temperature below $20°C$, and a relative humidity greater than 55%s (Mielke and Garabed 2020). In water, the median fomite survival time is 28.5 days (11 - 30 days); in biological fluids the median survival time is only 5 days (1 - 28+ days); in the air median survival was 3 days (1 - 5.5 days), yet survival analysis indicated that virus fomite survival could exceed 70% on day

150 if the surface was vegetation even when temperatures were 37°C (Mielke and Garabed 2020). Due to this dependence on environmental conditions, and a lack of available data on such conditions for our work, this hypothesis was not assessed in this work.

Identifying which drivers of continued transmission are relevant will aid in targeting data collection and policy recommendations. Mechanistic mathematical modelling can be a useful technique for exploratory analysis of the emergent dynamics of diseases, without the ethical considerations or expense of real-world animal experiments, and allowing the dynamics of the system to emerge from the known characteristics of the disease in question. Much work has been done modelling FMD in epidemic settings (Björnham, Sigg, and Burman 2020; Neil M. Ferguson, Donnelly, and Anderson 2001; Hayama et al. 2013; Kao 2002; M J Keeling et al. 2001; Schley, Simon Gubbins, and David J. Paton 2009; Michael J Tildesley, Rob Deardon, et al. 2008; Wada et al. 2017), however relatively few studies have looked at FMD in endemic settings (Kim et al. 2016; McLachlan et al. 2019; Laura W. Pomeroy et al. 2017; Ringa and Bauch 2014; Schnell 2019). Schnell (2019) used a farm level spatial stochastic model to investigate the hypotheses of carrier transmission and animal movements as drivers for endemicity in the Far North Region of Cameroon, although within-farm transmission was not included, and found that carrier animals were sufficient for maintenance of endemic FMD but that mobile pastoralism was not. Similar conclusions had been drawn by Kim et al. (2016) when they modelled pastoral herds in Cameroon (Kim et al. 2016). McLachlan et al. (2019) used a stochastic compartmental model to investigate individual herds, finding that outside introductions of disease were necessary for the maintenance of disease circulation regardless of the presence of carriers. The importance of carrier animals in endemic disease maintenance is not straightforward.

In this chapter we use the available detailed agricultural data from the Republic of Turkey ,and a modified version of the developed metapopulation model, to investigate and compare the plausibility of the carrier transmission and movement hypotheses of endemic FMD maintenance. We simulate combinations of relevant parameters, assuming one or the other hypotheses, and estimate the probability of persistence given those parameters. In addition, we use PRCC analysis to estimate the importance of different parameters to the probability of disease persistence.

Table 4.1: Summary of the regions modelled, approximate area in square kilometres, the number of farms modelled and the number of cattle. The value of these statistics with reduced farm densities is also provided to avoid duplication of effort, here density of farms is reduced to the specified percentage of original area, generated by randomly selecting farms with probability equal to the desired density, resulting in farm landscapes with the number of farms listed. Farm landscapes with densities < 100% are used later.

Region (Code)	**Area (km^2)**	**Density (%)**	**No. Farms**	**No. Cattle**
Eastern Region (ER)	120,305	100	5,170	2,048,283
		75	3,877	1,542,548
		50	2,585	1,023,206
		25	1,292	521,368
Intermediate 2 (I2)	81,537	100	4,014	1,838,563
		75	3,010	1,383,690
		50	2,007	904,877
		25	1,003	441,236
Intermediate 1 (I1)	42,083	100	2,109	922,808
		75	1,581	668,700
		50	1,054	423,767
		25	527	217,682
Erzurum Province (EZ)	25,066	100	1,108	605,177
		75	831	468,243
		50	554	298,569
		25	277	153,231

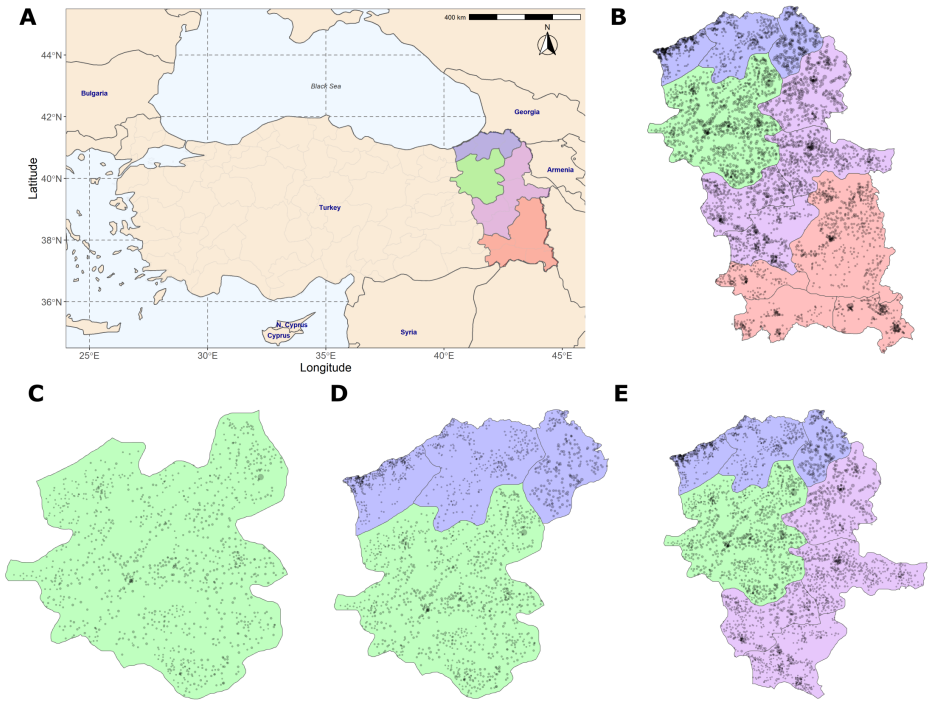

Figure 4.1: A: The regions of Turkey modelled, made up of sets of provinces. Four different areas were simulated, shown in different colours, relevant statistics for each of the regions being provided in Table 4.1. ER (red) contains I2, I2 (purple) contains I1, I1 (blue) contains EZ (green). **B:** The Eastern Region (ER), shown with farm locations as points. This region contains all of the others. **C:** Erzurum Province (EZ). **D:** Intermediate 1 (I1) region, containing Erzurum. **E:** Intermediate 2 (I2) region, containing the smaller I1 region.

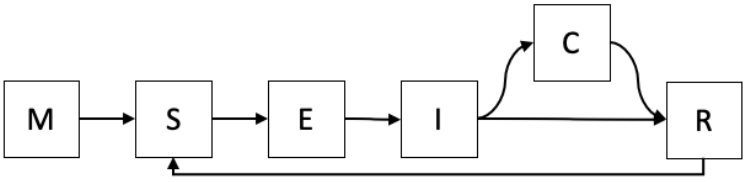

Figure 4.2: The basic disease compartments which animals in the model can be in. **(M)aternal**, **(S)usceptible**, **(E)xposed**, **(I)nfectious**, **(R)ecovered** and **(C)arrier**. Moving between these compartments is done at different rates, dependent on the population of each compartments as well as model inputs.

4.2 Methods

4.2.1 Data

In order to attain reasonable model running times and to explore the effect of changing the area under investigation, several geographical subsets of Turkey were used. These corresponded to those data in the thirteen easternmost provinces, split into nested regions. These regions were selected based on the express Turkish interest in the area, as well as the ability to split the overall region into relatively equal areas for the purposes of assessing the effect of area on persistence. The smallest region modelled was Erzurum Province (EZ); the next largest was Intermediate 1 Region (I1) which contained EZ and added Rize, Artvin and Ardahan. Intermediate 2 Region (I2) contained I1 and added Kars, Igdir, Agri, Mus and Bitlis. Finally, the largest region modelled contained I2 as well as Hakkari, Siirt, Sirnak, and Van, and was referred to as Eastern Region (ER). A map of these regions is shown in Figure 4.1, with the relevant statistics for each of them shown in Table 4.1.

4.2.2 Model

The metapopulation model developed in previous chapters, where each farm is considered a separate population and the within-farm and between-farm dynamics are modelled interdependently, is suitable for investigation of this with only minor changes. The structure of the model provides an advantage in modelling potential carrier transmission - any such transmission would almost certainly be constrained to those animals closest to the carrier, which can be realistically modelled by assuming carrier animals transmit in the within-farm model but do not effect the

between-farm dispersal kernel. Figure 4.2 demonstrates the modified compartmental model simulated within each farm, infectious animals now progress to either recover fully or become carrier animals, with those carrier animals eventually clearing the virus and naturally recovering themselves. The carrier compartment has 5 sub-compartments for a non-exponential distribution of carrier-periods. As control policies are not considered in this work, vaccine compartments are no longer included.

The modified compartments require modified ODEs to calculate the movement of animals between them, described in (4.1). The main changes are the addition of $\beta_C SC/N$ to the transmission term, representing the assumed transmission of carrier animals to susceptible animals, mediated by carrier-specific transmission parameter β_C. As described in Table 4.2, this is the carrier specific transmission parameter, where β_I is the transmission parameter for acutely infectious animals. In all values of β_C investigated, $\beta_I >> \beta_C$. λ_C is also added as the waning parameter for the carrier state, with λ_R now indicating the waning parameter for the recovered compartment in order to distinguish it. The other modification is the addition of k_C as a parameter, which decides the proportion of acutely infectious animals who will become carriers or recover naturally. k_C proportion will become carriers, $1-k_C$ proportion will recover naturally. As might be expected, setting $k_C = 0$ removes carrier animals from consideration by the model.

Livestock shipments in this model are simulated on a daily basis by replaying the animal movement data provided by the Republic of Turkey. Transmission via cattle shipments occurs in two ways, direct shipment of infected animals to the destination farm, or indirect transmission via fomite contamination of the vehicle, driver, or surroundings. Shipments are simulated as a random sample of cattle without replacement from the source farm, hence the probability of selecting at least one infected animal for shipment (and therefore direct transmission) is proportional to the shipment size and number of infected animals on the farm. In this model, indirect fomite transmission can also occur when the source farm is infected, and is included in the model as a simple probability that fomite transmission occurs given that the source farm is infected.

As before, at the beginning of the model timeline it is assumed that all animals are in the susceptible compartment. Although there is no effect from either carrier transmission or contaminated shipments on the dispersal kernel, the equation for this is included again for convenience ((4.2)), and the parameters are included in the parameter description table 4.2. The parameters used for the kernel are not the values identified in the model fitting work, as that work had not yet finished

when this work was undertaken. However, the kernel parameters are very similar, with this kernel providing slightly more probability to long range transmission and less to short range transmission than the kernel parameters fitted in Chapter 2. The sensitivity of the results to these parameters is investigated further on.

$$\begin{aligned}
\frac{dM}{dt} &= \alpha N \frac{R}{(N-M)} - \mu M - \Omega_n M, \\
\frac{dS}{dt} &= \alpha N (1 - \frac{R}{(N-M)}) + \mu M + \lambda_R R - \frac{\beta_I SI + \beta_C SC}{N} - \Omega_n S, \\
\frac{dE}{dt} &= \frac{\beta_I SI + \beta_C SC}{N} - \sigma E - \Omega_n E - \Omega_d E, \\
\frac{dI}{dt} &= \sigma E - \gamma I - \Omega_n I - \Omega_d I, \\
\frac{dR}{dt} &= (1 - k_C)\gamma I + \lambda_C C - \lambda_R R - \Omega_n R, \\
\frac{dC}{dt} &= k_C \gamma I - \lambda_C C - \Omega_n C.
\end{aligned} \tag{4.1}$$

$$\begin{aligned}
P(ls) &= 1 - e^{-TN_i^{inf} SN_j^{sus} K(d_{ij})}, \\
K(d_{ij}) &= \frac{1}{1 + (\frac{d}{scale})^{shape}}.
\end{aligned} \tag{4.2}$$

4.2.3 Design

Investigating Carriers

The model was simulated using different sets of parameters to investigate each hypothesis. The initial work on simulating carrier transmission is referred to as **carrier-1** as a shorthand, and the parameters shown in Table 4.3. Several parameters were investigated. The effect of farm populations as a modifier for the probability of persistence was assessed by multiplying farm populations by some constant, the population multiple parameter in Table 4.3. Likewise for shipments and k_C, which were included as a parameter as a null test to allow the effect to be isolated as due to the introduction of carrier transmission to the model. λ_R, λ_C, and β_C rounded out the parameter list, with β_C beginning at 2.67e-3 as a highest estimate from Tenzin et al. (2008).

For each combination of the parameter values outlined in Table 4.3, the model simulated a 5-year period (2007-2012) one hundred times. 5 years was chosen as the maximum time-period for which full data was available, and for which it could be

Table 4.2: Relevant parameters of the carrier ODEs and dispersal kernel, with their value(s) and sources.

Parameter	Description	Value(s)	Source(s)
α	Per-capita birth rate	2%/year	
β_I	Acutely infectious transmission rate	$\frac{6}{11}$	(Orsel, Dekker, et al. 2005; Orsel, Jong, et al. 2007; Tadesse et al. 2019)
β_C	Carrier transmission rate	variable	(Bertram, Vu, et al. 2018; Parthiban et al. 2015; Tenzin et al. 2008)
γ	Recovery rate	$\frac{1}{11}$ days	(Yadav et al. 2019)
λ_R	Average duration of recovered state	variable	(T. R. Doel 2005; E. El-Sayed et al. 2012)
λ_C	Average duration of carrier state	variable	(Bertram, Vu, et al. 2018; Tenzin et al. 2008)
μ	Maternal immunity waning rate	120 days	(Nicholls, Black, and M. M. Rweyemamu 1984)
σ	Symptomatic rate	$\frac{1}{1.5}$ days	(Yadav et al. 2019)
Ω_d	Infection mortality rate	2%	(Şentürk and Yalçin 2008)
Ω_n	Per-capita natural mortality rate	2%/year	
k_C	Proportion who become carriers	50%	(C. Stenfeldt et al. 2016; Carolina Stenfeldt and Jonathan Arzt 2020; Carolina Stenfeldt, Heegaard, et al. 2011; Paul Sutmoller, McVicar, and Cottral 1968)
T	Kernel per-capita transmission rate	6.806e-6	(M J Keeling et al. 2001; Michael J Tildesley, Savill, et al. 2006)
S	Kernel per-capita susceptibility rate	1.0	
scale	Kernel scale	1	(Jewell, M. J. Keeling, and Roberts 2009)
shape	Kernel shape	2	(Jewell, M. J. Keeling, and Roberts 2009)

Table 4.3: The parameter values investigated for carrier-mediated persistence, **carrier-1**. The combination of all of these values were simulated.

Parameter	Value Set
Population Multiple	x1, x2, x4
Shipments	simulated, not simulated
λ_R	365, 730, 1095, 1460 (days)
k_C	0.0, 0.5
λ_C	180, 540, 900, 1260 (days)
β_C	2.67e-3, 1.33e-3, 6.67e-4, 3.33e-4, 1.67e-4, 8.33e-5, 4.17e-5

Table 4.4: The parameter values investigated for carrier-mediated persistence, **carrier-2**. β_C was halved until all parameter sets no longer exhibited persistence. The combination of all of these values were simulated. Population Multiple, Shipments, and k_C were no longer varied due to the results of **carrier-1**.

Parameter	Value Set
Population Multiple	x1
Shipments	not simulated
λ_R	365, 730, 1095, 1460 (days)
k_C	0.5
λ_C	180, 540, 900, 1260 (days)
β_C	4.17e-5, 2.08e-5, 1.04e-5, 5.21e-6, 2.61e-6, 1.30e-6, 6.51e-7, 3.26e-7, 1.63e-7, 8.14e-8, 4.07e-8, 2.03e-8, 1.02e-8, 5.09e-9, 2.54e-9, 1.27e-9, 6.36e-10, 3.19e-10, 1.59e-10, 7.95e-11

reasonably assumed that disease persistence indicated endemicity. The proportion of these simulations where FMD was still present at the end of the year was assumed to approximate the probability of persistence given those parameters.

Subsequent to the simulation of the **carrier-1** parameters, and as an extension to it, the values of β_C investigated were extended by repeatedly dividing by 2 until all parameter sets no longer exhibited persistence, extending down to 7.951400e-11, these values are outlined in Table 4.4. For ease of reference this parameter set is referred to as **carrier-2**. Values of β_C below 4.17e-5 were investigated with the population multiple set to "x1", k_C at 0.5, and no shipments modelled due to the results obtained for **carrier-1**. λ_R and λ_C were investigated using the same values used in Table 4.3.

For both **carrier-1** and **carrier-2** parameter set, the probability of fomite transmission was 0.

To explore uncertainty in the dispersal kernel parameterisation, the **carrier-2** parameter set was re-simulated whilst independently increasing and decreasing

kernel parameters *shape*, *scale*, and T. Kernel *shape* was increased from 2 to 2.5 and 3.0. Kernel *scale* was halved to 0.5, and doubled to 2.0. T was halved to 4.301e-6, and doubled to 1.720e-5.

Additionally, to explore how the distribution of assumed transmission over time affects the results obtained, I simulated the **carrier-2** parameter set again with a linearly declining distribution of transmission. Instead of assuming a homogeneous distribution of carrier transmission over time, each sub-compartment had transmission equal to $\beta_c^i = \beta_C(1 + n_s - i)/\sum_{n=1}^{n_s} i$, where β_c^i is the transmission rate of the specific carrier, sub-compartment n_s is the number of sub-compartments, and i is the sub-compartment index. This meant that newly infected carrier animals were most infectious, with infectiousness declining linearly as the animals proceeded through the compartment.

Investigating Shipments & Fomites

Similar to carrier transmission, the ability of shipments to allow for FMD to persist over the 5 year period was investigated by simulating the model 100 times with every combination of the parameter values outlined in Table 4.5. Transmission via shipments is simulated in two ways: (i) by the movement of infected animals; (ii) by a probability of transmission if the source farm is infected, independent of whether the shipment is moving infected animals and representing assume fomite contamination of the vehicle. The parameters once again included a no-shipments null test. Simulating a smaller and larger area (Erzurum and Eastern Region) allows for the impact of a larger area for livestock shipments to spread in. Long range shipments also investigates this possibility that it is the long range possibility of livestock movements that present the most threat. The probability of fomite transmission represents the probability that a shipment from an infected source farm would transmit infection via fomites to a susceptible destination farm. No carriers were modelled ($k_C = 0.0$) for all of these parameter combinations.

Long Range (LR) shipments were defined as those shipments where the distance traversed was over 40 km (25 miles). This was chosen as the distance where a completely infected farm of median size (141 cattle) would have a 0.01 probability of infecting a completely susceptible farm of median size via local spread, given the power law dispersal kernel uses values $a = 1, scale = 1, shape = 2$. For EZ, excluding LR shipments reduced the number of records from 336,522 to 207,589 (-38.3%); for ER it reduced the number of records from 2,291,913 to 1,043,478 (-54.5%). The parameter sets outlined in Table 4.5 are referred to as **shipment-1**.

To disentangle the effect of the area modelled from the (correlated) number

Table 4.5: The parameter values which were investigated for shipment-mediated persistence, **shipment-1**. For all model simulations run with these parameters, $k_C = 0.0$ (i.e. there were no carrier simulated).

Parameter	Values
Shipments	simulated, not simulated
Area Modelled	EZ, ER
Probability of Fomite Transmission	0.0, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Long Range Shipments	simulated , not simulated
λ_R	365, 730, 1095, 1460 days

Table 4.6: The parameter values which were investigated for shipment-mediated persistence, **shipment-2**. For all model simulations runs with these parameters, $k_C = 0.0$ (i.e. there were no carriers simulated), and long range shipments simulated. Each combination of these parameters was simulated. Area Farm Density refers to the percentage of farms randomly selected from each area to be included in the simulation.

Parameter	Values
Shipments	simulated
Area Modelled	EZ, I1, I2, ER
Area Farm Density	25, 50, 75, 100 (%)
Probability of Fomite Transmission	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Long Range Shipments	simulated
λ_R	365, 730, 1095, 1460 days

of farms modelled on the probability of persistence, the area was split into four areas as previously defined (ER, I2, I1, EZ), and simulated with either 25%, 50%, 75% and 100% of the farms in that area included. Farms were selected randomly with probability equal to 25/50/75/100%, and a set of farms were only accepted if their convex hull area was within 1% of the actual approximate area covered by the 100% set of farms. For each parameter set with density < 100%, 4 replicates were taken and simulated to mitigate the effect of randomly missing possibly important nodes in the shipment network. Each combination of area and density was simulated for 5 years, and persistence assessed as previously and averaged for the replicated. The probability of persistence was assessed as normal. These parameter sets were referred to as **shipment-2** and are shown in Table 4.6.

Analysis

Analysis was done in *R 4.0.2* (R Core Team 2020). PRCC analysis was done using the package *epiR 2.0.19* (Mark Stevenson et al. 2021). Plots were done using *ggplot2 3.3.3* (Wickham 2016).

4.3 Results

4.3.1 Carrier-mediated persistence

Simulating the model with the combinations of parameters found in Table 4.3, it was found that combinations of parameters with infectious carriers could lead to the persistence of FMD in the population over the 5 year period simulated. This was true with values of β_C (carrier transmission) several orders of magnitude smaller than estimated by Tenzin *et al* in 2008.

In the **carrier-1** parameter set, β_C took the values on the furthest right in Figure 4.3, extending from 2.67e-3 down to 4.17e-5, whereas **carrier-2** included values down to 7.95e-11. As shown in Figure 4.4, no association of carrier transmission with persistence was found for the values of β_c investigated in the **carrier-1** parameter set, likely due to the restricted range of values assessed. Figure 4.3 highlights the range of these values in grey, it is clear that almost all of the values assessed in this parameter set resulted in persistence being a certainty for most parameters. λ_C and λ_R are significantly positively and negatively correlated respectively.

However, when the value of β_C is extended in the **carrier-2** parameter set, a clear relationship between β_C and the probability of persistence is visible. Additionally a pattern is visible in the relationship between λ_C, λ_R, and the probability

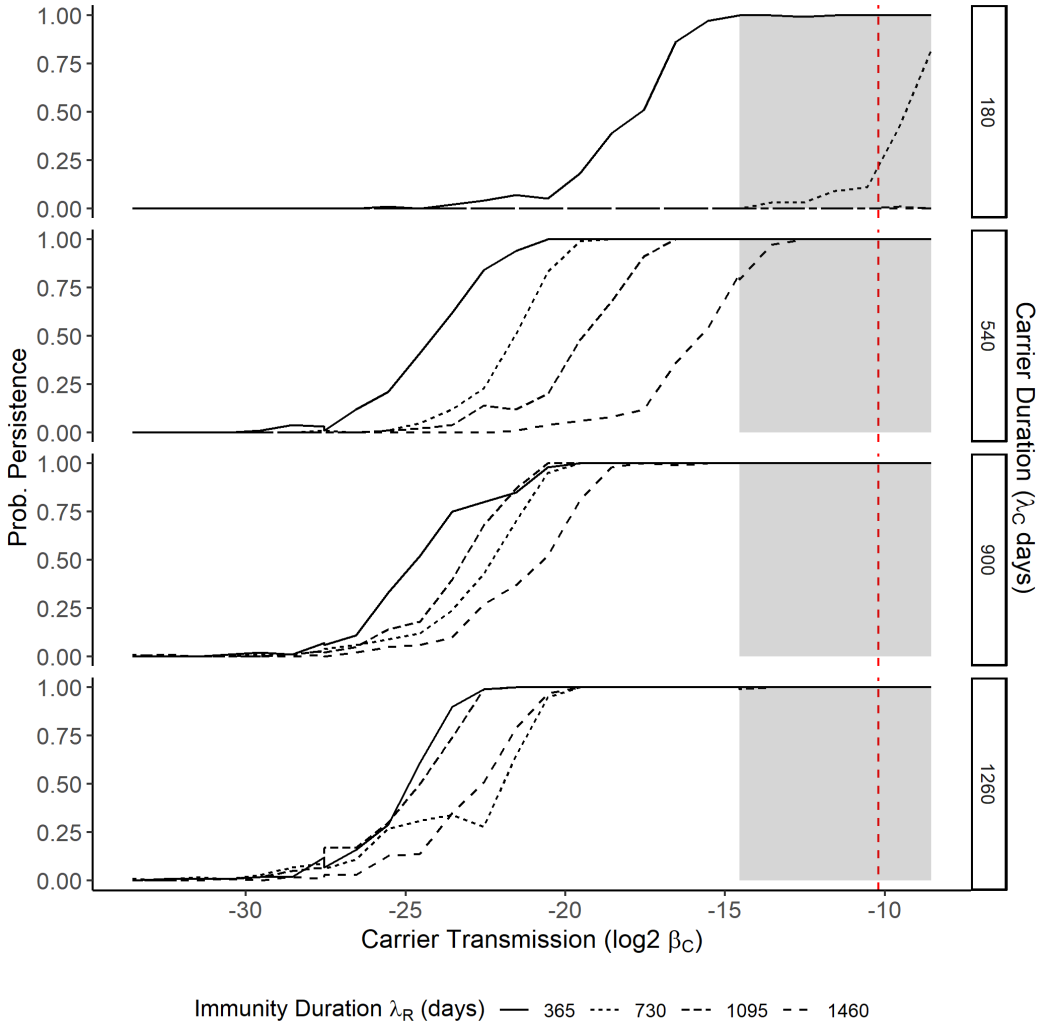

Figure 4.3: The observed relationship between the probability of persistence and carrier transmission for four different values of carrier duration (indicated on the right). Each type of line represents a given immunity duration (λ_R). The red vertical line indicates the estimated carrier transmission value by Tenzin et al 2008. The values explored in carrier-1 lie in the grey area to the right. For any given value of immunity duration (λ_R), an increase the duration of the carrier state (λ_C) increases the probability of persistence. For any given duration of the carrier state (λ_C), an increase in the duration of immunity decreases the probability of persistence.

of persistence in Figures 4.3 and 4.4. Population and the presence/absence of shipments remain uncorrelated with persistence. λ_R is weakly negatively correlated with persistence, a longer duration of immunity decreases the probability of persistence. β_C and λ_C are moderately positively correlated with persistence.

After performing PRCC analysis on the **carrier-1** results data, it was found that the parameter most strongly associated with changes to the probability of persistence is the presence or absence of carriers in the population (k_C), shown in Figure 4.4. Significantly associated but weakly correlated are λ_R (immunity duration) and λ_C (carrier duration). Figure 4.5 shows the average prevalence over the 5 year period in those simulations where persistence was observed, and 4.6 shows the same in those simulations where no persistence was observed. These are organised by λ_R and λ_C, and demonstrate the relatively minor effects these parameters have on the probability of persistence.

No significant association was found between the probability of persistence and population size, the presence/absence of shipments, or β_C. These results remain when restricting analysis to parameter sets where $k_C = 0.5$.

Whereas β_C is not significantly associated with persistence in the **carrier-1** parameter set, a clear and strong correlation between β_C and the probability of persistence is visible after analysis of the extended **carrier-2** parameter set, shown in Figure 4.3. Additionally a pattern is visible in the relationship between λ_C, which is strongly positively correlated with persistence, and λ_R, which is weakly to moderately negatively correlated with persistence. These patterns are visible in Figure 4.3, where after holding λ_C constant, a longer duration of immunity decreases the probability of persistence. Population and the presence/absence of shipments remain uncorrelated with the probability of persistence.

When $\lambda_C = \frac{1}{180}$, the probability of persistence is 0 at values of $\beta_C \lessapprox 2e-08$. When $\lambda_C = \frac{1}{540}, \frac{1}{900}$, or $\frac{1}{1260}$, the probability of persistence is close to 0 at values of $\beta_C \lessapprox 6e-10$.

4.3.2 Shipment-mediated persistence

Investigating scenarios where shipments can spread disease, and fomite transmission is simulated, we see that no persistence appears to be possible when the probability of fomite transmission is 0.0, whether simulating the smaller Erzurum Province (EZ) or simulating the Eastern Region (ER). The minimum probability of fomite transmission where persistence is observed is 0.2 for Erzurum Province, the minimum is 0.05 for the Eastern Region (Figure 4.7).

For the **shipment-1** parameter set, Figure 4.7 demonstrates clearly the re-

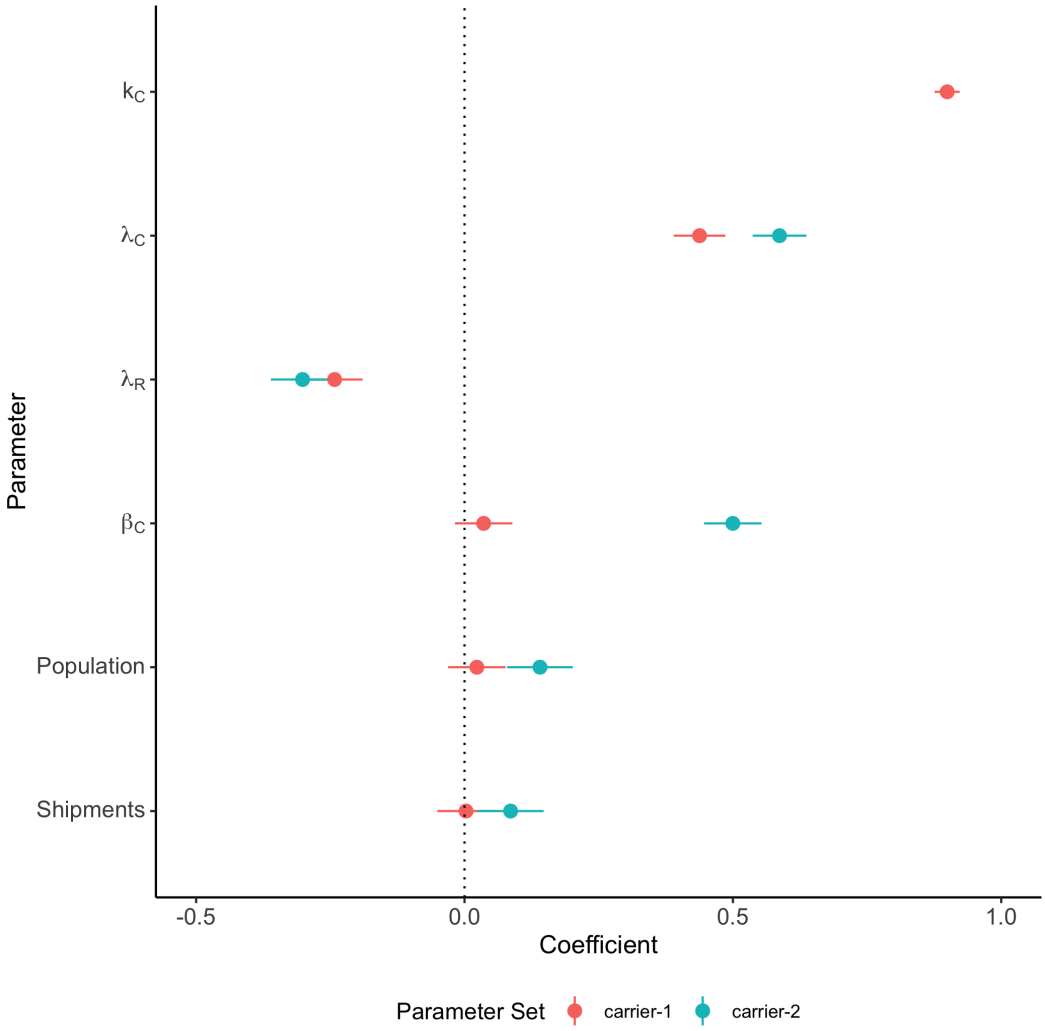

Figure 4.4: PRCC coefficients for **carrier-1** and **carrier-2** parameter sets, with error bars indicating 95% CI. k_C is strongly positively correlated with the probability of persistence in **carrier-1**. β_C is now moderately positively correlated with the probability of persistence.

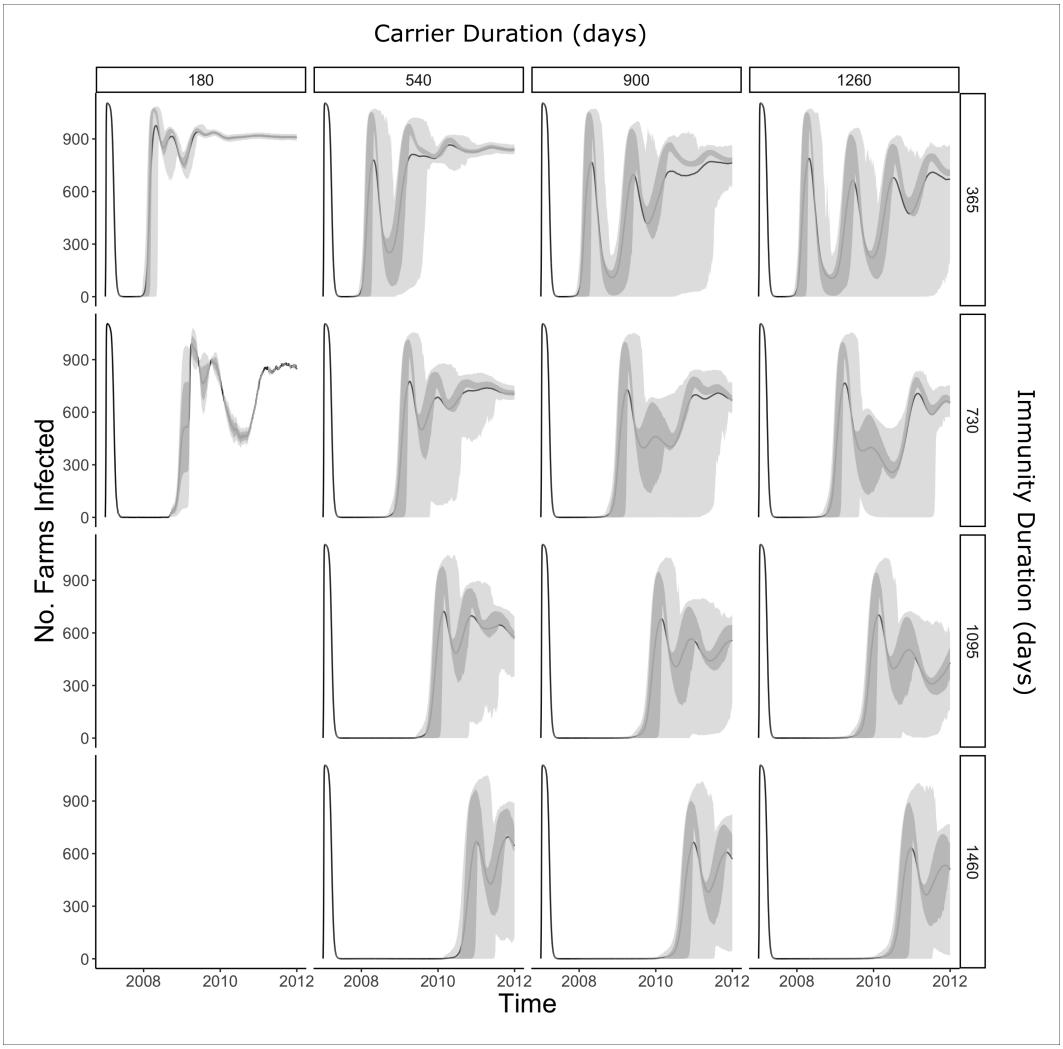

Figure 4.5: Simulated prevalence of FMD over time in simulations where the disease **does** persist over the 5 year period, organized by carrier (columns) and immunity (rows) duration, taken from the **carrier-1** and **carrier-2** results. Carrier duration and immunity duration were used as two of the most important parameters to illustrate the trends. Prevalence is defined as the number of farms where at least one animal is acutely infected. The black line indicates the average prevalence for simulations at that time point, the grey area is the IQR, and the light grey indicates the 5-95% range of results at that time-point. Blank plots indicate combinations of carrier and immunity duration where no simulation exhibited persistence. Where persistence occurred, there is a large gap between the initial outbreak before the carrier animals re-seed the outbreak and it proceeds towards endemicity.

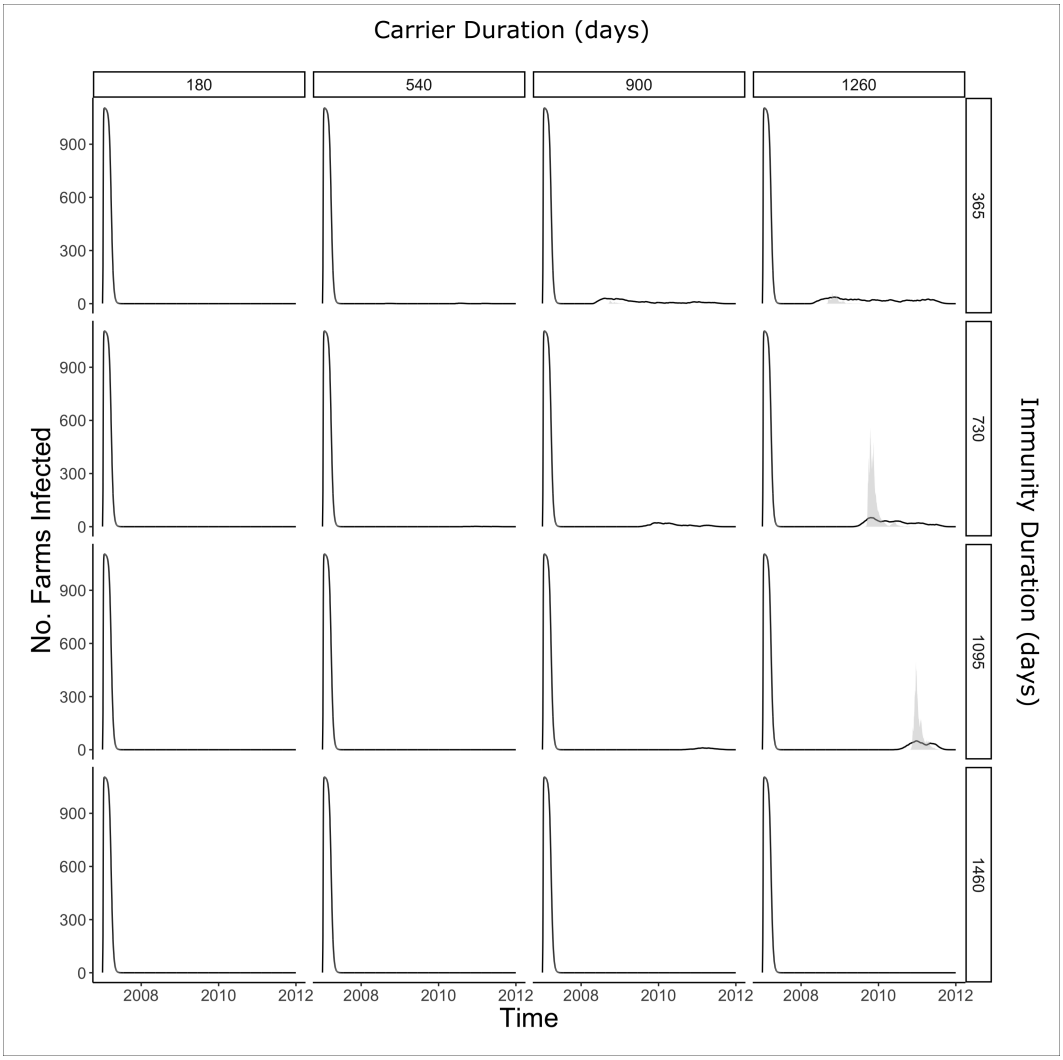

Figure 4.6: Simulated prevalence of FMD over time in simulations where the disease **does not** persist over the 5 year period, organized by carrier (columns) and immunity (rows) duration, taken from the **carrier-1** and **carrier-2** results. Carrier duration and immunity duration were used as two of the most important parameters to illustrate the trends. Prevalence is defined as the number of farms where at least one animal is acutely infected. The black line indicates the average prevalence for simulations at that time point, the grey area is the IQR, and the light grey indicates the 5-95% range of results at that time-point. Blank plots indicate combinations of carrier and immunity duration where no simulation exhibited persistence. In these cases, after the initial outbreak burned itself out, there was often no revival of the disease. With some combinations of parameters there was occasionally a small outbreak following the decline in immunity, but this did not last to the end of the 5 year period.

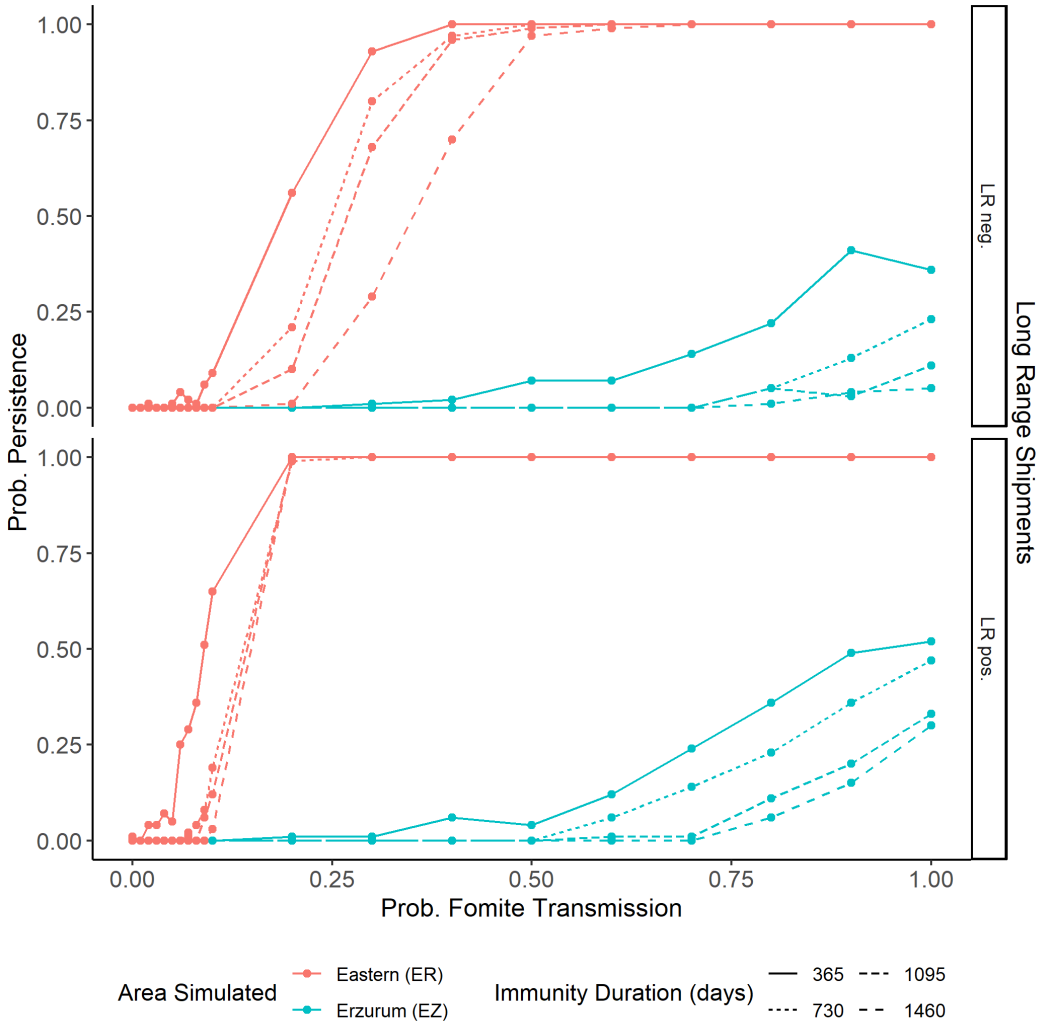

Figure 4.7: The observed relationship between the probability of fomite transmission and the probability of persistence for **shipment-1**. The top half of the plot contains results when no long range shipments were simulated, the bottom half when long range shipments were simulated. Each linetype indicates a different duration of immunity (λ_R), and each colour the area being simulated. As the probability of fomite transmission increases, the probability of persistence also increases. Erzurum Province (EZ) requires much a higher probability of fomite transmission for persistence than Eastern Region (ER), as it has both a smaller area and fewer farms. Within each area, increasing immune duration increased the probability of fomite transmission required for persistence by a small amount. There is little difference whether long range shipments are simulated or not.

lationship between the probability of fomite transmission and persistence, with the persistence curve seen depending in large part on the area simulated. For the Eastern Region (ER), persistence is very likely at low probabilities of fomite transmission, reaching 1 at probabilities of approximately 0.2-0.3 depending on λ_R. For Erzurum Province there is a large difference, with persistence rare until the probability of fomite transmission of approximately 0.4 - 0.5, again varying with λ_R. Removing long range shipments results in a small reduction in the probability of persistence, as does assuming a longer duration of immunity.

PRCC analysis of this **shipment-1** parameter set suggests that the area simulated and the probability of fomite transmission are significantly and strongly positively associated with the persistence measure when shipments are simulated, as shown in Figure 4.9. The presence of long-range movements is weakly correlated with persistence, and the duration of immunity (λ_R) is weakly negatively correlated with persistence.

The **shipment-2** parameter set attempts to disentangle the effect of a larger simulated area from simulating a larger number of farms. Figure 4.8 outlines the relationship between the probability of fomite transmission and persistence. An increasing number of farms simulated leads to a greater probability of persistence *ceteris paribus*, independent of the area simulated. This can be seen in the first two mini-plots of Figure 4.8: the two plots have similar persistence curves despite the second simulating an area almost 5 times larger.

PRCC analysis on the results of the **shipment-2** parameter sets (including the 4-region simulations ER, I2, I1, EZ) revealed a strong positive correlation with the number of farms simulated, in addition to a moderate-to-strong positive correlation with the probability of fomite transmission (Figure 4.9. No correlation between the area simulated and the probability of persistence was observed.

4.3.3 Sensitivity

The results obtained appear to be generally robust against large variations in the parameters of the dispersal kernel. Doubling or halving the per-capita transmission (T) parameter increases or decreases the observed probability of persistence *ceteris paribus*, but not to the extent that low rates of carrier transmission no longer support persistence (Figure 4.12).

The same pattern is seen with the kernel *scale* parameter, seen in Figure 4.11, and the *shape* parameter shown in Figure 4.10. For *scale*, doubling this value to 2.0 leads to very similar probabilities of persistence as when it is not doubled. Halving it to 0.5 results in a slight decrease in the probability of persistence, but

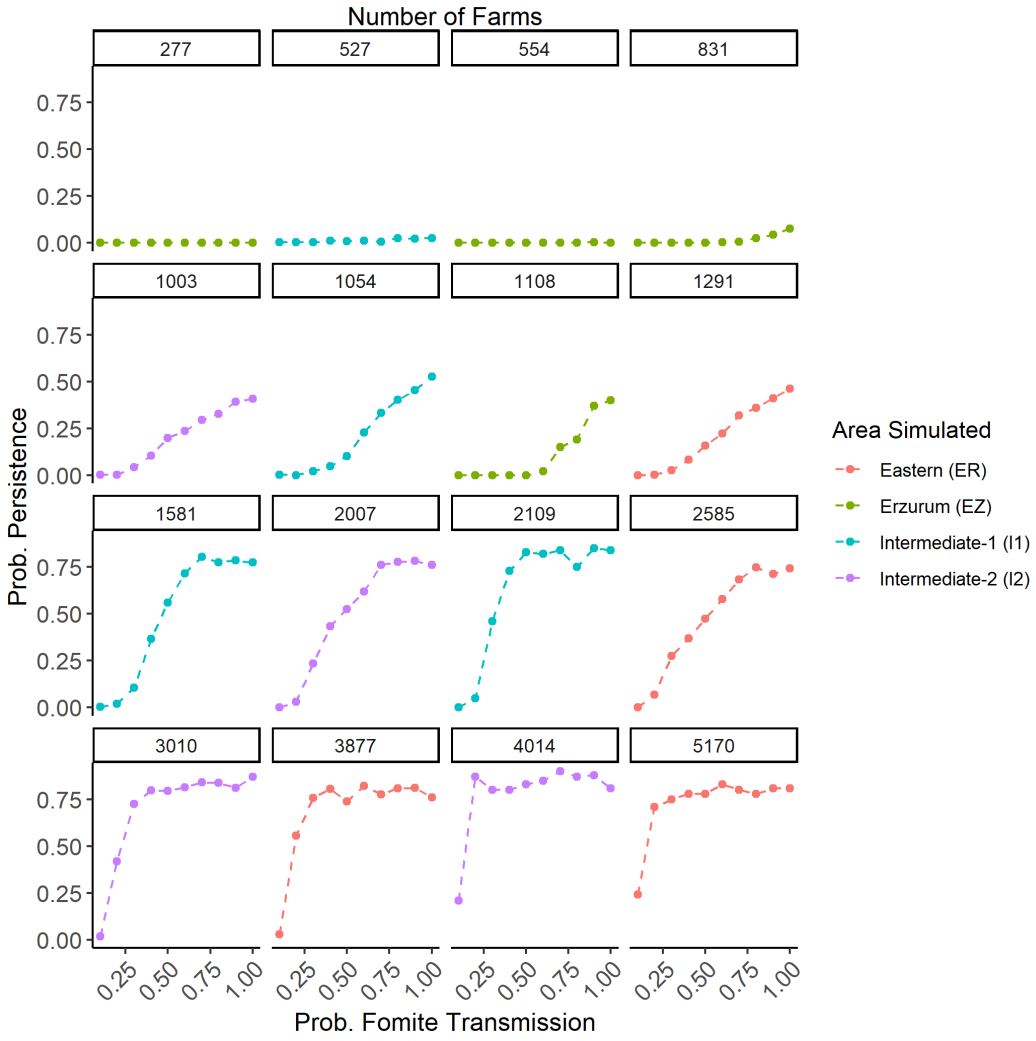

Figure 4.8: The observed relationship between the probability of fomite transmission and the probability of persistence for **shipment-2**. Each mini-plot indicates the number of farms simulated for these results above it, and the point type indicates the region simulated. Simulating a greater number of farms leads to a greater probability of persistence for a given probability of fomite transmission, with the actual area (km^2) simulated being less important. Persistence curves are most similar to each other when the number of farms simulated is similar, with the different areas (colour) not clustering together in the same manner.

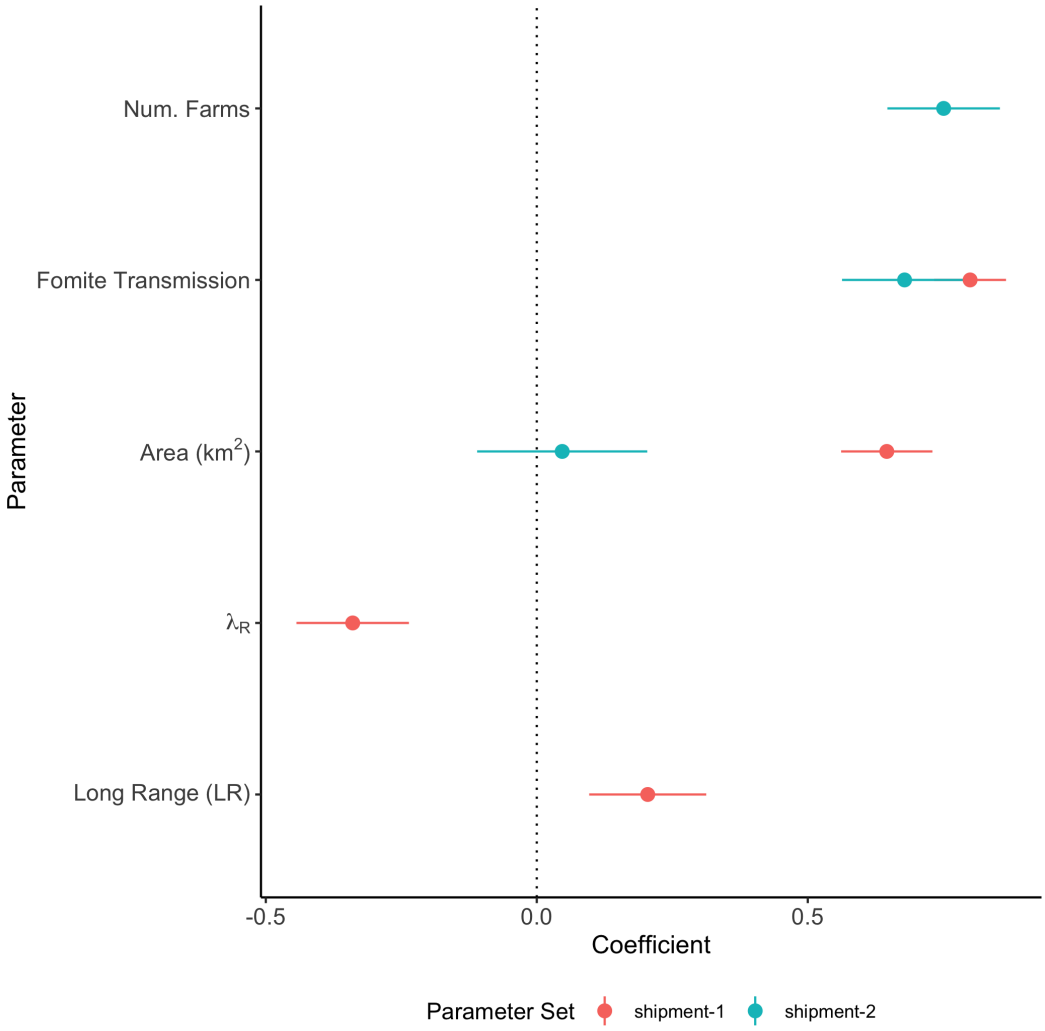

Figure 4.9: The PRCC coefficients for the shipment parameter sets, with error bars indicating the 95% confidence intervals. The colour of the bars indicates the coefficients seen in **shipment-1** or **shipment-2**.

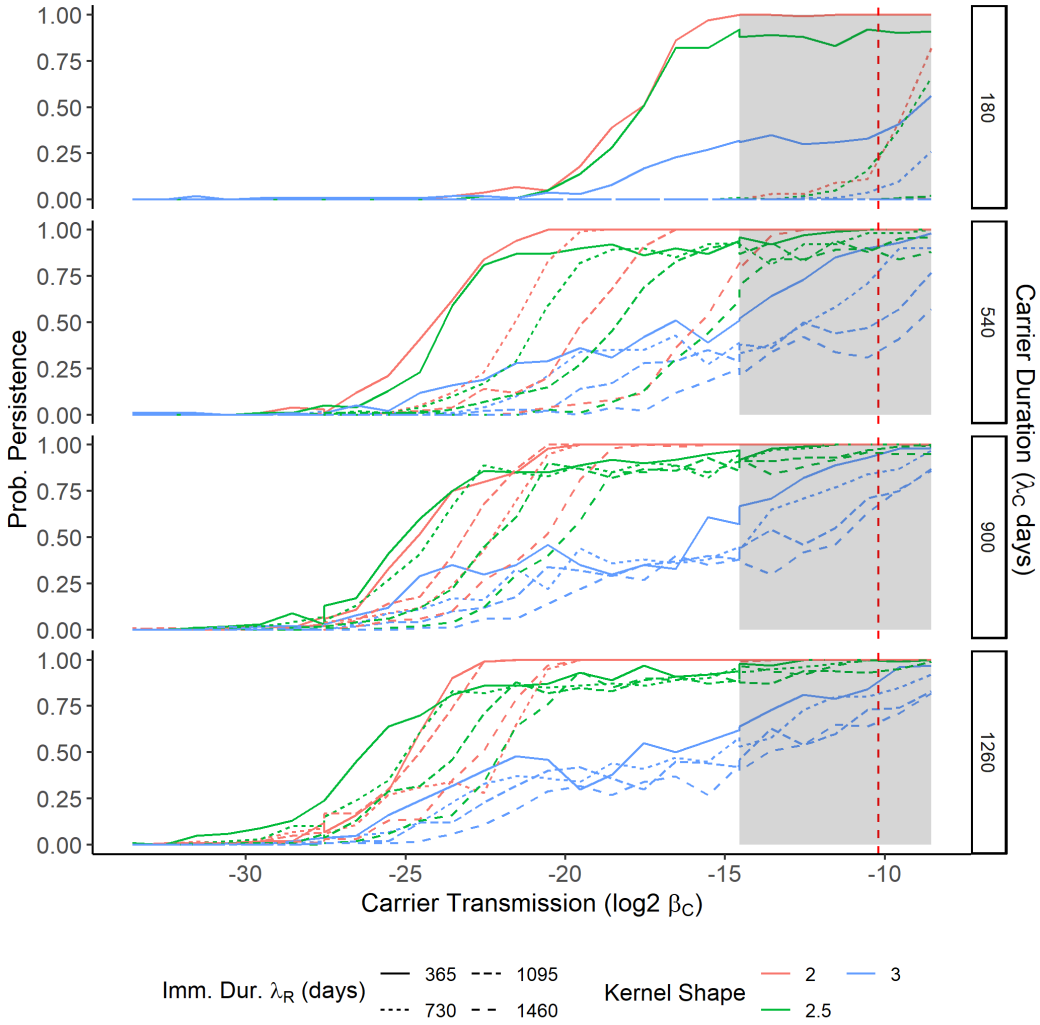

Figure 4.10: The observed relationship between the probability of persistence and carrier transmission for four different values of carrier duration (indicated on the right). Each type of line represents a given immunity duration (λ_R). Each colour line indicates a different value of the kernel shape parameter, with red lines referring to the original value of 2.0. The red vertical line indicates the estimated carrier transmission value by Tenzin et al 2008. The values explored in carrier-1 lie in the grey area to the right. For any given value of immunity duration (λ_R), an increase the duration of the carrier state increases the probability of persistence. For any given duration of the carrier state (λ_C), an increase in the duration of immunity decreases the probability of persistence. Increasing the shape parameter leads to persistence becoming less probable as transmission becomes more local. However, the same overall pattern is still seen with any value of the transmission parameter.

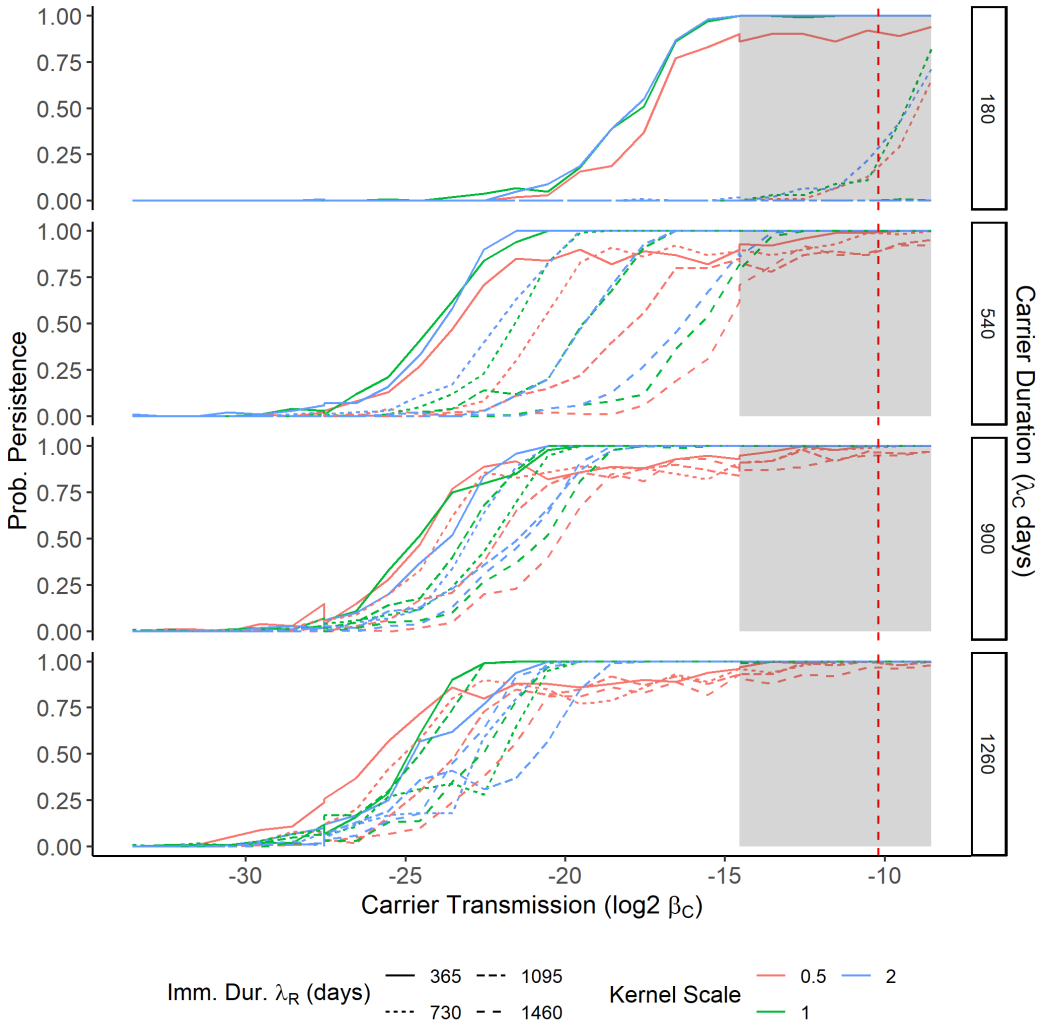

Figure 4.11: The observed relationship between the probability of persistence and carrier transmission for four different values of carrier duration (indicated on the right). Each type of line represents a given immunity duration (λ_R). Each colour line indicates a different value of the kernel scale parameter, with green lines referring to the original value of 1.0. The red vertical line indicates the estimated carrier transmission value by Tenzin et al 2008. The values explored in carrier-1 lie in the grey area to the right. For any given value of immunity duration (λ_R), an increase the duration of the carrier state increases the probability of persistence. For any given duration of the carrier state (λ_C), an increase in the duration of immunity decreases the probability of persistence. Increasing the scale parameter leads to persistence becoming more probable, decreasing it leads to persistence being less probable. Greater durations of the carrier state (λ_C) leads to compression of the probabilities towards each other, with the lower scale parameter sometimes leading to a greater probability of persistence than the greater values. However, the same overall pattern is still seen with any value of the transmission parameter.

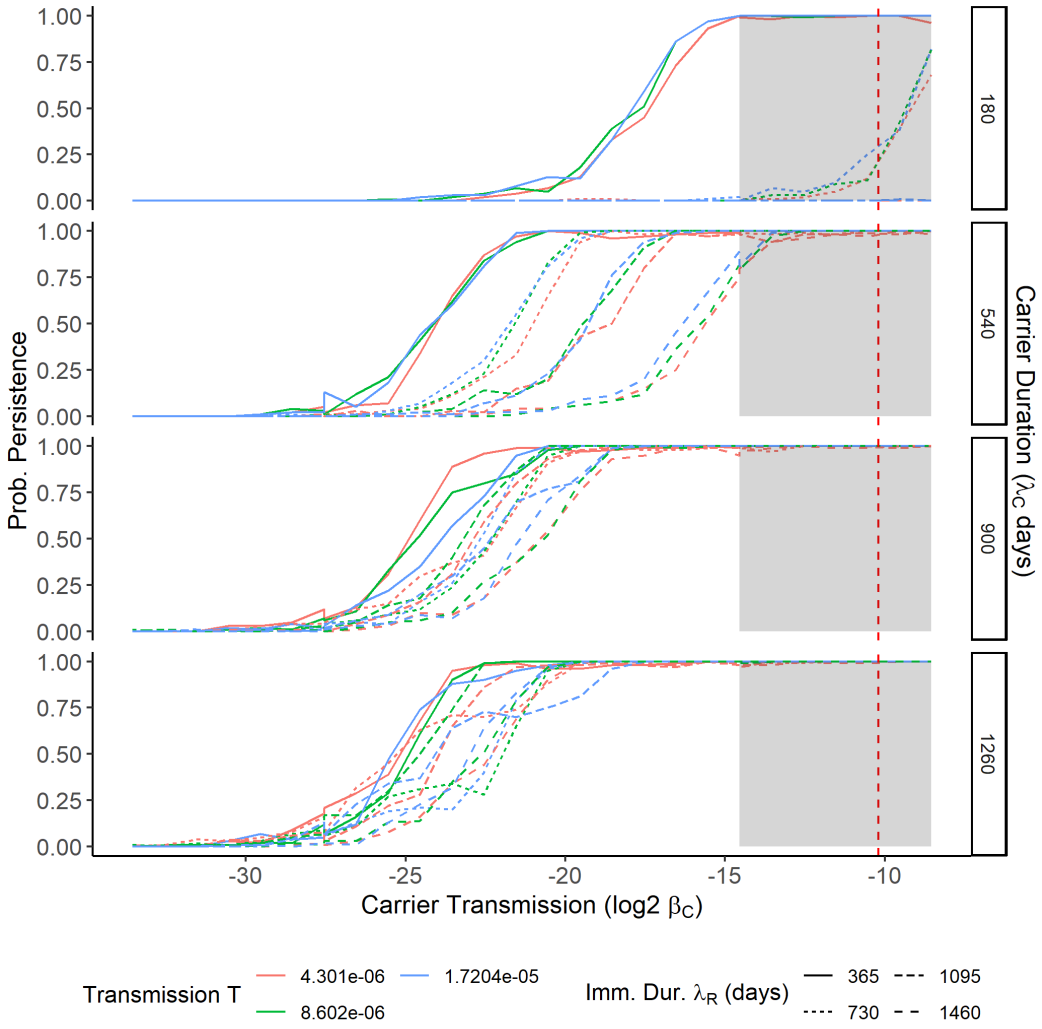

Figure 4.12: The observed relationship between the probability of persistence and carrier transmission for four different values of carrier duration (indicated on the right). Each type of line represents a given immunity duration (λ_R). Each colour line indicates a different value of the transmission kernel parameter (T), with green lines referring to the original value of 8.602e-6. The red vertical line indicates the estimated carrier transmission value by Tenzin et al 2008. The values explored in carrier-1 lie in the grey area to the right. For any given value of immunity duration (λ_R), an increase the duration of the carrier state (λ_C) increases the probability of persistence. For any given duration of the carrier state (λ_C), an increase in the duration of immunity decreases the probability of persistence. Increasing the transmission parameter leads to persistence becoming more likely, decreasing it to persistence being less probable. However, the same overall pattern is still seen with any value of the transmission parameter.

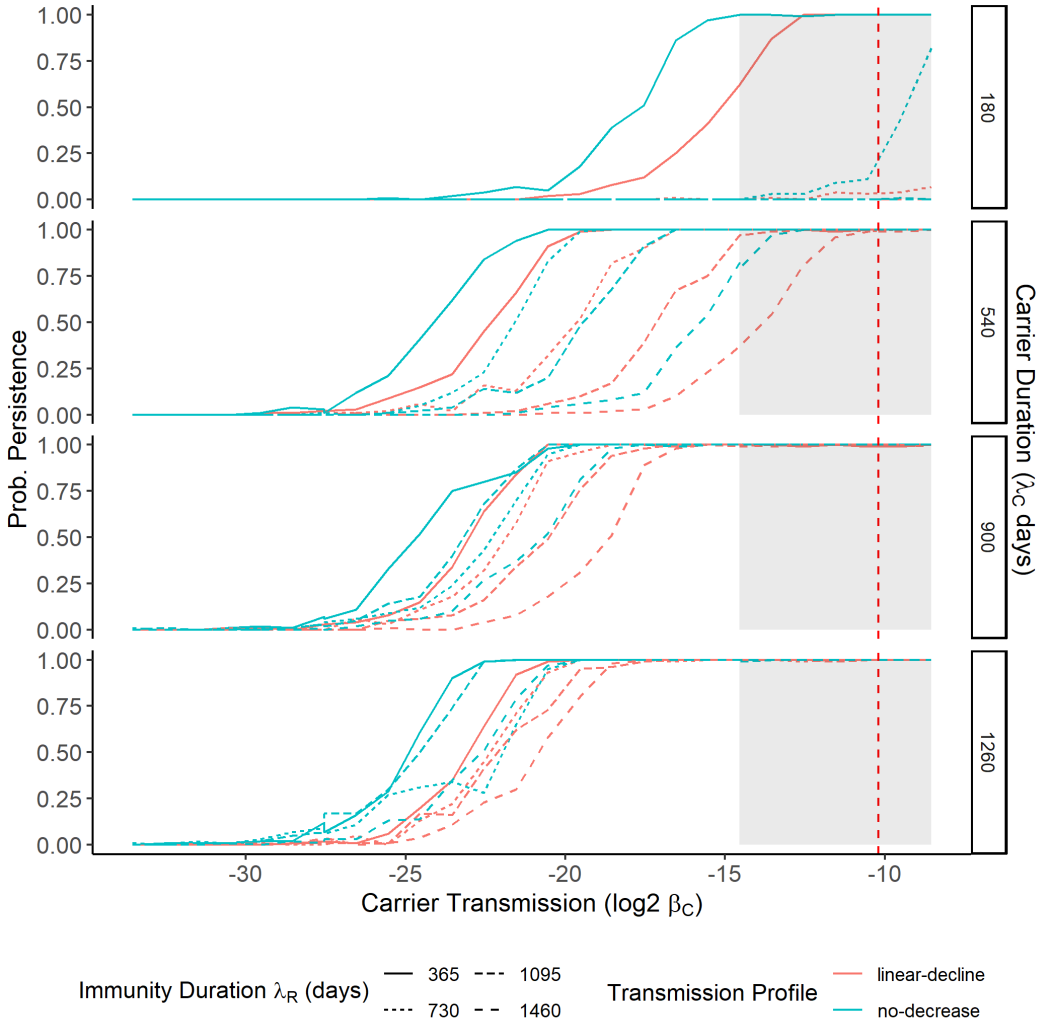

Figure 4.13: A comparison between the probability of persistence for given parameter values assuming either no decline of carrier transmission over time, or a linear decrease. Carrier durations λ_C are indicated on the right of each quarter panel. Each type of line represents a given immunity duration (λ_R). The red vertical line indicates the estimated carrier transmission value by Tenzin et al 2008. Although the assumption of carrier transmission decreasing through time reduced the likelihood of persistence *ceteris paribus*, larger assumptions of λ_C retain persistence even at very low values of β_C

once again not to the extent necessary. For $shape$, increasing this value decreases the probability of persistence, but the highest value assessed does not make carrier-mediated persistence impossible even at low rates of transmission.

The results also appear robust against the assumption of non-declining carrier transmission, as shown in Figure 4.13. Although the assumption of declining-through-time carrier transmission does reduce the probability of persistence all else being equal, carrier transmission retains the ability to cause persistence even at very low values of β_C.

4.4 Discussion

The results obtained suggest that persistence of FMD in populations is possible even with very small per-capita probabilities of transmission and no other pro-persistence factor. This suggests that carriers should not yet be set aside as a possible cause for the persistence of FMD. This effect seemed to be independent of greater population size, suggesting that current realistic farm sizes are already large enough for this effect to take place.

The values of β_C (carrier transmission) investigated are much smaller than the value estimated by Tenzin et al. (2008), which was itself an overestimate due to an inability to calculate species-specific β_C. Depending on assumptions about the duration of the carrier state and natural immunity, per-capita transmission rates of 2.03e-8 lead to an even probability of persistence, approximately 1 in 49 million. These results are not very sensitive to the dispersal kernel parameters. Given the expense and ethical difficulties with experimental livestock studies, it is unlikely that an experiment with power sufficient to detect a transmission rate of this magnitude could be undertaken. However, it may perhaps be possible through meta-analysis of all studies and experimental field studies, including more recent work (Bertram, Vu, et al. 2018; Hayer et al. 2018; Parthiban et al. 2015).

Further work to refine estimates of critical parameters would also help to narrow down the likely range of β_C sufficient for evasion of experimental evidence and epidemiological relevance. For our work on carrier animals, the two main factors affecting carrier-mediated persistence were the average duration of immunity to FMD, and the average duration of the carrier state. Realistic estimates of these parameters may therefore be important in determining whether carrier-mediated persistence is a realistic proposition. Many different studies support different values, with some supporting shorter durations of 6-12 months and others supporting longer durations of up to several years (Bertram, Yadav, et al. 2020; Hayer et al. 2018; P.

Moonen and Schrijver 2000). Assuming a shorter carrier duration of 6 months, durations of natural immunity longer than 1.5 years appear to rule out undetected transmission from carrier animals, and evidence suggests immunity can last much longer (T. R. Doel 2005). However, assuming a longer duration of the carrier state relaxes this constraint, with realistic durations of immunity theoretically allowing both carrier transmission to be happening and to have remain undiscovered by experiments to date.

An assumption of this work was that carrier transmission is homogeneous through time, meaning that a persistently-infected animal is as likely to infect a nearby susceptible animal 1 day before it clears the infection as it is 28 days after infection. Our work with a linear decline model of carrier transmission indicates that this is an unnecessary assumption - our results also appear valid even with declining transmission. However, since we have difficulty demonstrating carrier transmission at all there is no evidence which might inform whether or how transmission might change over time. Further work should be done on this area, which might enable better parameterisation of a decline curve.

Our work also addresses fomite contamination of vehicles as a mechanism for persistence. In the absence of explicitly modelled fomite transmission, the shipment of potentially infected cattle from infected farms to susceptible farms did not lead to persistence. Fomite transmission was necessary for persistence to be observed. This result suggests that the shipment of infected animals to uninfected areas plays less of a role in persistence, but that contamination of vehicles plays more of a role, supporting the importance of farm bio-security in controlling the spread of FMD. This matches the evidence, it is known that indirect transmission through fomite contamination played an important role in the 2001 UK outbreak, and that environmental transmission is sufficient to maintain an FMD epidemic without contributions from direct transmission (Bravo de Rueda et al. 2015; L.M et al. 2011).

The minimum probability of fomite transmission necessary for the probability of persistence to be greater than 0 declined as the number of farms modelled increased, suggesting that even small probabilities of fomite transmission would be sufficient for persistence to happen in regions with large numbers of farms, or larger regions. Our work suggests that it is large numbers of farms that are more important for this factor, perhaps because as the number of farms increases the probability of spread to at least one farm increases, or because the number of shipments between farms increases. Due to the lack of data on actual vehicle movements (as opposed to the movement of cattle which are assumed to be in one vehicle), we cannot address the case of one vehicle visiting multiple farms in a row. Our assumption of single-

farm shipments would mitigate the effect of contamination, suggesting our estimate of its importance is an underestimate. Additionally we assume that fomites are only transmitted when the source farm is actively infected. In reality virus can survive on fomites for up to 6-9 months in the environment given favourable conditions, expanding the time period where fomites might contaminate vehicles and likely reducing further the minimum necessary to contribute to persistence (Mielke and Garabed 2020). Shipments therefore appear to represent a viable alternate mechanism for supporting persistence when fomite transmission is explicitly modelled.

A limitation of this work was the inability to properly address fomite transmission, which has a more important role than simulated here due to the contamination of the environment. This represents an important alternate hypothesis for the maintenance of endemic FMD in these regions. As previously noted by Mielke and Garabed (2020), currently endemic regions are predominantly in tropical and sub-tropical regions, where temperatures and relative humidity are high. In their work, fomites exhibited their highest survival rate at day 150 in these conditions. It would be useful to begin incorporating environmental data and explicit environmental contamination into this work, in order to better represent this hypothesis.

This work found that: (i) carrier transmission can support the persistence of FMD in a region; (ii) the rate of carrier transmission necessary for this to occur is much lower than has been ruled out experimentally; (iii) the movement of infected cattle alone did not support the persistence of FMD; (iv) the additional assumption of fomite contamination of cattle shipments was sufficient to allow persistence; and (v) this effect was significantly mediated by the number of farms rather than the area simulated.

In conclusion, this work suggests that carrier-mediated persistence cannot yet be discounted as a possibility, with our modelling approach demonstrating the ability of even very sporadic carrier transmission events that are unlikely to be detected to support persistence within a greater population. The main factors that affect the plausibility of carrier transmission being epidemiologically relevant to persistence are the duration of the carrier state and the immune state – further work on elucidating those are likely to narrow the range of values at which potential carrier transmission can be epidemiologically relevant and simultaneously undetected. However, shipment-mediated persistence is a viable alternate mechanism by which persistence might occur and requires only small probabilities of fomite transmission. As fomite transmission is a recognised and well evidenced mechanism, whereas carrier transmission has still not been shown to occur in the field, this study suggests that shipment-mediated persistence remains the more likely of the two hypotheses

to be occurring. It should also be remembered that epidemiological relevance is not necessarily policy-relevance - the values of β_C investigated are very low and unlikely to have much effect in the face of mass vaccination of animal herds.

Chapter 5

Assessing Control Policy Performance With Assumptions of Persistence Mechanisms

5.1 Introduction

In FMD-endemic regions of the world, it is hypothesised that carrier transmission, the movement of infected animals, or fomite contamination might contribute to the maintenance of the disease. Previous work in Chapter 4 assessed two of these hypotheses (carrier transmission and livestock movements), and found that they were both plausible with different assumptions. However, given processes being epidemiologically plausible does not necessarily imply policy relevance.

As stated before, the fundamental concepts for the control of animal diseases such as FMD are: (i) to prevent access of the virus to susceptible hosts; (ii) to control contact between infected and susceptible animals; (iii) to reduce the number of infected animals; (iv) to reduce the number of susceptible animals (Premashthira et al. 2011). The practical versions of these policies for FMD control are: movement controls such as quarantine, or zoning; planned culling of infected animals or herds; and vaccination of susceptible animals.

Previous work in Chapter 3 assessed the potential FMD control policies from the perspective of an endemic country, finding that the optimal policy for both controlling the disease and potentially eliminating it was a combination of biannual mass vaccination and reactive ring vaccination. However, this did not include assumptions about the drivers of persistence, which may affect which policy is optimal

as well as the predicted costs and benefits of specific policies. As has been noted before however, the existence of persistently-infected animals (and mildly-symptomatic infections of small ruminants such as sheep) has not prevented the elimination of FMD from Europe by vaccination (P. Sutmoller and Casas 2002).

This chapter uses the stochastic metapopulation model already developed, with the addition of the persistence drivers discussed in Chapter 4, to investigate if and how those mechanisms change the optimal policies for controlling and eliminating FMD within an endemic region's borders.

5.2 Methods

5.2.1 Model Adjustments

To investigate control policies with the assumption of two different drivers for persistence, the model had to be slightly adjusted for the addition of vaccination. It was assumed that vaccination did not work on persistently-infected animals due to the ongoing uncleared infection. This resulted in the disease status compartments shown in Figure 5.1, the progression between which is described by the equations in Eq. (5.1). As before, carriers can be removed from this model by setting $k_C = 0$. This is done for the shipment-spread assumption.

The parameter values used for this model are described in Table 5.1.

$$
\begin{aligned}
\frac{dM}{dt} &= \alpha N \frac{(R + V_S + V_R)}{(N - M)} - \mu M - \Omega_n M, \\
\frac{dS}{dt} &= \alpha N (1 - \frac{(R + V_S + V_R)}{(N - M)}) + \mu M + \lambda_R R + \lambda_{V_R} V_R + \lambda_{V_S} V_S - \frac{\beta_I SI + \beta_I SC}{N} - \Omega_n S, \\
\frac{dE}{dt} &= \frac{\beta_I SI + \beta_C SC}{N} - \sigma E - \Omega_n E - \Omega_d E, \\
\frac{dI}{dt} &= \sigma E - \gamma I - \Omega_n I - \Omega_d I, \\
\frac{dR}{dt} &= (1 - k_C)\gamma I - \lambda_R R - \Omega_n R, \\
\frac{dC}{dt} &= k_C \gamma I - \lambda_C C - \Omega_n C. \\
\frac{dV_R}{dt} &= -\lambda_{V_R} V_R - \Omega_n V_R \\
\frac{dV_S}{dt} &= -\lambda_{V_S} V_S - \Omega_n V_S
\end{aligned}
\tag{5.1}
$$

Table 5.1: Relevant parameters of the carrier ODEs and dispersal kernel, with their value(s) and sources.

Parameter	Description	Value(s)	Source(s)
α	Per-capita birth rate	2%/year	
β_I	Acutely infectious transmission rate	$\frac{6}{11}$	(Orsel, Dekker, et al. 2005; Orsel, Jong, et al. 2007; Tadesse et al. 2019)
β_C	Carrier transmission rate	0.00267	(Bertram, Vu, et al. 2018; Parthiban et al. 2015; Tenzin et al. 2008)
γ	Recovery rate	$\frac{1}{11}$ days	(Yadav et al. 2019)
λ_R	Average duration of recovered state	250 days	(T. R. Doel 2005; E. El-Sayed et al. 2012)
λ_C	Average duration of carrier state	1260 days	(Bertram, Vu, et al. 2018; Tenzin et al. 2008)
μ	Maternal immunity waning rate	120 days	(Nicholls, Black, and M. M. Rweyemamu 1984)
σ	Symptomatic rate	$\frac{1}{1.5}$ days	(Yadav et al. 2019)
Ω_d	Infection mortality rate	2%	(Şentürk and Yalçin 2008)
Ω_n	Per-capita natural mortality rate	2%/year	
k_C	Proportion who become carriers	50%	(C. Stenfeldt et al. 2016; Carolina Stenfeldt and Jonathan Arzt 2020; Carolina Stenfeldt, Heegaard, et al. 2011; Paul Sutmoller, McVicar, and Cottral 1968)
λ_{V_R}	Average duration of vaccinated recovered (V_R) state	150 days	(Cox et al. 2010; T. R. Doel 2003; T J D Knight-Jones, Bulut, et al. 2015)
λ_{V_S}	Average duration of vaccinated susceptible (V_S) state	$\max(\lambda_R, \lambda_{V_R})$	(Cox et al. 2010; T. R. Doel 2003; T J D Knight-Jones, Bulut, et al. 2015)
T	Kernel per-capita transmission rate	4.980e-6	Chapter 2
S	Kernel per-capita susceptibility rate	1.0	
scale	Kernel scale	1.23	Chapter 2
shape	Kernel shape	2.09	Chapter 2

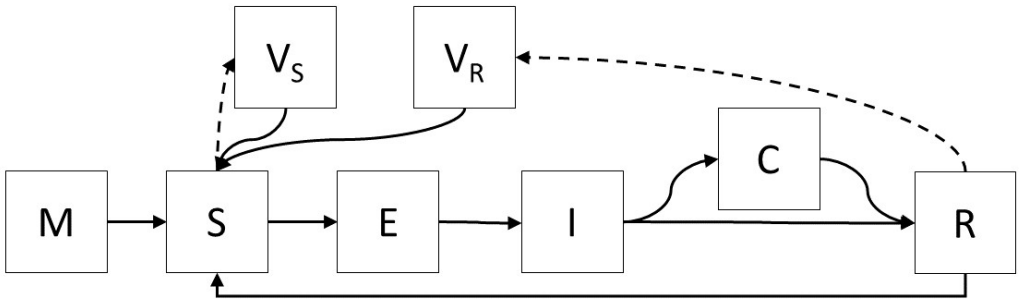

Figure 5.1: The disease compartments which animals in the model can progress through, with vaccination. **Maternally Immune (M)**, **Susceptible (S)**, **Exposed/Latent (E)**, **Infectious (I)**, **Recovered (R)**, **Carrier (C)**, **Vaccinated-Susceptible (V_S)**, and **Vaccinated-Recovered (V_R)**.

5.2.2 Scenarios

After adjusting the model to include both carrier animals and controls, the scenarios from Chapter 3 were used, shown in Table 5.2. An endemic situation was generated by simulating Erzurum Province (EZ) with no controls implemented for 5 years, and using the result as an initial start scenario for the imposition of controls. Separate endemic simulations were used for the carrier transmission assumption and the shipment contamination assumption.

As the aim was to investigate the effect of these assumptions on optimal control policies, the most pessimistic assumptions for each persistence driver was used. For carrier transmission, it was assumed that the average period of the carrier state (λ_C) was 3.5 years (1260 days), and that carrier transmission (β_C) was 0.00267, the highest rate assessed. For shipment contamination, it was assumed the probability of fomite transmission given that a shipment was from an infected farm was 100%, and independent of whether the cattle being moved was infected.

For each of these assumptions, the carrier-transmission assumption and the shipment-spread assumption, the same 81 policy combinations (Table 5.2) were simulated, to allow comparison with prior results. Each policy combination was simulated 100 times for 5 years, starting from the relevant endemic situation for that persistence assumption. Once again, the outcomes of interest were the total number of infected farms, the proportion of simulations where the disease was eliminated, and the time to elimination (in simulations where this occurred).

Table 5.2: The different control strategy parameter values which were assessed in combination, yielding 81 total policy combinations. For ring vaccination and movement bans, a radius of 0 km indicates that the policy was not implemented. For mass vaccination, an interval of ∞ indicates that the policy was not implemented.

Parameter	Parameter Values (unit)
Vaccine Efficacy	{65, 80, 90} %
Ring Vaccination Radius	{0, 5, 10} km
Movement Ban Radius	{0, 5, 10} km
Mass Vaccination Interval	{∞, 365, 182} days

5.3 Results

5.3.1 Assumed Carrier Transmission

No Controls

All control policies were compared to the scenario of no controls, each other, and the results obtained when no persistence driver was assumed (Chapter 3). For reference, the average total incidence observed when no persistence driver was assumed and no controls were implemented, was 7845.77 (σ = 93.13) over the 5-year simulated period.

When the persistence driver of carrier transmission was assumed, and no controls were implemented, the disease prevalence did not follow the normal damped oscillations around an equilibrium but instead remained very high at approximately 800 of the 1108 farms simulated, seen in Figure 5.2. On average, there were 16954 (σ = 133) infected farms over the 5-year period simulated, more than twice that seen without the persistence driver.

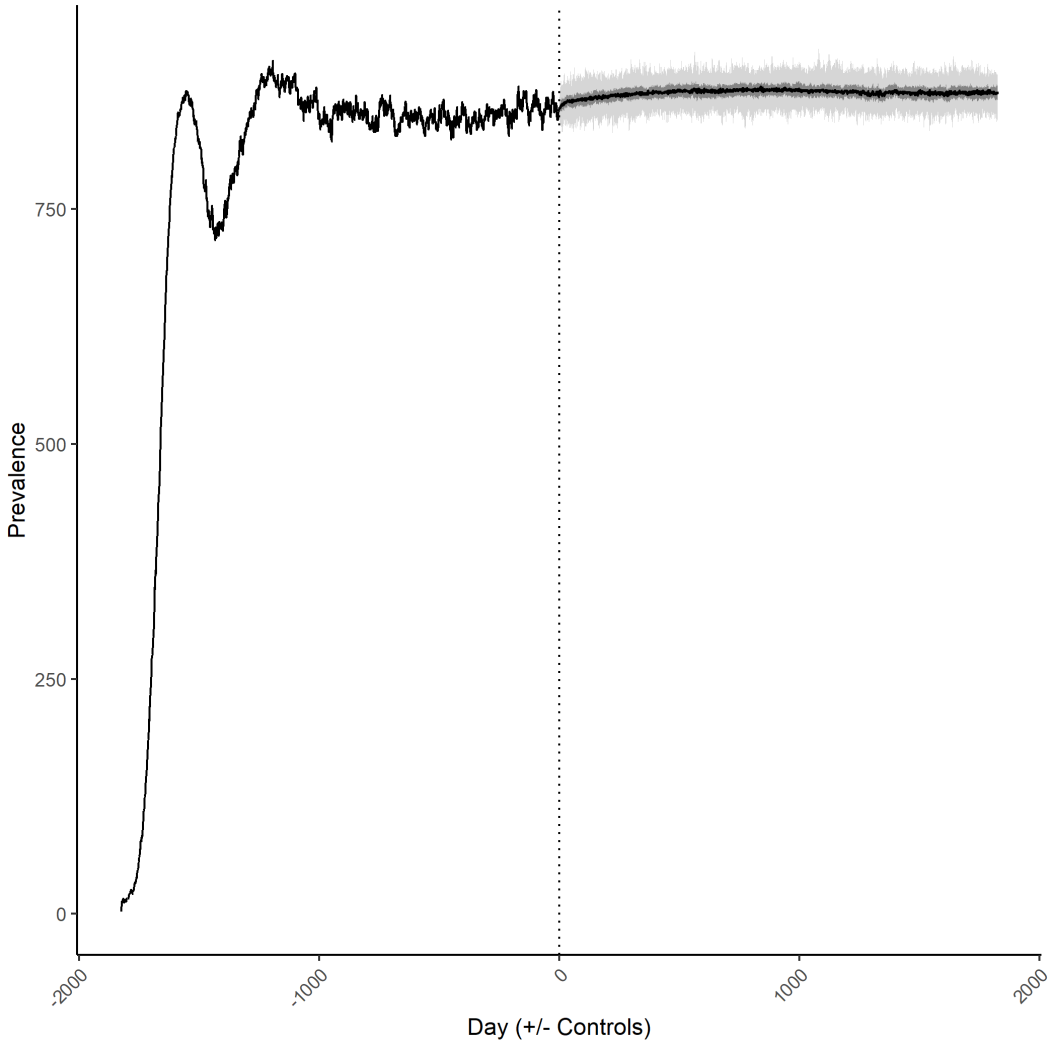

Figure 5.2: Average Prevalence of FMD with no implementation of control policies simulated. The vertical dotted line indicates the when the simulated implementation of the control policy would have begun, on day 0. The line to the right of this indicates the average prevalence over time, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values.

Ring Vaccination

With assumed carrier transmission, RV policies were able to produce a reduction in the circulation of the disease as a policy on their own, however at a reduced efficacy compared to without the persistence driver (Figure 5.3). Table 5.3 shows the change in average total incidence, varying from +2.72% compared to no controls when using the least efficacious vaccine, to -17.05% when using the most efficacious with the largest ring radius. VE appears to have a large effect on the policy efficacy in these scenarios, and ring radius a small effect. Incidence remained high regardless of RV policy implemented, and the probability of elimination was 0.

Movement Bans

Once again, MB policies did not appear to have any effect on the prevalence or incidence of FMD in these simulations (Figure 5.4). Table 5.4 shows that the variation from the scenario with no controls was minimal, ranging from an average of -0.03% to +0.04% total incidence, despite almost 2 million ban days implemented.

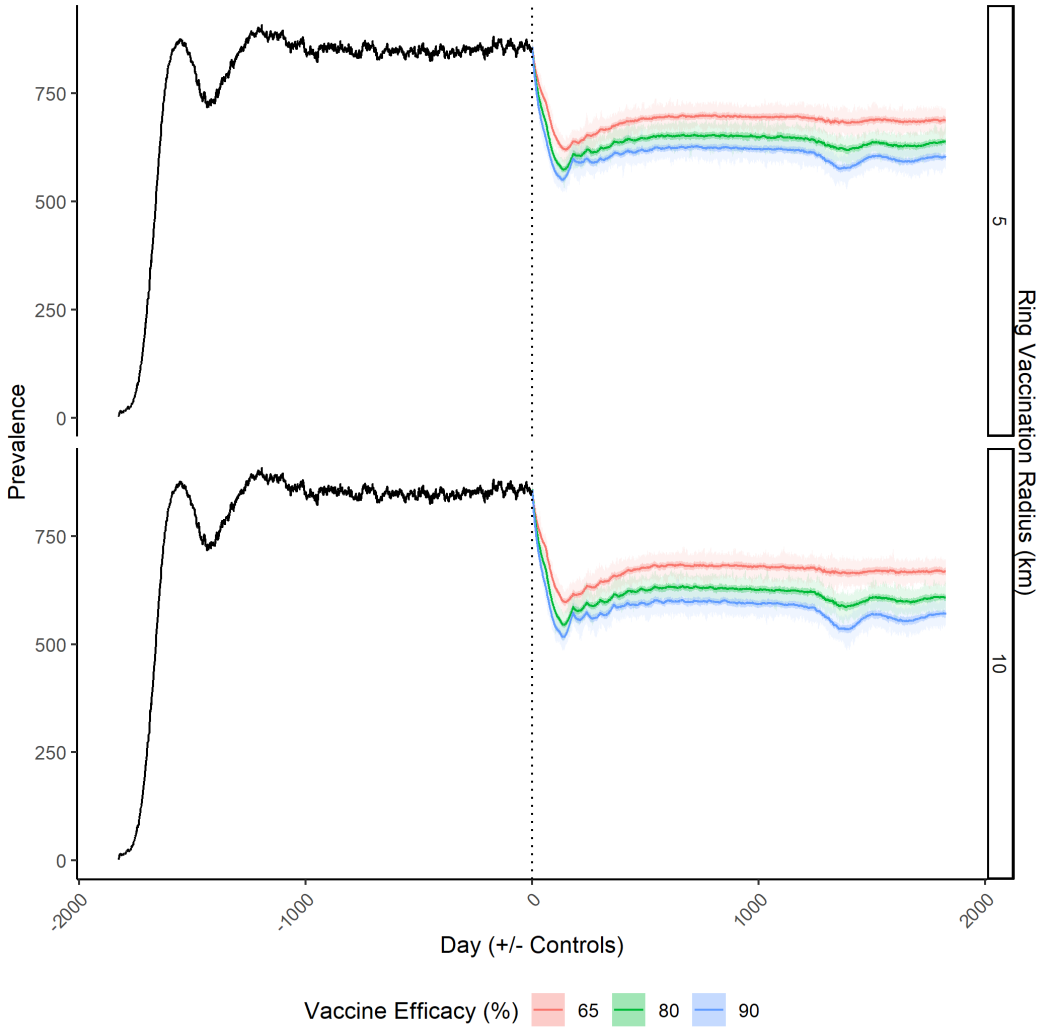

Figure 5.3: Average Prevalence of FMD after implementation of **ring vaccination** alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Both radii lead to a large reduction in prevalence compared to the prior endemic state, with the larger radius leading to a larger decrease. There is a large overlap between different VE values. Elimination is not observed.

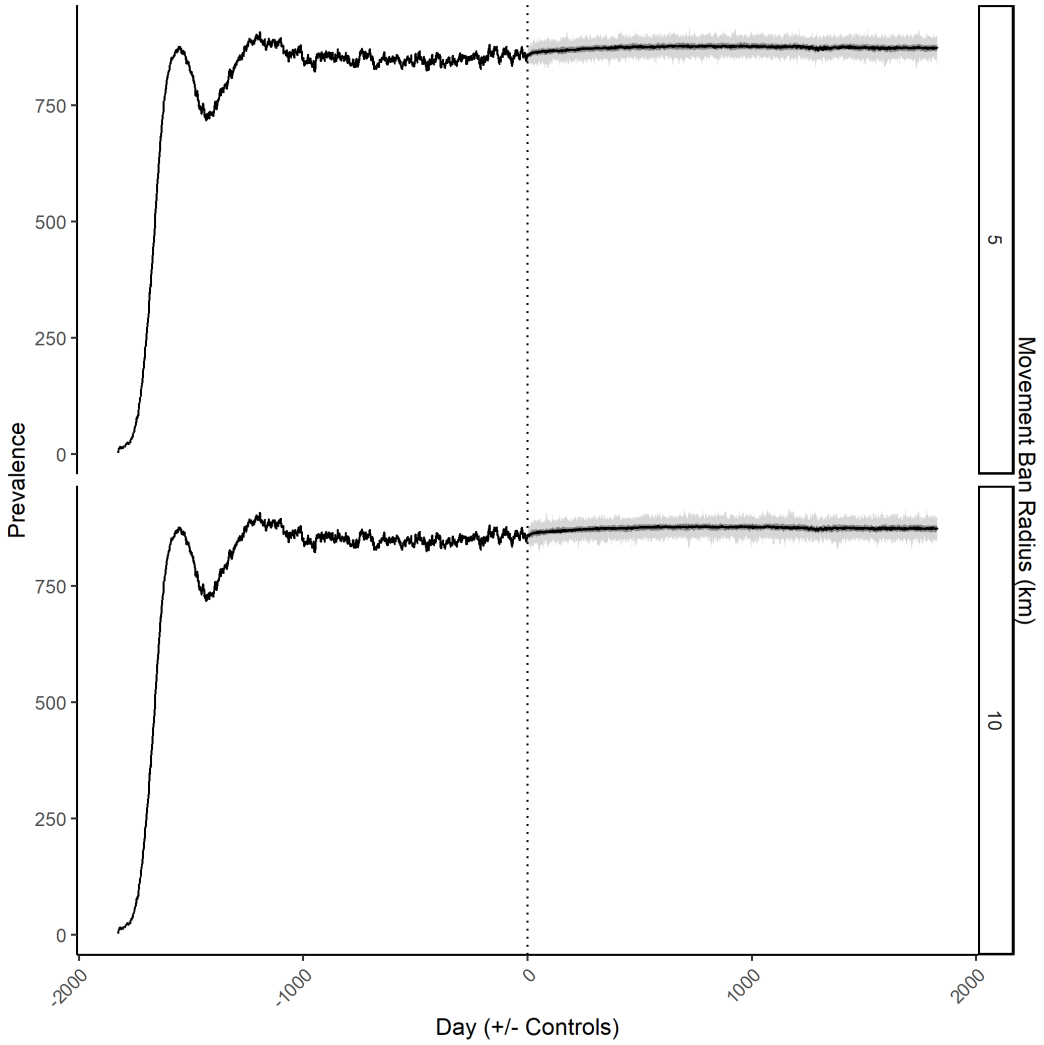

Figure 5.4: Average Prevalence of FMD after implementation of movement bans alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. The line indicates the average prevalence for the given movement ban radius, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Movement bans on their own do not lead to a reduction in prevalence of FMD when simulated for an already endemic state.

Table 5.3: Statistics of the standalone Ring Vaccination (RV) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Radius	VE	Incidence	P(E)	TTE	Vaccinated
5 km	65%	17414.4 (2.72%)	0	-	15,804.26
	80%	15827.3 (-6.65%)	0	-	16,379.88
	90%	14285.54 (-15.74%)	0	-	16,649.02
10 km	65%	17407.13 (2.67%)	0	-	17,451.62
	80%	15726.3 (-7.24%)	0	-	18,351.68
	90%	14064.02 (-17.05%)	0	-	18,829.59

Table 5.4: Statistics of the standalone Movement Ban (MB) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average total number of days farms spent under a movement ban (Ban-days).

Radius	Incidence	P(E)	TTE	Ban-days
5 km	16961.02 (0.04%)	0	-	1,975,629
10 km	16949.09 (-0.03%)	0	-	2,003,573

Mass Vaccination

Assuming carrier transmission, implementing MV policies stand-alone no longer leads to large reductions in the prevalence or incidence of FMD in the simulations. Figure 5.5 shows the previous pattern of periodic reductions in prevalence, however all VE values now lead to a return to the disease prevalence of the pre-implementation period. Implementing MV every 6 months appears to have a small effect in reducing the prevalence to which the disease bounces back to.

Table 5.5 shows the recorded average total incidence of these scenarios increased compared to the no controls scenario, varying from +20.1% to +55.01% depending on vaccination interval and VE. Comparing this to Figure 5.5 reveals that this is likely a result of measuring incidence, the large drops in prevalence seen mean that more farms are recorded as "newly infected" when they are reinfected during the disease resurgence. Measuring prevalence in the period of time after a pulse of mass vaccination, an interval of 6 months sees an average of -21.6% to

-43.3% reduction in prevalence as vaccine efficacy increases, and -28.5% to -56.0% when the interval is 12 months. As expected, there was no possibility of elimination.

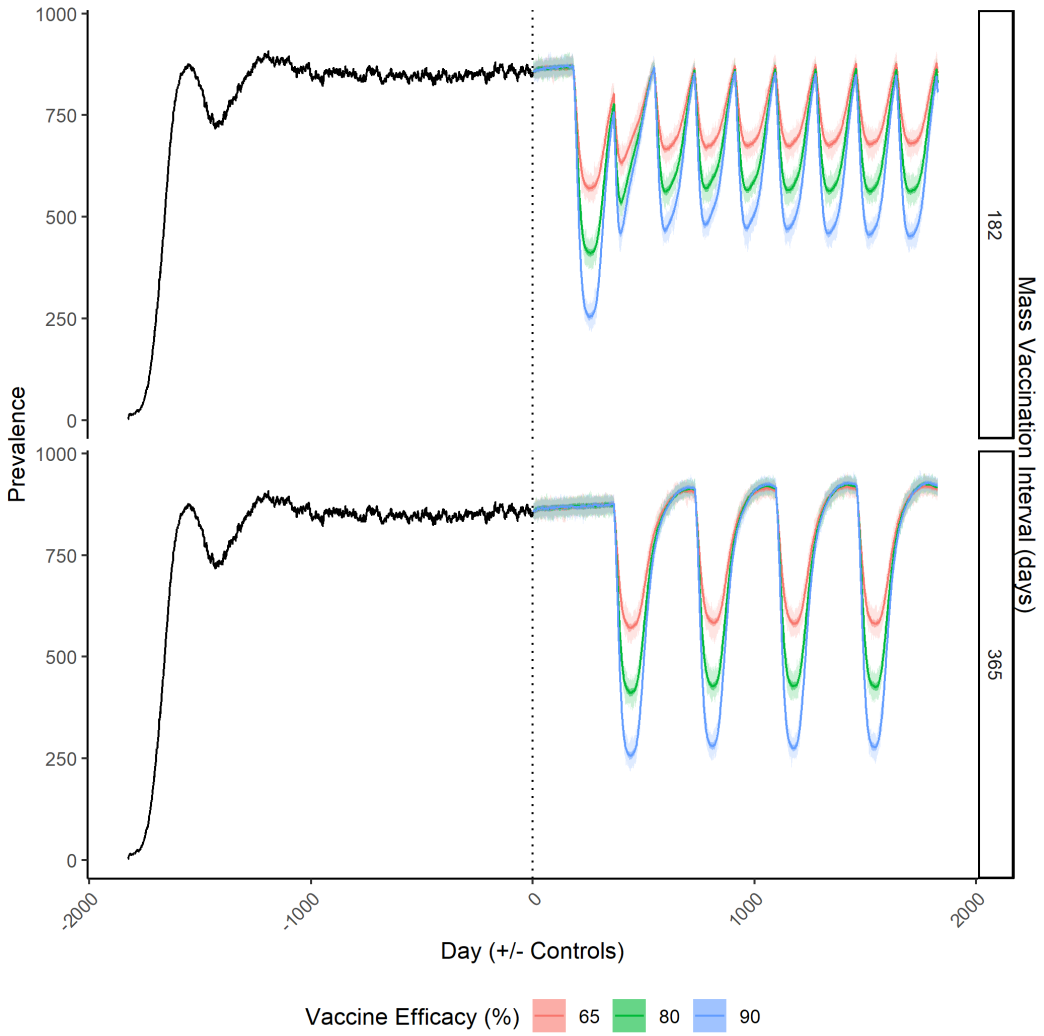

Figure 5.5: Average Prevalence of FMD after implementation of mass vaccination alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 182 day (6 month) mass vaccination interval, and the bottom facet for a 365 day interval. Mass vaccination can lead to a large reduction in the prevalence of FMD compared to the prior endemic state, although the wrong interval can blunt this effect as the reduction is much smaller for yearly mass vaccination compared to biannual vaccination. Greater VE leads to a greater reduction in prevalence, especially in the annual mass vaccination scenario.

Table 5.5: Statistics of the standalone Mass Vaccination (MV) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Interval	VE	Incidence	P(E)	TTE	Vaccinated
182 days	65%	23722.1 (39.92%)	0	-	10,968.56
	80%	25687.04 (51.51%)	0	-	10,970.62
	90%	26280.54 (55.01%)	0	-	10,971.34
365 days	65%	20678.63 (21.97%)	0	-	5,486.17
	80%	21148.73 (24.74%)	0	-	5,485.56
	90%	20361.62 (20.1%)	0	-	5,484.95

Ring Vaccination and Movement Bans

As seen when comparing control policies with no persistence drivers, when implementing RV policies in concert with MB policies no interaction is seen, and the effects on prevalence and incidence are close to identical to those seen with the policies in isolation. Figure 5.6 shows the same pattern as Figure 5.3, a significant reduction in prevalence with ring vaccination which is strongly dependent on the VE used. The addition of MB policies appears to have no effect, also similar to those policies on their own.

Table 5.6 shows a similar range of incidence values, ranging from +2.71% to -17.11% total incidence compared to no controls at all (although still assuming carrier transmission).

Ring Vaccination and Mass Vaccination

Combining MV and RV policies leads to an interaction, seen in Figure 5.7. RV policies reduce the average level of prevalence, and MV policies produce periodic extra reductions in prevalence before returning to the level set by the ring vaccination. Increased VE reduces the average prevalence.

Table 5.7 shows that this effects incidence in the same manner as before ranging from +7.1% compared to no controls, to +32.85% compared to no controls, depending on the specific combination of RV and MV used. Little variation in incidence with RV is seen, most of the variation appears to come with MV and VE. Measuring prevalence in the period of time after a pulse of mass vaccination, an interval of 6 months sees an average of -19.1% to -38.4% reduction in prevalence as vaccine efficacy increases, and -21.5% to -44.7% when the interval is 12 months.

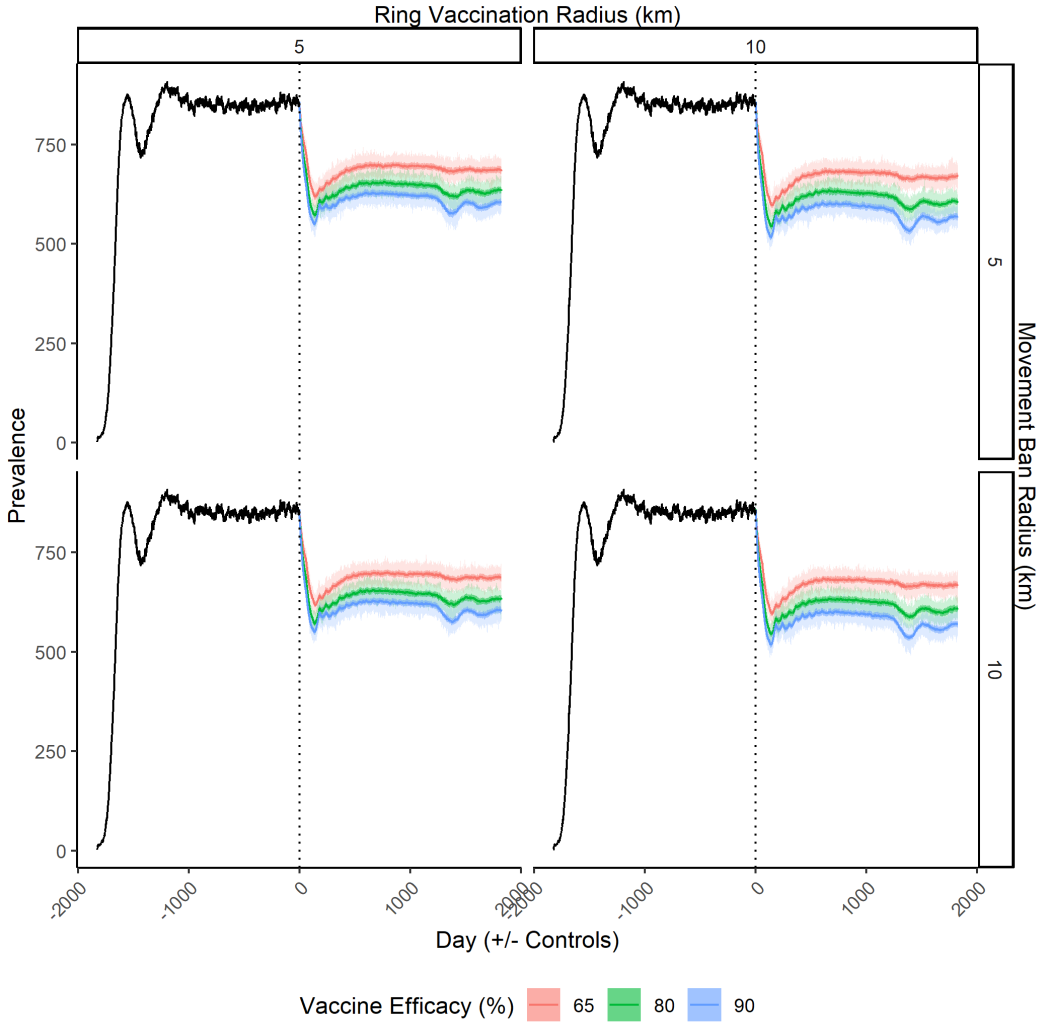

Figure 5.6: Prevalence of FMD after implementation of both ring vaccination and movement bans. Each column indicates either 5 or 10 km radius for ring vaccination, and each row a 5 or 10 km radius for movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. Ring vaccination leads to a reduction in prevalence, however even in concert with this movement bans do not lead to a further reduction.

Table 5.6: Statistics of the combined Ring Vaccination (RV) and Movement Ban (MB) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

RV Radius	MB Radius	VE	Incidence	P(E)	TTE	Vaccinated	Ban-days
5 km	5 km	65%	17389.04 (2.57%)	0	-	15,813.38	1,933,737
		80%	15844.57 (-6.54%)	0	-	16,384.60	1,920,425
		90%	14280.87 (-15.77%)	0	-	16,634.84	1,912,453
	10 km	65%	17394.23 (2.6%)	0	-	15,793.37	2,001,173
		80%	15848.62 (-6.52%)	0	-	16,400.75	2,000,517
		90%	14258.5 (-15.9%)	0	-	16,622.22	2,000,129
10 km	5 km	65%	17413.93 (2.71%)	0	-	17,457.41	1,896,889
		80%	15725.7 (-7.24%)	0	-	18,362.86	1,865,439
		90%	14058.49 (-17.08%)	0	-	18,837.81	1,841,771
	10 km	65%	17381.99 (2.52%)	0	-	17,445.36	1,996,537
		80%	15705.13 (-7.37%)	0	-	18,340.83	1,993,136
		90%	14053.38 (-17.11%)	0	-	18,845.50	1,990,642

The probability of elimination remains 0, and the number of vaccines used is a large increase on either MV or RV alone.

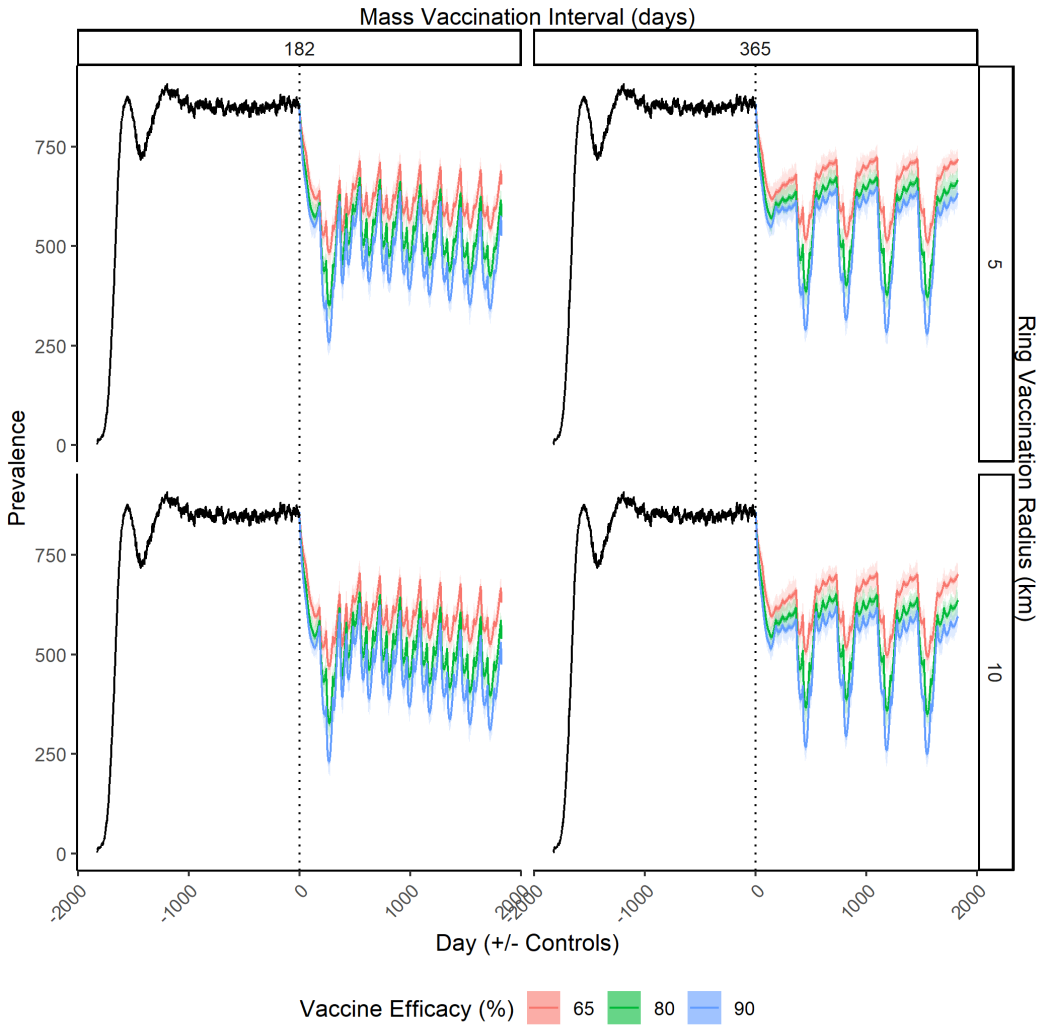

Figure 5.7: Prevalence of FMD after implementation of both reactive ring vaccination and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive ring vaccination. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination is clearly better than annual mass vaccination, though both lead to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. A larger ring vaccination radius leads to an additional reduction in virus circulation.

Table 5.7: Statistics of the combined Ring Vaccination (RV) and Mass Vaccination (MV) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Interval	**Radius**	**VE**	**Incidence**	**P(E)**	**TTE**	**Vaccinated**
182 days	5 km	65%	22404.8 (32.15%)	0	-	26,647.46
		80%	22523.95 (32.85%)	0	-	27,785.11
		90%	22026.22 (29.92%)	0	-	28,288.63
	10 km	65%	22212.91 (31.02%)	0	-	28,740.42
		80%	22149.11 (30.64%)	0	-	30,472.90
		90%	21467.51 (26.62%)	0	-	31,498.25
365 days	5 km	65%	20440.07 (20.56%)	0	-	21,531.78
		80%	19674.76 (16.05%)	0	-	22,424.82
		90%	18395.64 (8.5%)	0	-	22,774.21
	10 km	65%	20375.95 (20.18%)	0	-	23,399.22
		80%	19497.91 (15%)	0	-	24,784.69
		90%	18157.15 (7.1%)	0	-	25,557.75

Movement Bans and Mass Vaccination

Using both MV and MB together replicated the results of MV alone, with prevalence periodically being reduced as farms are vaccinated before recovering to the previous level, seen in Figure 5.8. The radius of the MB policy was not relevant and appears to have no effect, similar to the policy on its own.

Table 5.8 shows a similar pattern to MV alone, with incidence compared to no controls ranging from +20.1% to +54.92%, no possibility of elimination, the number of farms vaccinated varying from 5500 to 11000 depending on the MV interval, and almost 2 million ban-days. Measuring prevalence in the period of time after a pulse of mass vaccination, an interval of 6 months sees an average of -21.6% to -43.3% reduction in prevalence as vaccine efficacy increases, and -28.3% to -56.0% when the interval is 12 months.

5.3.2 Ring Vaccination, Movement Bans, and Mass Vaccination

Combining all of the control policies together with the assumption of carrier transmission, prevalence can be maximally reduced with biannual mass vaccination combined with ring vaccination of either 5 or 10 km. As MB policies do not appear to cause a reduction in disease circulation when using this persistence driver, Figure 5.9 shows the same pattern observed for MV and RV combined without MB.

Average total incidence was relatively similar for all combinations of the three policies, ranging from +6.82% to +32.97% compared to no controls at all (Table 5.9. Measuring prevalence in the period of time after a pulse of mass vaccination, an interval of 6 months sees an average of -19.1% to -38.5% reduction in prevalence as vaccine efficacy increases, and -21.5% to -44.7% when the interval is 12 months.

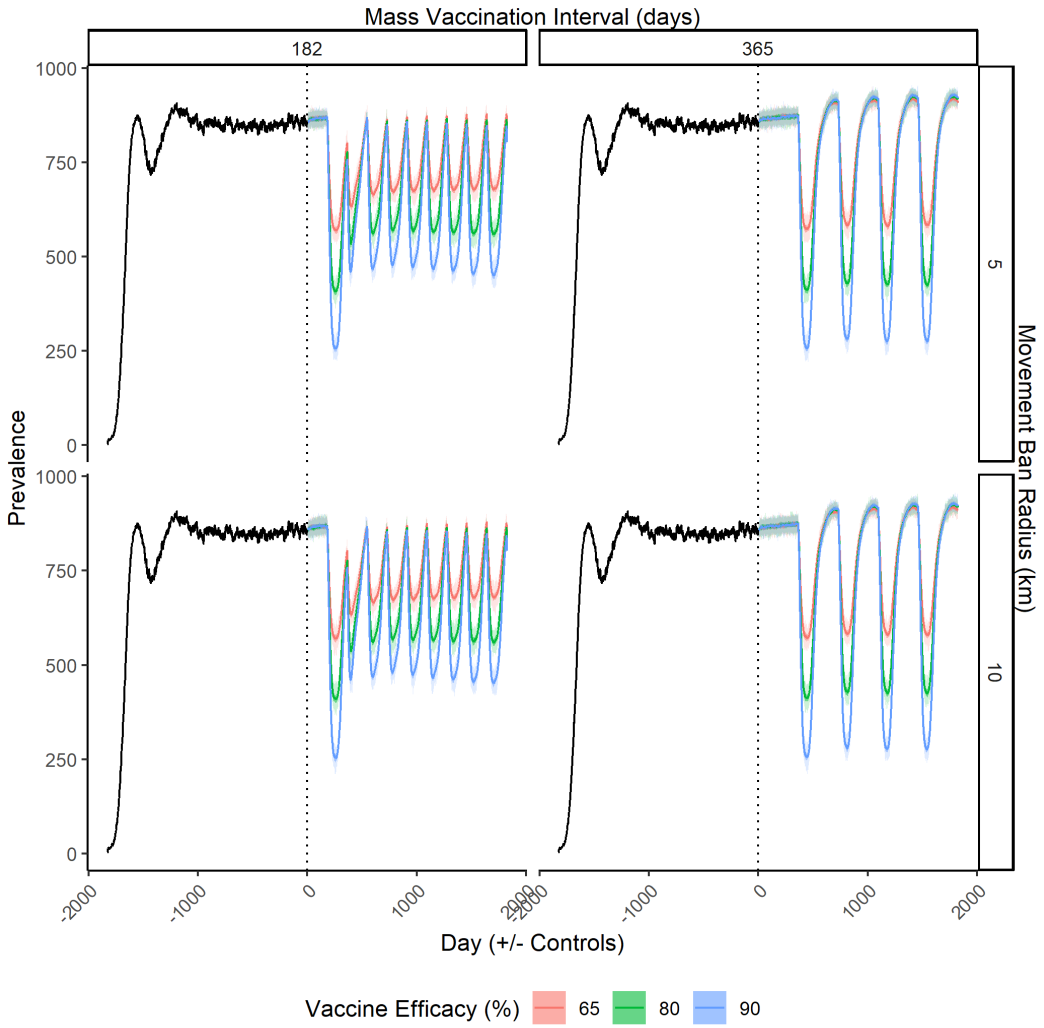

Figure 5.8: Prevalence of FMD after implementation of both reactive movement bans and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Movement bans appear to make no difference to the prevalence, regardless of which mass vaccination policy they are combined with.

Table 5.8: Statistics of the combined Movement Ban (MB) and Mass Vaccination (MV) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	**Radius**	**VE**	**Incidence**	**P(E)**	**TTE**	**Vaccinated**	**Ban-days**
182 days	5 km	65%	23747.44 (40.07%)	0	-	10,969.42	1,928,106
		80%	25675.19 (51.44%)	0	-	10,971.81	1,893,487
		90%	26265.45 (54.92%)	0	-	10,969.34	1,850,883
	10 km	65%	23735.1 (40%)	0	-	10,972.26	1,992,039
		80%	25728.53 (51.75%)	0	-	10,969.78	1,984,428
		90%	26248.93 (54.82%)	0	-	10,970.52	1,974,349
365 days	5 km	65%	20681.93 (21.99%)	0	-	5,484.82	1,946,424
		80%	21169.79 (24.87%)	0	-	5,483.92	1,919,101
		90%	20361.09 (20.1%)	0	-	5,485.34	1,875,688
	10 km	65%	20698.67 (22.09%)	0	-	5,485.00	1,996,730
		80%	21180.16 (24.93%)	0	-	5,484.06	1,991,052
		90%	20374.57 (20.18%)	0	-	5,485.25	1,981,110

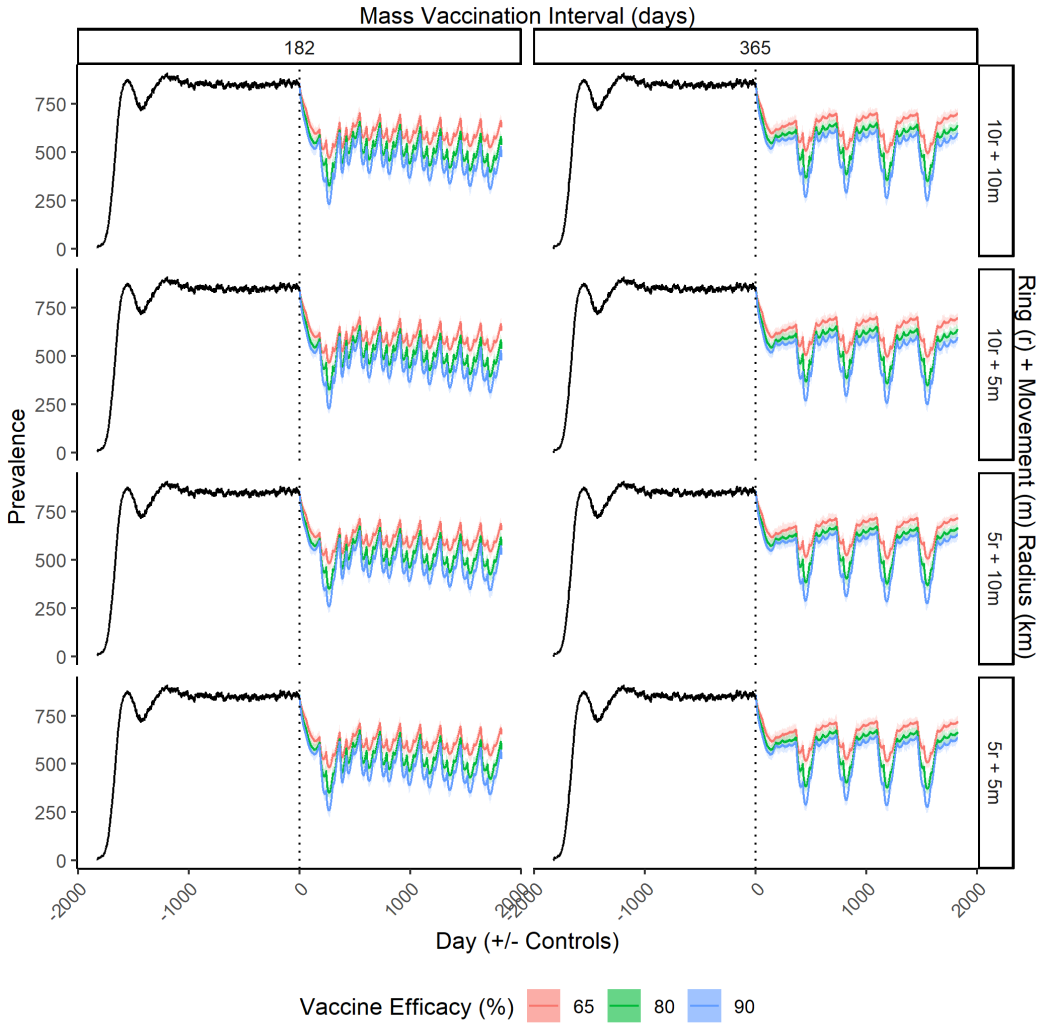

Figure 5.9: Prevalence of FMD after implementation of all three of reactive ring vaccination, reactive movement bans, and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a combination of a 5 or 10 km radius for reactive ring vaccination (indicated by r) and movement bans (indicated by m). The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Ring vaccination additionally reduces the prevalence of disease, however movement bans appear to make no difference to the prevalence, regardless of which policy they are combined with.

Table 5.9: Statistics of the combined Ring Vaccination (RV), Movement Ban (MB), and Mass Vaccination (MV) policies, when an assumed **carrier transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	RV Radius	MB Radius	VE	Incidence	P(E)	TTE	Vaccinated	Ban-days
182 days	5 km	5 km	65%	22365.66 (31.92%)	0	-	26,640.55	1,887,078
			80%	22527.22 (32.87%)	0	-	27,779.99	1,839,757
			90%	22008.08 (29.81%)	0	-	28,289.31	1,796,874
		10 km	65%	22394.42 (32.09%)	0	-	26,654.21	1,988,858
			80%	22543.69 (32.97%)	0	-	27,772.16	1,979,942
			90%	22018.88 (29.87%)	0	-	28,293.62	1,971,245
	10 km	5 km	65%	22207.51 (30.99%)	0	-	28,755.94	1,854,799
			80%	22153.98 (30.67%)	0	-	30,484.40	1,793,640
			90%	21457.06 (26.56%)	0	-	31,487.95	1,738,964
		10 km	65%	22201.83 (30.95%)	0	-	28,743.62	1,984,104
			80%	22158.43 (30.7%)	0	-	30,462.81	1,971,892
			90%	21465.26 (26.61%)	0	-	31,505.53	1,960,463
365 days	5 km	5 km	65%	20409.08 (20.38%)	0	-	21,536.41	1,909,921
			80%	19686.26 (16.12%)	0	-	22,412.69	1,876,917
			90%	18433.87 (8.73%)	0	-	22,759.37	1,848,005
		10 km	65%	20436.83 (20.54%)	0	-	21,540.67	1,994,530
			80%	19695.27 (16.17%)	0	-	22,412.86	1,989,090
			90%	18399.32 (8.52%)	0	-	22,767.46	1,983,294
	10 km	5 km	65%	20331.41 (19.92%)	0	-	23,388.51	1,876,083
			80%	19502.53 (15.03%)	0	-	24,785.86	1,826,365
			90%	18112.08 (6.83%)	0	-	25,543.82	1,781,655
		10 km	65%	20340.59 (19.98%)	0	-	23,392.58	1,990,143
			80%	19498.08 (15.01%)	0	-	24,792.58	1,981,760
			90%	18110.57 (6.82%)	0	-	25,544.41	1,973,641

5.3.3 Assumed Shipment Transmission

No Controls

When the persistence driver of fomite contaminated shipments was assumed and no controls were implemented, disease prevalence continued damped oscillations toward an endemic equilibrium (Figure 3.1). An average total incidence of 7896 (σ = 85) was observed. For reference, the average total incidence observed when no persistence driver was assumed and no controls were implemented, was 7845.77 (σ = 93) over the 5-year simulated period. There was very little difference in the prevalence or incidence observed when assuming contaminated shipments.

Ring Vaccination

Similar to that seen with no persistence driver, the RV policy was able to produce a strong reduction in the circulation of the disease as a policy on its own, seen in Figure 5.11. There remained a large overlap in the prevalence seen for different VE values.

Table 5.10 shows a reduction of -54.12% to -85.26% in average total incidence compared to a no control scenario, which is almost identical to the results seen when no persistence driver was assumed. Elimination was not observed, except for once with a radius of 10 km and VE of 90%, which took 542 days to occur. The number of farms ranged from approximately 14500 to approximately 19000.

Movement Bans

Once again, the MB policy on its own does not appear to have any effect on the prevalence of FMD, merely continuing a trend of damped oscillations towards the endemic equilibrium (Figure 5.12). Table 5.11 shows that the total incidence for all combinations of MB policies ranged from -0.13% to +0.02%, within the range of error of the scenario where no controls were implemented.

Mass Vaccination

Implementing MV as a stand-alone policy leads to a large reduction in the prevalence of FMD even when shipments are assumed to be contaminated and always transmit infection. Similar to the no persistence drivers scenario, biannual vaccination lead to a much larger reduction in prevalence and incidence compared to annual mass vaccination (Figure 5.13). The same pattern of periodic resurgences in prevalence is seen with annual vaccination.

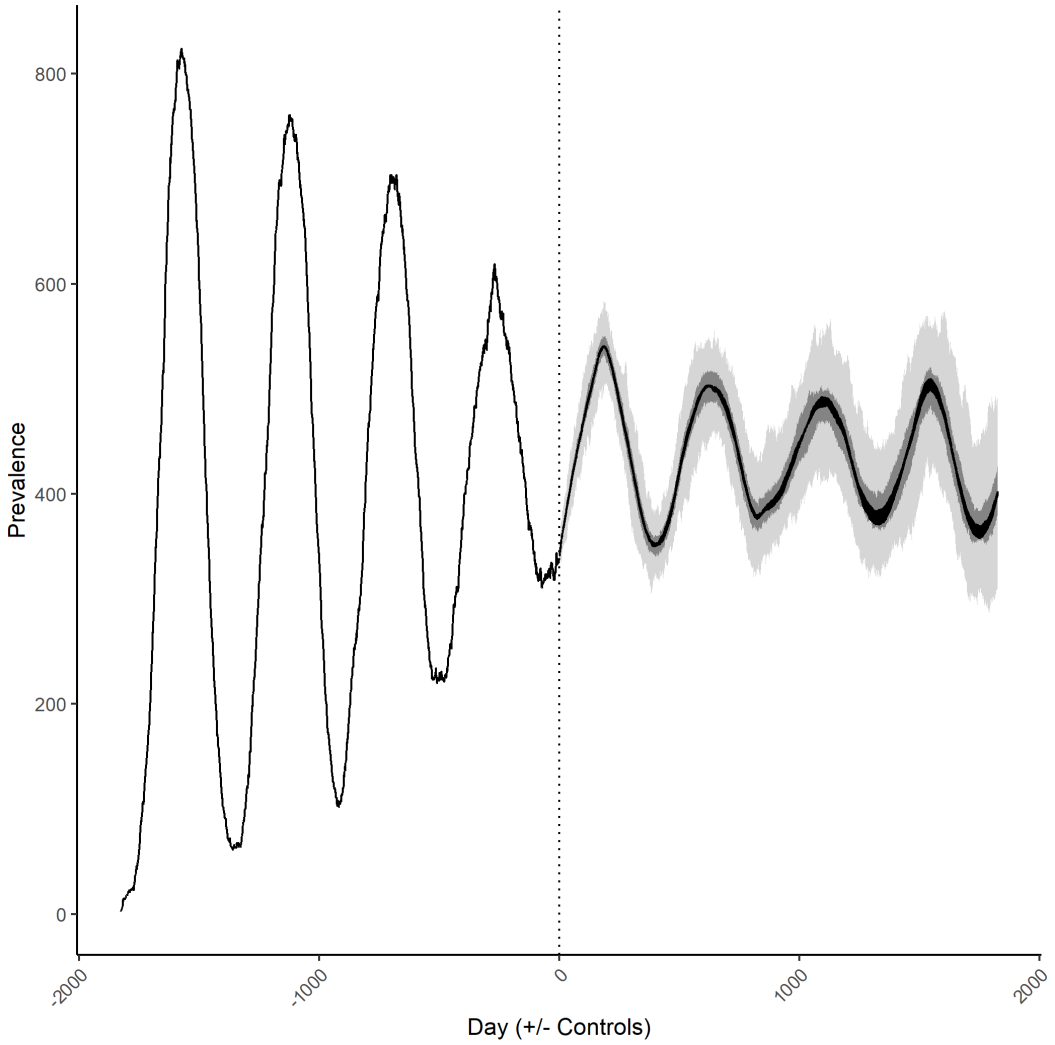

Figure 5.10: Average Prevalence of FMD with no implementation of control policies simulated. The vertical dotted line indicates the when the simulated implementation of the control policy would have begun, on day 0. The line to the right of this indicates the average prevalence over time, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values.

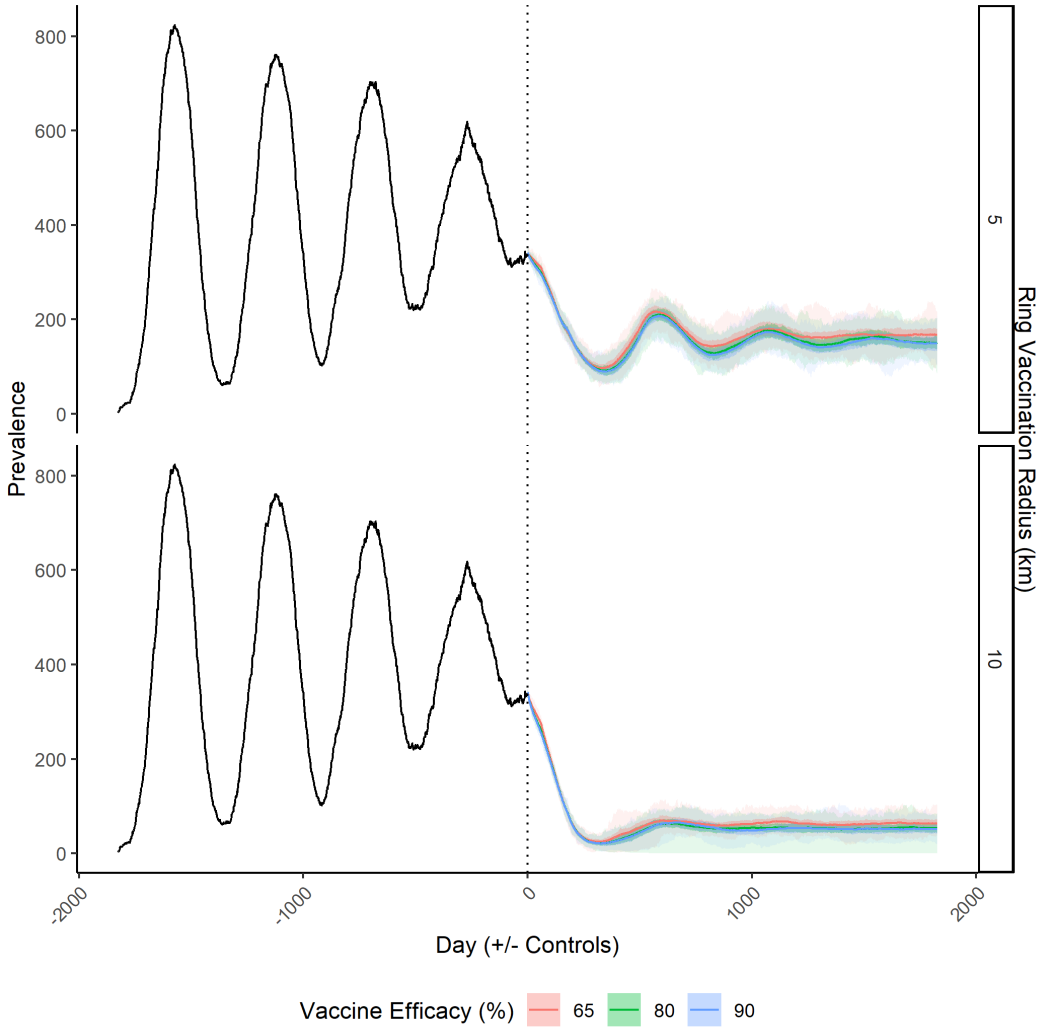

Figure 5.11: Average Prevalence of FMD after implementation of **ring vaccination** alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Both radii lead to a large reduction in prevalence compared to the prior endemic state, with the larger radius leading to a larger decrease. There is a large overlap between different VE values. Elimination is not observed.

Table 5.10: Statistics of the standalone Ring Vaccination (RV) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Radius	VE	Incidence	P(E)	TTE	Vaccinated
5 km	65%	3622.99 (-54.12%)	0.00	-	15,129.65
	80%	3214.01 (-59.3%)	0.00	-	14,774.91
	90%	3044.33 (-61.44%)	0.00	-	14,611.68
10 km	65%	1498.6 (-81.02%)	0.00	-	19,151.65
	80%	1163.82 (-85.26%)	0.01	541	18,176.95
	90%	1076.88 (-86.36%)	0.00	-	18,140.47

Table 5.11: Statistics of the standalone Movement Ban (MB) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average total number of days farms spent under a movement ban (Ban-days).

Radius	Incidence	P(E)	TTE	Ban-days
5 km	7885.41 (-0.13%)	0	-	1,548,974
10 km	7897.54 (0.02%)	0	-	1,890,435

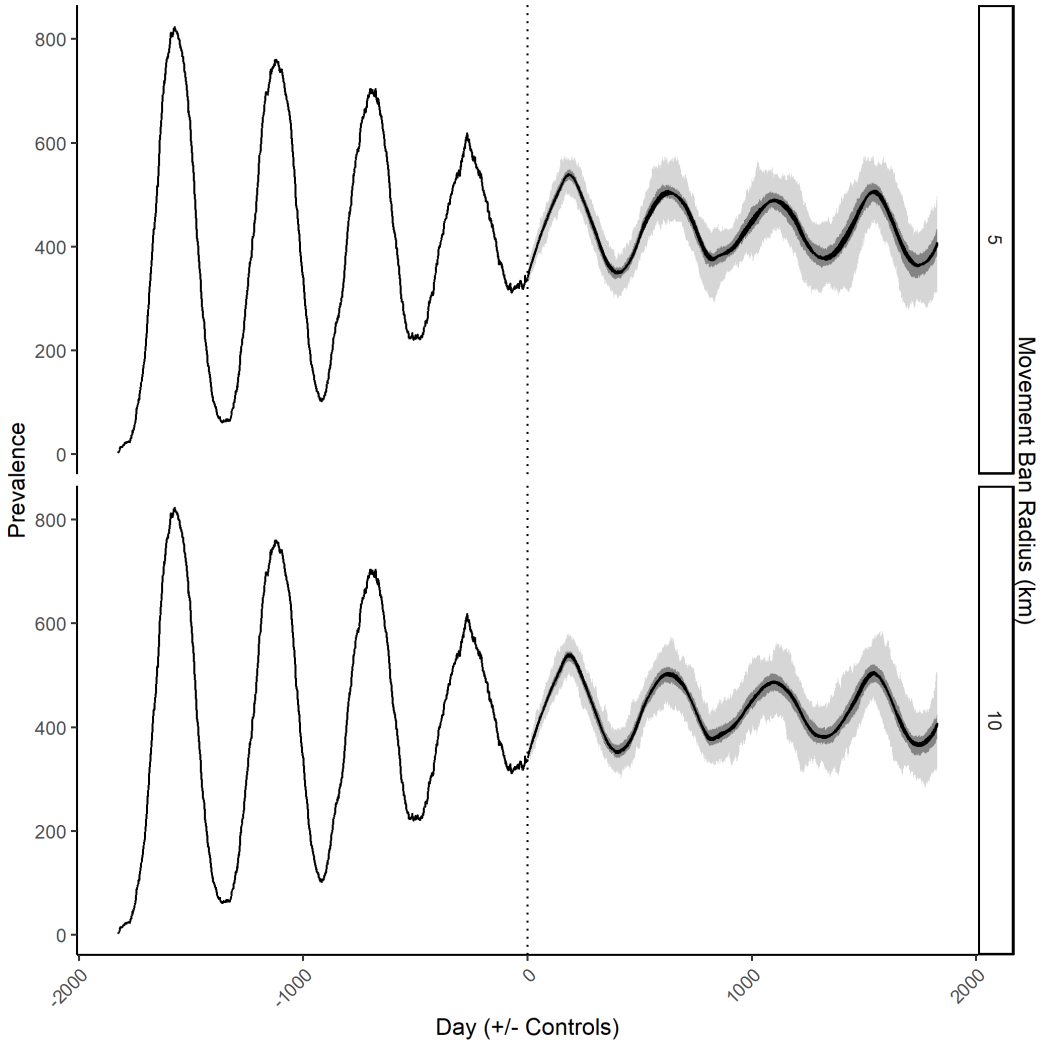

Figure 5.12: Average Prevalence of FMD after implementation of movement bans alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. The line indicates the average prevalence for the given movement ban radius, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 5 kilometre radius, and the bottom facet for a 10 km radius. Movement bans on their own do not lead to a reduction in prevalence of FMD when simulated for an already endemic state.

Table 5.12: Statistics of the standalone Mass Vaccination (MV) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Interval	**VE**	**Incidence**	**P(E)**	**TTE**	**Vaccinated**
182 days	65%	948.8 (-87.98%)	0.99	516.27	10,972.68
	80%	926.06 (-88.27%)	1.00	381.72	10,969.69
	90%	921.11 (-88.33%)	1.00	367.9	10,972.19
365 days	65%	4852.78 (-38.54%)	0.04	681	5,485.09
	80%	2044.7 (-74.1%)	0.85	701.71	5,484.37
	90%	1755.32 (-77.77%)	0.97	647.10	5,485.37

Table 5.12 shows that this can reduce the average total incidence to 921 over the 5 years simulated. Biannual vaccination makes elimination almost certain, with annual vaccination this is less so but is positively correlated with VE. VE also decreases the TTE, declining to an average of 367.9 with biannual vaccination and 90% VE.

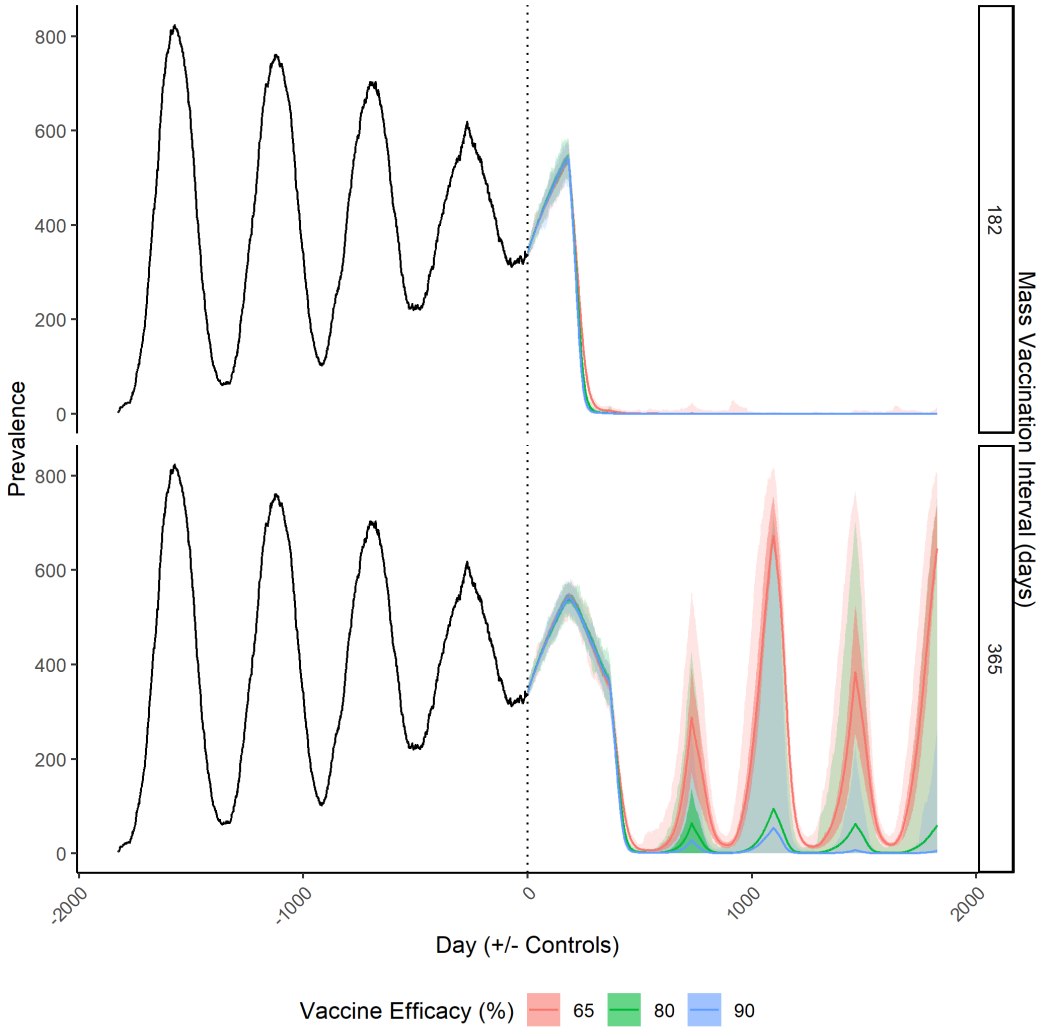

Figure 5.13: Average Prevalence of FMD after implementation of mass vaccination alone. The vertical dotted line indicates the simulated implementation of the control policy on day 0. Each coloured line indicates the average prevalence for the given VE, with a darker coloured area around indicating the IQR of values, and the lighter coloured ribbon indicating the full range of values. The top facet displays results for a 182 day (6 month) mass vaccination interval, and the bottom facet for a 365 day interval. Mass vaccination can lead to a large reduction in the prevalence of FMD compared to the prior endemic state, although the wrong interval can blunt this effect as the reduction is much smaller for yearly mass vaccination compared to biannual vaccination. Greater VE leads to a greater reduction in prevalence, especially in the annual mass vaccination scenario.

Ring Vaccination and Movement Bans

Implementing ring vaccination in concert with movement bans is the same as implementing ring vaccination alone due to the inefficacy of MB policies. Figure 5.14 shows a significant decrease in the prevalence of FMD is observed compared to no controls, with a larger decrease in prevalence when using a larger radius. The radius of MB policies has no effect.

Table 5.13 also demonstrates this, the decline in average total incidence observed range from -54.21% to -61.52% when RV radius is 5 km, but range from -81.27% to -86.57% when it is 10 km, regardless of MB radius. These are very similar to those observed for RV as a stand-alone policy.

Elimination is not observed for any of these policy combinations.

Ring Vaccination and Mass Vaccination

Combining Mass Vaccination and Ring Vaccination leads to a much reduced prevalence of FMD (Figure 5.15), most especially when combining biannual MV with RV of either radius. Elimination of the disease was seen in all of the simulations where this combination of policies was implemented (Table 5.14). Annual MV did not lead to elimination with the same probability, ranging from 0.05 to 1.00 depending on the specific combination of annual MV, RV, and VE. Similarly to when no persistence driver was used, the interaction of RV reduced the periodic resurgences seen with annual MV. Incidence reductions ranged from -74.5% to -99.01%.

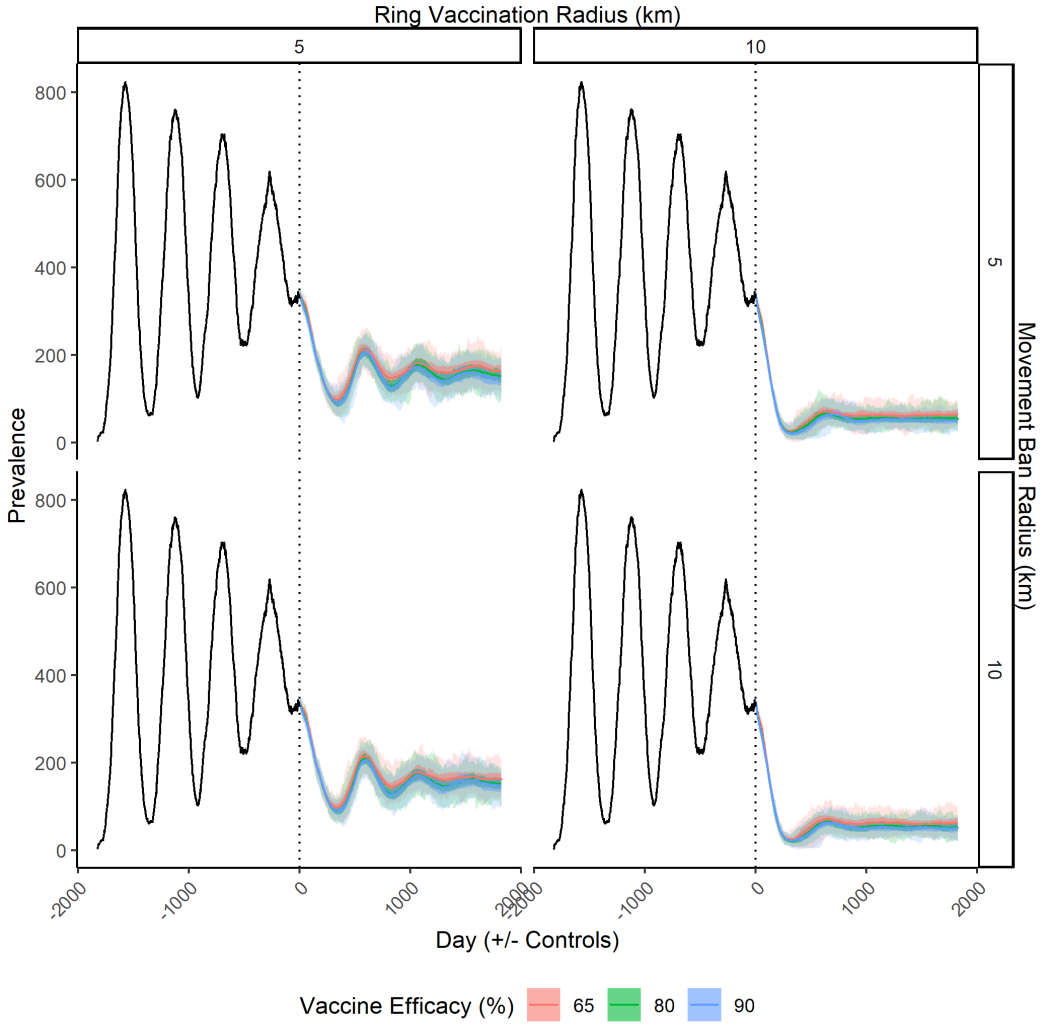

Figure 5.14: Prevalence of FMD after implementation of both ring vaccination and movement bans. Each column indicates either 5 or 10 km radius for ring vaccination, and each row a 5 or 10 km radius for movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. Ring vaccination leads to a reduction in prevalence, however even in concert with this movement bans do not lead to a further reduction.

Table 5.13: Statistics of the combined Ring Vaccination (RV) and Movement Ban (MB) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

RV Radius	MB Radius	VE	Incidence	P(E)	TTE	Vaccinated	Ban-days
5 km	5 km	65%	3611.67 (-54.26%)	0	-	15,113.75	1,089,794.0
		80%	3202.63 (-59.44%)	0	-	14,750.51	1,060,575.8
		90%	3038.75 (-61.52%)	0	-	14,640.62	1,054,505.2
	10 km	65%	3615.49 (-54.21%)	0	-	15,126.20	1,682,809.0
		80%	3211.02 (-59.33%)	0	-	14,724.14	1,660,836.5
		90%	3055.05 (-61.31%)	0	-	14,633.76	1,659,800.8
10 km	5 km	65%	1478.64 (-81.27%)	0	-	18,980.18	558,727.4
		80%	1192.26 (-84.9%)	0	-	18,461.24	526,916.6
		90%	1060.19 (-86.57%)	0	-	17,992.94	509,347.1
	10 km	65%	1477.63 (-81.29%)	0	-	18,961.98	1,120,293.0
		80%	1172.91 (-85.15%)	0	-	18,308.12	1,077,181.7
		90%	1064.19 (-86.52%)	0	-	18,109.10	1,067,776.2

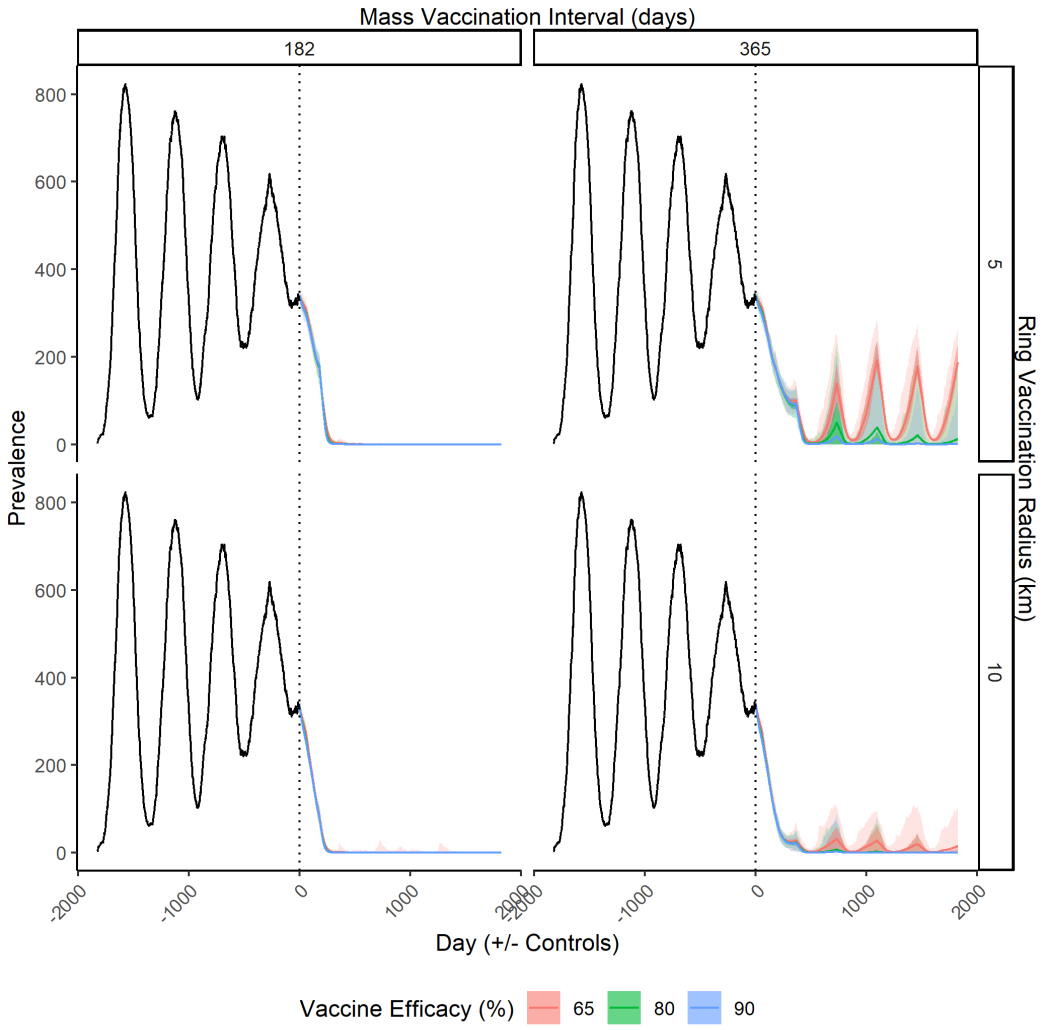

Figure 5.15: Prevalence of FMD after implementation of both reactive ring vaccination and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive ring vaccination. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination is clearly better than annual mass vaccination, though both lead to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. A larger ring vaccination radius leads to an additional reduction in virus circulation.

Table 5.14: Statistics of the combined Ring Vaccination (RV) and Mass Vaccination (MV) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, and the average number of farms vaccinated.

Interval	Radius	VE	Incidence	P(E)	TTE	Vaccinated
182 days	5 km	65%	332.2 (-95.79%)	1.00	469.06	12,856.02
		80%	282.73 (-96.42%)	1.00	365.23	12,780.45
		90%	269.36 (-96.59%)	1.00	341.37	12,756.29
	10 km	65%	147.45 (-98.13%)	1.00	412.55	13,762.09
		80%	95.32 (-98.79%)	1.00	312.62	13,615.36
		90%	78.22 (-99.01%)	1.00	303.3	13,583.78
365 days	5 km	65%	2013.18 (-74.5%)	0.05	675.6	13,322.05
		80%	709.89 (-91.01%)	0.90	760.52	9,206.78
		90%	514.96 (-93.48%)	0.99	604.85	8,559.69
	10 km	65%	436.25 (-94.48%)	0.73	850.95	12,002.10
		80%	165.03 (-97.91%)	1.00	566.4	9,480.51
		90%	127.96 (-98.38%)	1.00	491.21	9,196.34

Movement Bans and Mass Vaccination

Due to the amply demonstrated inefficacy of MB policies, using MV in concert with MB policies did not lead to a larger reduction in prevalence and incidence, but a very similar reduction to MV alone (Figure 5.16). There was also no mitigating interaction, seen with RV policies, which could reduce the large resurgences seen with annual MV.

As with MV alone, reductions in incidence ranged from -38.48% to -88.34%, and P(E) from 0.04 to 1.00.

5.3.4 Ring Vaccination, Movement Bans, and Mass Vaccination

Combining all of the control policies together is very similar to the combination of MV and RV: disease circulation can be reduced to elimination of FMD with biannual mass vaccination, and large reductions are observed annual mass vaccination (Figure 5.17). Ring vaccination at a 10 km radius reduces prevalence further in the case of annual vaccination. Movement bans had no effect on prevalence or incidence.

Reductions in incidence ranged from -75.74% to -98.99%, and elimination can be almost certain with biannual mass vaccination and ring vaccination. The average TTE varied from as high as 694 to as low as 294.73, and the number of farms vaccinated between approximately 8500 to 14000.

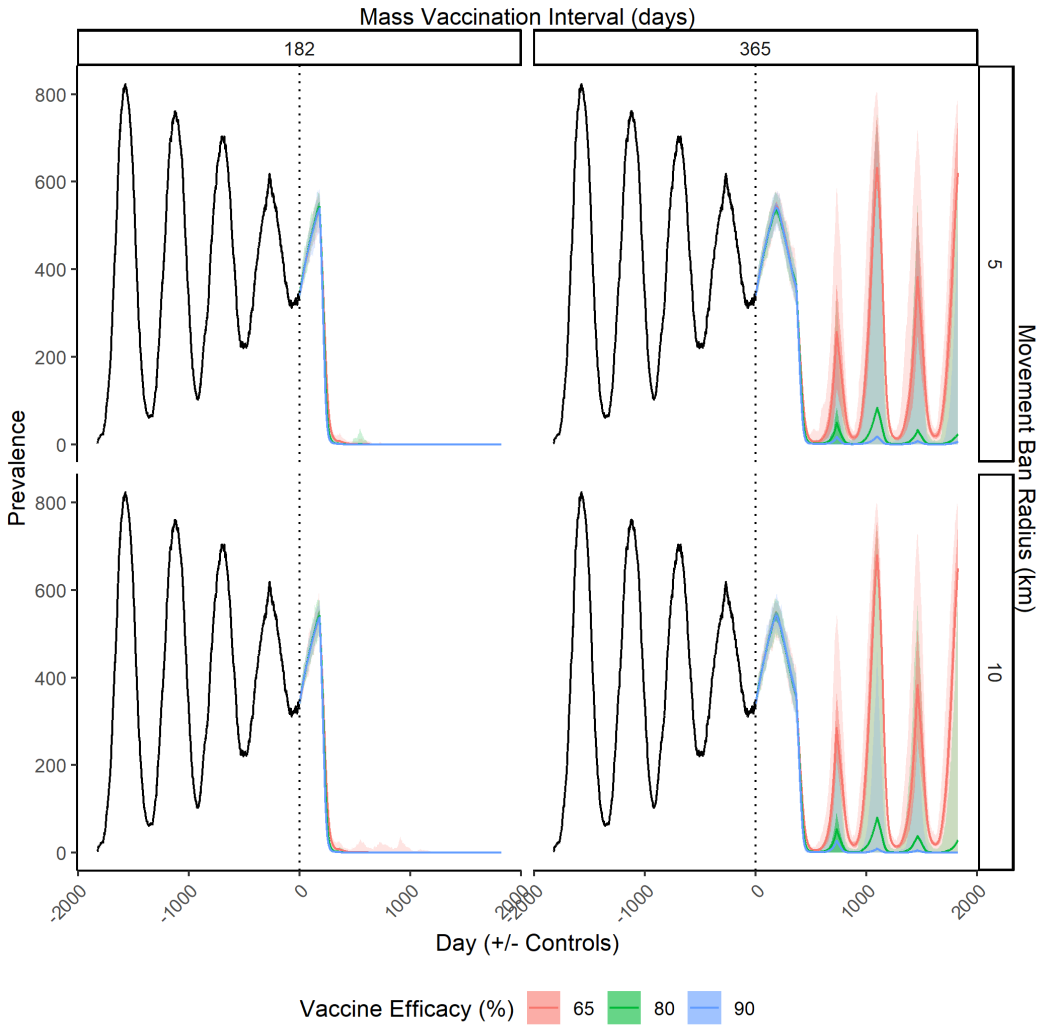

Figure 5.16: Prevalence of FMD after implementation of both reactive movement bans and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a 5 or 10 km radius for reactive movement bans. The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Movement bans appear to make no difference to the prevalence, regardless of which mass vaccination policy they are combined with.

Table 5.15: Statistics of the combined Movement Ban (MB) and Mass Vaccination (MV) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	Radius	VE	Incidence	P(E)	TTE	Vaccinated	Ban-days
182 days	5 km	65%	940.18 (-88.09%)	1.00	510.42	10,969.92	226,184.3
		80%	934.46 (-88.17%)	1.00	383.83	10,971.49	212,335.0
		90%	921.97 (-88.32%)	1.00	367.1	10,971.56	205,985.1
	10 km	65%	948.74 (-87.98%)	1.00	538.68	10,970.16	302,633.3
		80%	929.92 (-88.22%)	1.00	383.01	10,969.37	274,427.2
		90%	920.68 (-88.34%)	1.00	369.18	10,969.36	264,970.5
365 days	5 km	65%	4687.63 (-40.63%)	0.07	658	5,485.79	813,271.1
		80%	1902.34 (-75.91%)	0.95	770.25	5,483.94	400,926.9
		90%	1686.4 (-78.64%)	0.98	625.49	5,484.05	363,814.2
	10 km	65%	4857.58 (-38.48%)	0.04	864.25	5,485.48	1,172,719.9
		80%	1927.92 (-75.58%)	0.91	728.92	5,486.22	527,259.7
		90%	1670.76 (-78.84%)	1.00	627.07	5,486.23	462,438.9

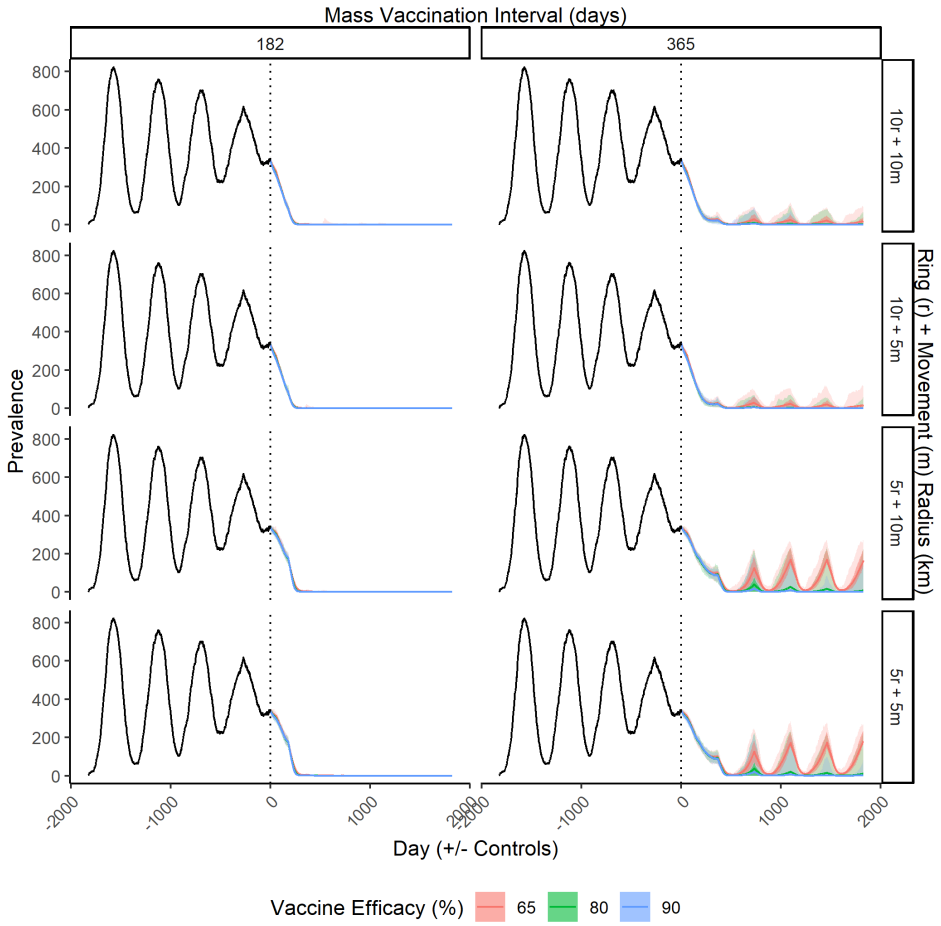

Figure 5.17: Prevalence of FMD after implementation of all three of reactive ring vaccination, reactive movement bans, and proactive mass vaccination. Each column indicates a mass vaccination interval of either 182 or 265 days, and each row a combination of a 5 or 10 km radius for reactive ring vaccination (indicated by r) and movement bans (indicated by m). The vertical dotted lines indicate the simulated implementation of the control policies on day 0. Lines to the right of this on each plot indicates the average prevalence for the given day, with different coloured lines and ribbons referencing different average vaccine efficacy. A darker coloured area around each line indicates the IQR of values, and the lighter coloured ribbon indicating the full range of values. The implementation of biannual mass vaccination clearly leads to lower prevalence than annual mass vaccination, though both cause to a strong reduction in prevalence. With annual mass vaccination, there is a potential for resurgences depending on VE, with higher VE reducing this risk. Ring vaccination additionally reduces the prevalence of disease, however movement bans appear to make no difference to the prevalence, regardless of which policy they are combined with.

Table 5.16: Statistics of the combined Ring Vaccination (RV), Movement Ban (MB), and Mass Vaccination (MV) policies, when an assumed **shipment transmission** persistence driver is in place. This summarises the average total incidence, the percentage difference this average is from the baseline no control scenario, the estimated probability of elimination P(E), the average time to elimination TTE, the average number of farms vaccinated, and the average total number of days farms spent under a movement ban (Ban-days).

Interval	RV Radius	MB Radius	VE	Incidence	P(E)	TTE	Vaccinated	Ban-days
182 days	5 km	5 km	65%	333.73 (-95.77%)	1.00	466.27	12,869.42	159,891.4
			80%	283.49 (-96.41%)	1.00	374.41	12,773.73	152,761.0
			90%	265.56 (-96.64%)	1.00	341.29	12,747.22	151,016.9
		10 km	65%	334.14 (-95.77%)	1.00	488.67	12,869.13	247,158.0
			80%	284.16 (-96.4%)	1.00	370.32	12,776.46	232,089.0
			90%	268.14 (-96.6%)	1.00	355.3	12,757.27	227,681.9
	10 km	5 km	65%	145.58 (-98.16%)	1.00	390.66	13,718.40	116,833.6
			80%	98.42 (-98.75%)	1.00	324.9	13,643.68	113,947.6
			90%	79.89 (-98.99%)	1.00	295.93	13,586.00	111,943.9
		10 km	65%	147.43 (-98.13%)	1.00	404.48	13,747.61	194,812.9
			80%	96.31 (-98.78%)	1.00	332.83	13,646.16	187,864.0
			90%	79.81 (-98.99%)	1.00	294.73	13,597.86	183,914.2
365 days	5 km	5 km	65%	1915.56 (-75.74%)	0.12	694	12,997.95	552,688.3
			80%	630.08 (-92.02%)	0.92	685.98	8,912.57	263,489.3
			90%	503.56 (-93.62%)	0.99	581.81	8,521.02	237,069.8
		10 km	65%	1864.74 (-76.38%)	0.16	696.19	12,821.37	922,436.9
			80%	649.57 (-91.77%)	0.92	738.78	8,987.37	449,889.8
			90%	500.69 (-93.66%)	0.99	577.01	8,531.76	386,634.8
	10 km	5 km	65%	427.27 (-94.59%)	0.74	791.05	11,878.22	209,445.5
			80%	165.57 (-97.9%)	0.98	564.35	9,456.61	143,623.5
			90%	134.4 (-98.3%)	1.00	511.67	9,289.44	140,006.0
		10 km	65%	424.18 (-94.63%)	0.69	723.01	11,875.54	402,891.7
			80%	187.45 (-97.63%)	0.97	586.96	9,718.20	275,102.4
			90%	136.11 (-98.28%)	1.00	501.99	9,273.50	249,721.8

5.4 Discussion

The results demonstrate that the assumption of carrier transmission can reduce the effectiveness in reducing infections of individual control policies, drastically reducing the effectiveness of mass vaccination. The pessimistic assumption of the greatest infectiousness of carrier animals, with the longest duration, increased the average number of infections in the no-controls scenario to 16,954, and reduced the oscillations around the endemic equilibrium compared to the scenario where no assumption of carrier transmission was made.

RV policies alone remained relatively effective as control policies with this persistence driver assumption, although the average reduction in incidence fell from a maximum of -87% with no persistence drivers, to a maximum of -17%. VE also appeared more relevant in this scenario, as there was less overlap between the observed prevalence for each VE. RV policies were also relatively more effective compared to MV policies, with the assumption of carrier transmission, as the only policy that permanently reduced the prevalence of FMD in the simulations.

MB policies were once again not useful as control policies with the assumption of carrier transmission, failing to reduce the circulation of FMD in the simulations when implemented as stand-alone policies or in concert with other control policies. This was similar to that observed when no persistence driver was assumed, and is to be expected as the assumption of carrier transmission does not increase the transmission potential of livestock shipments.

MV policies were also rendered much less effective when carrier transmission was assumed to be occurring; instead of reducing the prevalence of FMD to a low and manageable level, or eliminating the disease entirely, the periodic mass vaccination of farms only reduced prevalence temporarily before a resurgence to the prevalence seen prior to vaccination. This is a consequence of the pessimistic assumption about the carrier transmission parameters, which are very infectious and remain so for a long time, but also because vaccination does not induce clearance of the virus in carrier animals. Because of this limitation, prophylactic vaccination of a farm will leave many still-infectious carrier animals behind, acting as a reservoir of disease to infect other animals when their immunity wanes. Due to the pulse-like nature of mass vaccination, this occurs all at one time, whereas ring vaccination is a constant reactive process and so constantly vaccinates farms, reaching an equilibrium level where vaccination is matched by reinfections from carrier animals that vaccination cannot cure. As might be expected with these assumptions, none of the control policies could cause elimination of the disease.

Whether or not the optimal policy with this pessimistic assumption is RV alone or in combination with MV depends on the relative importance of reducing average prevalence or incidence. Although the combination of RV and MV policies produced the lowest average prevalence seen with this persistence driver and assumptions, the purpose of implementing control policies such as these is to produce lasting changes in the burden and distribution of disease, and by this criteria only RV policies can be called effective within this set of assumptions. However, it is likely that the effectiveness of MV policies would be greatly improved with less pessimistic assumptions about the infectiousness and duration of the carrier state.

The assumption of the fomite-contaminated shipments driver appears to have no effect on the relative rankings or actual effectiveness of the control policies simulated. With this assumption, RV and MV policies are most effective and MB policies have no effect. This was unexpected, as the assumption that all shipments from an infected farm will infect the source farm should raise the importance of this transmission route, and make efforts to address it more important. This would tend to support prior theorising that, at the scale of simulation, livestock shipments are not an important transmission route. A limitation of the model simulation is the lack of data on vehicles: in reality a contaminated vehicle can infect multiple farms, possibly being contaminated for several days, which would increase the importance of this transmission route. In our simulation, due to a lack of data, this cannot be tracked and it is assumed only the initial movements from an infected farm to another farm cause infection. This model would therefore tend to underestimate the importance of this transmission route. Additionally, RV and MV can efficiently reduce the prevalence of infected premises, which are necessary for this transmission route to occur in the simulation at all.

A limitation of this work is the assumption of completely protective vaccines. It is known that vaccinated animals are sometimes sub-clinically infected (dependent on vaccine strength and time before challenge), and that vaccination does not prevent cattle from becoming carriers, and in this model therefore carriers (Carolina Stenfeldt and Jonathan Arzt 2020). It is likely that this would further reduce the efficacy of RV and MV policies, as vaccination would become less effective in preventing infection and the formation of a (in this model) disease reservoir of carrier animals. This work should be done to see if this effect does indeed occur.

Another limitation is the lack of vehicle data, and more direct modelling of fomite contamination of the environment. It is unfortunate that this requires access to vehicle-specific movement data, as well as the environmental data of the farms simulated, but work to simulate this important transmission route with more fidelity

is likely to improve the accuracy and relevance of the results obtained.

This may be compared to real-world implementations of mass vaccination campaigns against FMD, where the campaigns take much longer for elimination of the disease to occur but elimination is possible. In Turkey, mass vaccination campaigns have allowed the reduction in prevalence of FMD to only 6 outbreaks in the last quarter of 2021 (FAO 2022). On the strength of the evidence, mass vaccination with reactive ring vaccination is the optimal control policy for endemic countries with enough resources to contemplate elimination, and the results of this theoretical work with high carrier transmission may (conditional on the model) be taken as evidence against the assumed rate of carrier transmission.

In summary, the assumption of different persistence drivers does make a difference in the optimal disease control policy if (high) carrier transmission and duration is assumed. Ring vaccination policies become relatively more effective as the only policy that produces a lasting change in the prevalence and distribution of the disease, whereas mass vaccination is much reduced in efficacy and movement bans remain of little importance. However, assuming high transmission from livestock movements does not affect the efficacy of the control policies assessed, and therefore the optimal control policy combination with this assumption remains a combination of biannual mass vaccination and ring vaccination. Given that different assumed persistence drivers may lead to different optimal control policies, it is important that we research the mechanisms underlying persistence in reality, in order to investigate their potential as roadblocks to elimination of FMD from more regions of the world.

Chapter 6

Conclusions

In this thesis we have outlined our development of an endemic epidemiological modelling framework, and explored the dynamics of FMD in endemic regions of the world. This model was applied to assess different policies used to control the disease in endemic regions, in addition to exploring the effects of hypothetically infectious carrier animals and comparing these to other hypothesised persistence drivers.

In Chapter 2 we described the development of a stochastic spatial metapopulation model, keeping in mind the specific challenges of simulating endemic FMD which have led to a dearth of epidemiological models assessing such disease environments. In particular, the lack of good data is a common handicap for research into this area due to the many other problems that countries with endemic FMD may face, fortunately ameliorated for our research due to the data available from Turkey. The model includes birth and death demographics, maternal immunity, and waning immunity, but could not include multiple serotypes at the scale used because of a lack of explicit serotype data. Identification analysis indicated that the data available was sufficient for the parameterisation of the transmission dispersal kernel, and fitting of this model framework resulted in estimation of this kernel using the quality data available. This indicated that between-farm transmission in this environment was likely to be slightly less likely than observed in the UK 2001 FMD outbreak, as all of the most likely parameter values varied a minor amount in the direction of more local transmission compared to the values found for that epidemic.

Resolving some of this parameter uncertainty allowed for a more robust exploration of plausible endemic FMD control policies in Chapter 3. We applied these parameter estimates and knowledge of common control policies for FMD to exhaustively assess the efficacy of such policies in reducing the prevalence of FMD in regions where the disease was endemic, in addition to the potential for elimination and speed

of doing so. In our analysis we found that reactive ring vaccination in combination with biannual mass vaccination was optimal, in that these combinations were most likely to eliminate the disease within the area assessed, and the fastest to do so. An unexpected results was the failure of controls over livestock movements to have an effect on disease prevalence or incidence. It was hypothesised that shipments were a less relevant transmission route in regions where the disease is already widespread, or that the simulated region was too small for the effect of livestock movements to be observed. Sensitivity analysis of these control policies indicated that the mass vaccination interval and coverage, as well as the ring vaccination radius, were most important for the success of these control policies.

Chapter 4 used the model to explore the potential effects of infectious carrier cattle as a driver for persistence, and compared it to the alternate hypothesis of movements of infected animals spreading FMD to susceptible areas. This exploration found that infectious carrier animals could act as a persistence driver even at very low rates of transmission, suggesting that current research cannot yet rule out the epidemiological relevance of this potential transmission route. Sensitivity analysis suggested routes to narrow down the feasible values for this hypothesised transmission further. The movement of infected animals was found not to support persistence without an assumption of contaminated vehicles, supporting the importance of bio-security measures for controlling the spread of FMD. Persistence through this transmission route depended on the number of premises under investigation rather than the area, suggesting that the number of shipments was more important than long-range shipments for this transmission route.

Following this, the potential effects of the two persistence drivers on the efficacy of FMD control policies were assessed in Chapter 5. Using pessimistic assumptions about the persistence drivers, carrier transmission as a persistence driver led to dramatic changes in the baseline prevalence of the disease, and significantly limited the effectiveness of each control policy assessed. Ring vaccination fared best with these pessimistic assumptions, whereas mass vaccination was rendered ineffective. These results suggest the impact of (high) carrier transmission would be large, and might also act as Bayesian evidence in favour of low (or 0) carrier transmission rates due to the severity of the effects. In contrast, the assumption of contaminated livestock movements had no effect on the effectiveness of the control policies, and the optimal control policies remained the same. This persistence driver has a larger evidence base in support of its existence, in comparison to carrier transmission, and this therefore suggests current policies are sufficient to control the disease in the presence of this contamination.

The model developed differs from the most common FMD models in the intention behind it and the mechanisms that have been included. As discussed in Zaheer, Mo D. Salman, et al. (2020b), the vast majority of stochastic spatial models are intended for use simulating epidemics of FMD, and do not include relevant features of endemic FMD such as births and deaths, multiple circulating serotypes, and routine prophylactic vaccination. This model is spatial and stochastic, but also includes the demographics of births and deaths and routine prophylactic vaccination. It is also capable of simulating multiple circulating serotypes, although this was not used in the thesis due to data issues discussed in Chapter 2. These features of the model make it well-suited to simulating endemic FMD disease and addressing questions of control policy, where the others are not. Finally, the model differs from normal in the explicit modelling of within-farm transmission and synchronisation of this with between-farm transmission. This allowed for the more natural expression of carrier transmission as a within-farm phenomenon rather than a more clunky construct of entire herds being in the carrier state as in Schnell (2019).

The analysis of control policies mostly found results that accorded with expectations about the effectiveness of different control policies. It is known that, given a rigorous enough mass vaccination campaign in combination with adequate biosecurity, FMD can be eliminated from a region. This has worked in Europe and most of South America, and the PCP for FMD acknowledges that freedom from FMD without vaccination entails going through a stage of managing the disease through vaccination (Leforban 1999; Naranjo and Cosivi 2013; K. Sumption, Domenech, and Ferrari 2012). Control policies once freedom from FMD is achieved tend to differ from endemic control policies in their use of culling, the economic importance of livestock to the countries that are currently endemic for FMD mitigates against reactive culling in response to an outbreak. There is also likely an effect of what equilibrium a country is used to: countries that are free have adapted to not having FMD and having unrestricted livestock trade; countries that are endemic are used to having FMD and restricted livestock trade, so they likely see the costs of another outbreak as lower resulting in less political support for culling. As this work was based on endemic regions, and Turkey does not cull, culling was not included as a control policy option.

The most unexpected result was the lack of efficacy of movement restrictions to reduce the observed incidence of FMD. Modelling of the 2001 UK epidemic found that movement restrictions resulted in a reduction of predicted FMD spread relative to the counterfactual, however the movement of entire infected herds in endemic regions of Cameroon was not enough to support endemic FMD (Schnell 2019; M. J.

Tildesley et al. 2019). This result therefore suggests that movement restrictions are much less efficacious in endemic settings, but remain important in epidemic settings. We explored a scenario of fomite transmission in Chapter 5 that assessed potential contamination of the vehicles used to ship the recorded shipments, which also found no effect of movement restrictions. However, structural uncertainty remains, as our shipment records are unlikely to be a full accounting of animal movements in the region, and certainly do not include informal movements of people or vehicles. Reactive movement bans are common in both epidemic and endemic countries, however the benefit of them may be less than expected in endemic regions, and this work adds to the uncertainty.

The analysis of carrier transmission and animal movements as potential drivers of endemic FMD demonstrated that both mechanisms were capable of supporting endemicity. However, it did not include all possible drivers of endemic FMD. For example, fomite contamination of the environment also occurs and is known to be a significant contributor of overall transmission on a farm (Bravo de Rueda et al. 2015). Unfortunately this could not be included due to the lack of adequate data on farm environments. Another possibility is the repeated importation of FMD across borders, likely due to illegal or unrecorded animal movements which happen in many regions, which have been recognised as a factor contributing to the failure of control schemes in South East Asia (Blacksell et al. 2019). This is essentially the mechanism investigated in this work, of patch extinction and reintroduction from a currently infected area, but the movements would be unrecorded and so were not in the model. However, the results of this work should still apply to these unregistered movements, rather the control policies need to effect the unregistered movements to have the effect intended. Animal reservoirs are another source of endemic FMD, it is known that African Buffalo are chronic carriers of FMD and can transmit to uninfected cattle, this is a significant factor in the recurrent outbreaks in South Africa and nearby countries (Brückner et al. 2002). Again, this is already essentially the investigated carrier transmission model and the results obtained should be applicable.

The importance of fomite contamination to transmission accords with the evidence that has accumulated. Indirect contamination routes are relatively understudied due to the difficulty of accessing data on the informal contacts between farms, assuming such data exists; in endemic areas many farmers do not record who visits the farm and when. Data on these contacts in free countries is generally collected through farmer surveys or commercial data, which have their own difficulties (Sansamur et al. 2020; Sanson et al. 1993). Given the right conditions however,

virus particles can survive in the environment for days to months, and experimental tests of indirect transmission found that roughly 44% of transmission was through this route (Bravo de Rueda et al. 2015; Mielke and Garabed 2020). This indirect transmission route is relevant in both epidemic and endemic scenarios (even public access to the countryside may be a risk (Auty 2019)), and is the target of movement restrictions control policies. Our work supports the importance of this transmission route, and the importance of biosecurity measures to prevent fomite contamination.

The results here are likely to be scalable to larger regions, as the area and number simulated is already quite large; Erzurum Province is 25,000 km^2 and the entire Eastern Region is 120,000 km^2 (approximately the size of England). As previously discussed, the control policy results are generally in accordance with what is known to be possible; mass vaccination has led to the elimination of FMD from the entirety of Europe. However, a major determining factor in the success or failure of the policies concerned is state capacity: the ability of states to actually accomplish its policy goals. The model developed allows some variation in the efficacy of different policy options but cannot account for features not included in the model which can effect the spread of FMD and which a government attempting to control FMD needs to be concerned with. One of those factors is the illegal movements of animals (or people), which are not recorded. The UK 2001 outbreak was found to be due to illegal importation of infected feed, and transboundary animal importation is known to be a large industry in the South East Asia (Blacksell et al. 2019; L.M et al. 2011). A state's capacity to control this is likely to be critical to the success of their efforts.

The work within this thesis suggests a number of potential avenues to pursue. One possibility is to reduce the complexity of the model by reducing or removing the within-farm stochastic compartmental model, with the aim of sufficient speed to be able to simulate, and use data for, the entirety of Turkey. This would allow more data for parameter estimates, also assisting in the addition of multiple serotypes to the model, which was infeasible due to the lack of serotype-specific data at the scale the model was used at. On the other hand, this might lead to the removal of demographics and explicit maternal immunity from the model, reducing the accuracy of different areas of the model. Simulations covering larger areas might also allow investigation of which spatial scales livestock shipments begin to have material effects on control policies. As discussed in Chapter 3, where preventing the movement of livestock failed to impact on FMD prevalence, the spatial scale simulated might change the impact of the long-range disease spread events which livestock movements present a risk of.

Other avenues include explicitly simulating the spread of multiple simultaneous serotypes, and the circumstances in which this does or does not alter optimal control strategies. Our modelling framework could also be adapted to add more varied and targeted surveillance strategies, which might be combined with the simulation of multiple serotypes to investigate which surveillance and control strategies are most robust to the introduction of strains which have escaped vaccine-induced immunity. Other directions to pursue include but are not limited to directly attempting to simulate fomite contamination of farms; simulation of farm-level biosecurity variation; and comparisons between state-led and farmer-directed disease controls. Finally, the high-quality data available for Turkey might also allow artificially degrading the data to investigate which sections of the data are most important to collect for different objectives, which could inform surveillance strategies in many regions where the disease remains endemic.

Whilst there is much to be done, we have made contributory steps in analysing the spread of Foot-and-Mouth Disease in endemic regions, as well as contributing to the debate over the existence of infectious persistently-infected livestock animals. We hope to continue this work into the future, and see where the future leads.

Bibliography

A, Di Nardo, Knowles N.J, and Paton D.J (Apr. 2011). "Combining livestock trade patterns with phylogenetics to help understand the spread of foot and mouth disease in sub-Saharan Africa, the Middle East and Southeast Asia". In: 30.1, pp. 63–85. ISSN: 0253-1933. DOI: 10.20506/rst.30.1.2022.

Alexandersen, S., M. Quan, C. Murphy, J. Knight, and Z. Zhang (Nov. 1, 2003). "Studies of Quantitative Parameters of Virus Excretion and Transmission in Pigs and Cattle Experimentally Infected with Foot-and-Mouth Disease Virus". In: *Journal of Comparative Pathology* 129.4, pp. 268–282. ISSN: 0021-9975. DOI: 10.1016/s0021-9975(03)00045-8.

Alexandersen, S., Z. Zhang, S. M. Reid, G. H. Hutchings, and A. I. Donaldson (2002). "Quantities of infectious virus and viral RNA recovered from sheep and cattle experimentally infected with foot-and-mouth disease virus O UK 2001". In: *Journal of General Virology* 83.8, pp. 1915–1923. ISSN: 1465-2099. DOI: https://doi.org/10.1099/0022-1317-83-8-1915.

Alexandersen, Soren, Zhidong Zhang, and Alex I. Donaldson (Aug. 2002). "Aspects of the persistence of foot-and-mouth disease virus in animals–the carrier problem". In: *Microbes and Infection* 4.10, pp. 1099–1110. ISSN: 12864579. DOI: 10.1136/vr.110.3.53.

Anastassopoulou, Cleo, Lucia Russo, Athanasios Tsakris, and Constantinos Siettos (Mar. 2020). "Data-based analysis, modelling and forecasting of the COVID-19 outbreak". In: *Plos One* 15.3, pp. 1–21. DOI: 10.1371/journal.pone.0230405.

Anderson, Roy M. and Robert M. May (Aug. 1979). "Population biology of infectious diseases: Part I". In: *Nature* 280.5721, pp. 361–367. ISSN: 1476-4687. DOI: 10.1038/280361a0.

Arnold, M.E, D.J Paton, E Ryan, S.J Cox, and J.W Wilesmith (Jan. 7, 2008). "Modelling studies to estimate the prevalence of foot-and-mouth disease carriers after reactive vaccination". In: *Proceedings of the Royal Society B: Biological Sciences* 275.1630. Publisher: Royal Society, pp. 107–115. ISSN: 0962-8452, 1471-2954. DOI: 10.1098/rspb.2007.1154.

Arzt, J., N. Juleff, Z. Zhang, and L. L. Rodriguez (2011). "The Pathogenesis of Foot-and-Mouth Disease I: Viral Pathways in Cattle". In: *Transboundary and Emerging Diseases* 58.4, pp. 291–304. DOI: https://doi.org/10.1111/j.1865-1682.2011.01204.x.

Arzt, Jonathan, Graham J. Belsham, Louise Lohse, Anette Bøtner, and Carolina Stenfeldt (Sept. 12, 2018). "Transmission of Foot-and-Mouth Disease from Persistently Infected Carrier Cattle to Naive Cattle via Transfer of Oropharyngeal Fluid". In: *mSphere* 3.5. ISSN: 2379-5042. DOI: 10.1128/mSphere.00365-18.

Auty, Harriet (2019). "The Risk of Foot and Mouth Disease Transmission Posed by Public Access to the Countryside During an Outbreak". In: *Frontiers in Veterinary Science* 6, p. 12.

Bertram, Miranda R, Le T Vu, et al. (July 2018). "Lack of transmission of foot-and-mouth disease virus from persistently infected cattle to naïve cattle under field conditions in Vietnam". en. In: *Front. Vet. Sci.* 5, p. 174. DOI: 10.3389/fvets.2018.00174.

Bertram, Miranda R, Shankar Yadav, Carolina Stenfeldt, Amy Delgado, and Jonathan Arzt (May 2020). "Extinction dynamics of the foot-and-mouth disease virus carrier state under natural conditions". en. In: *Front. Vet. Sci.* 7, p. 276. DOI: 10.3389/fvets.2020.00276.

Björnham, Oscar, Robert Sigg, and Jan Burman (May 26, 2020). "Multilevel model for airborne transmission of foot-and-mouth disease applied to Swedish livestock". In: *Plos One* 15.5. Publisher: Public Library of Science, e0232489. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0232489.

Blacksell, Stuart D., Jarunee Siengsanan-Lamont, Somjai Kamolsiripichaiporn, Laurence J. Gleeson, and Peter A. Windsor (2019). "A history of FMD research and control programmes in Southeast Asia: lessons from the past informing the future". In: *Epidemiology and Infection* 147, e171. DOI: 10.1017/S0950268819000578.

Blancou, Jean (2002). "History of the control of foot and mouth disease". In: *Comparative Immunology, Microbiology and Infectious Diseases* 25.5, pp. 283–

296. ISSN: 0147-9571. DOI: https://doi.org/10.1016/S0147-9571(02)00026-7.

Bolker, B M and B T Grenfell (1996). "Impact of vaccination on the spatial correlation and persistence of measles dynamics." In: *Proceedings of the National Academy of Sciences* 93.22, pp. 12648–12653. DOI: 10.1073/pnas.93.22.12648.

Bouma, A., A. R. W. Elbers, A. Dekker, A. de Koeijer, C. Bartels, P. Vellema, P. van der Wal, E. M. A. van Rooij, F. H. Pluimers, and M. C. M. de Jong (Mar. 20, 2003). "The foot-and-mouth disease epidemic in The Netherlands in 2001". In: *Preventive Veterinary Medicine* 57.3, pp. 155–166. ISSN: 0167-5877. DOI: 10.1016/s0167-5877(02)00217-9.

Bouma, A., A.R.W. Elbers, A. Dekker, A. de Koeijer, C. Bartels, P. Vellema, P. van der Wal, E.M.A. van Rooij, F.H. Pluimers, and M.C.M. de Jong (2003). "The foot-and-mouth disease epidemic in The Netherlands in 2001". In: *Preventive Veterinary Medicine* 57.3, pp. 155–166. ISSN: 0167-5877. DOI: https://doi.org/10.1016/S0167-5877(02)00217-9.

Bourn, John, Richard Eales, Pamela Thomas, David Bostock, Stewart Lingard, Ian Derbyshire, Allison Burmiston, and Howard Kitson (June 14, 2002). *The 2001 Outbreak of Foot and Mouth Disease*. UK National Audit Office.

Branscum, A. J., A. M. Perez, W. O. Johnson, and M. C. Thurmond (June 2008). "Bayesian spatiotemporal analysis of foot-and-mouth disease data from the Republic of Turkey". In: *Epidemiology and Infection* 136.6, pp. 833–842. ISSN: 0950-2688. DOI: 10.1017/s0950268807009065.

Brauer, Fred (2008). "Compartmental Models in Epidemiology". In: *Mathematical Epidemiology* 1945, pp. 19–79. DOI: 10.1007/978-3-540-78911-6_2.

— (Nov. 2009). "Mathematical epidemiology is not an oxymoron". In: *BMC Public Health* 9.1. Number: 1 Publisher: BioMed Central, pp. 1–11. ISSN: 1471-2458. DOI: 10.1186/1471-2458-9-s1-s2.

Bravo de Rueda, Carla, Mart CM de Jong, Phaedra L. Eblé, and Aldo Dekker (Apr. 2015). "Quantification of transmission of foot-and-mouth disease virus caused by an environment contaminated with secretions and excretions from infected calves". In: *Veterinary Research* 46.1, p. 43. ISSN: 1297-9716. DOI: 10.1186/s13567-015-0156-5.

Brito, B. P., L. L. Rodriguez, J. M. Hammond, J. Pinto, and A. M. Perez (Apr. 2017). "Review of the Global Distribution of Foot-and-Mouth Disease Virus from 2007 to 2014". In: *Transboundary and Emerging Diseases* 64.2, pp. 316–332. ISSN: 18651674. DOI: 10.1111/tbed.12373.

Bronsvoort, Barend M. deC., Ian G. Handel, Charles K. Nfon, Karl-Johan Sørensen, Viviana Malirat, Ingrid Bergmann, Vincent N. Tanya, and Kenton L. Morgan (July 2016). "Redefining the "carrier" state for foot-and-mouth disease from the dynamics of virus persistence in endemically affected cattle populations". In: *Scientific Reports* 6.1, p. 29059. ISSN: 2045-2322. DOI: 10.1038/srep29059.

Brown, Fred (Jan. 2003). "The history of research in foot-and-mouth disease". en. In: *Virus Res.* 91.1, pp. 3–7. DOI: 10.1016/s0168-1702(02)00268-x.

Brückner, G K et al. (Dec. 2002). "Foot and mouth disease: the experience of South Africa". en. In: *Rev. Sci. Tech.* 21.3, pp. 751–764.

Caporale, V, A Giovannini, and C Zepeda (Dec. 2012). "Surveillance strategies for foot and mouth disease to prove absence of disease and absence of viral circulation". en. In: *Rev. Sci. Tech.* 31.3, pp. 747–759. DOI: 10.20506/rst.31.3.2156.

Colenutt, Claire, Emma Brown, Noel Nelson, David J Paton, Phaedra Eblé, Aldo Dekker, José L Gonzales, and Simon Gubbins (Aug. 2020). "Quantifying the transmission of foot-and-mouth disease virus in cattle via a contaminated environment". en. In: *MBio* 11.4.

Condy, J. B, R. S Hedger, C Hamblin, and I. T. R Barnett (Jan. 1, 1985). "The duration of the foot-and-mouth disease virus carrier state in African buffalo (i) in the individual animal and (ii) in a free-living herd". In: *Comparative Immunology, Microbiology and Infectious Diseases* 8.3, pp. 259–265. ISSN: 0147-9571. DOI: 10.1016/0147-9571(85)90004-9.

Cox, Sarah J., B. Veronica Carr, Satya Parida, Pip A. Hamblin, Helen Prentice, Bryan Charleston, David J. Paton, and Paul V. Barnett (2010). "Longevity of protection in cattle following immunisation with emergency FMD A22 serotype vaccine from the UK strategic reserve". In: *Vaccine* 28.11, pp. 2318–2322. ISSN: 0264-410x. DOI: https://doi.org/10.1016/j.vaccine.2009.12.065.

Dawson, Peter Michael (Nov. 2016). "On the analysis of livestock networks and the modelling of foot-and-mouth disease." PhD thesis. University of Warwick.

Doel, T. R. (Jan. 2003). "FMD vaccines". In: *Virus Research.* Foot-and-Mouth Disease 91.1, pp. 81–99. ISSN: 0168-1702. DOI: 10.1016/s0168-1702(02)00261-7.

— (2005). "Natural and Vaccine Induced Immunity to FMD". In: *Foot-and-Mouth Disease Virus.* Ed. by Brian W.J. Mahy. Current Topics in Micro-

biology and Immunology. Berlin, Heidelberg: Springer, pp. 103–131. ISBN: 978-3-540-27109-3. DOI: 10.1007/3-540-27109-0_5.

Doel, T.R (Jan. 1999). "Optimisation of the immune response to foot-and-mouth disease vaccines". In: *Vaccine* 17.13, pp. 1767–1771. ISSN: 0264410x. DOI: 10.1016/s0264-410x(98)00444-7.

Domingo, Esteban, Eric Baranowski, Cristina Escarmis, and Francisco Sobrino (2002). "Foot-and-mouth disease virus". In: *Comparative Immunology, Microbiology and Infectious Diseases* 25.5, pp. 297–308. ISSN: 0147-9571. DOI: https://doi.org/10.1016/S0147-9571(02)00027-9.

Donaldson, A. I., J. Gloster, L. D. Harvey, and D. H. Deans (Jan. 16, 1982). "Use of prediction models to forecast and analyse airborne spread during the foot-and-mouth disease outbreaks in Brittany, Jersey and the Isle of Wight in 1981". In: *The Veterinary Record* 110.3, pp. 53–57. ISSN: 0042-4900. DOI: 10.1136/vr.110.3.53.

FAO (2022). *Foot-and-mouth disease. Quarterly report, October–December 2021.* DOI: 10.4060/cb8492en.

Ferguson, N. M. (May 11, 2001). "The Foot-and-Mouth Epidemic in Great Britain: Pattern of Spread and Impact of Interventions". In: *Science* 292.5519, pp. 1155–1160. ISSN: 00368075, 10959203. DOI: 10.1126/science.1061020.

Ferguson, Neil M., Christl A. Donnelly, and Roy M. Anderson (Oct. 4, 2001). "Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain". In: *Nature* 413.6855, pp. 542–548. ISSN: 0028-0836, 1476-4687. DOI: 10.1038/35097116.

Fèvre, Eric M., Barend M. de C. Bronsvoort, Katie A. Hamilton, and Sarah Cleaveland (Mar. 1, 2006). "Animal movements and the spread of infectious diseases". In: *Trends in Microbiology* 14.3, pp. 125–131. ISSN: 0966-842x. DOI: 10.1016/j.tim.2006.01.004.

Fine, Paul, Ken Eames, and David L. Heymann (Apr. 2011). ""Herd Immunity": A Rough Guide". In: *Clinical Infectious Diseases* 52.7, pp. 911–916. ISSN: 1058-4838. DOI: 10.1093/cid/cir007.

Garner, MG and SD Beckett (2005). "Modelling the spread of foot-and-mouth disease in Australia". In: *Australian Veterinary Journal* 83.12, pp. 758–766. DOI: https://doi.org/10.1111/j.1751-0813.2005.tb11589.x.

Gilbert, M, S Aktas, H Mohammed, P Roeder, K Sumption, M Tufan, and J Slingenbergh (June 2005). "Patterns of spread and persistence of foot-and-mouth disease types A, O and Asia-1 in Turkey: a meta-population approach". en. In: *Epidemiol. Infect.* 133.3, pp. 537–545. DOI: 10.1017/s0950268804003516.

Gillespie, Daniel T. (1975). "An Exact Method for Numerically Simulating the Stochastic Coalescence Process in a Cloud". In: *Journal of Atmospheric Sciences* 32.10, pp. 1977–1989. DOI: 10.1175/1520-0469(1975)032<1977:aemfns>2.0.co;2.

— (2001). "Approximate accelerated stochastic simulation of chemically reacting systems". In: *The Journal of Chemical Physics* 115.4, pp. 1716–1733. DOI: 10.1063/1.1378322.

Grubman, Marvin J. and Barry Baxt (Apr. 2004). "Foot-and-mouth disease". In: *Clinical Microbiology Reviews* 17.2, pp. 465–493. ISSN: 0893-8512. DOI: 10.1128/cmr.17.2.465-493.2004.

Harvey, Neil, 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 (2007). "The North American Animal Disease Spread Model: A simulation model to assist decision making in evaluating animal disease incursions". In: *Preventive Veterinary Medicine* 82.3, pp. 176–197. ISSN: 0167-5877. DOI: https://doi.org/10.1016/j.prevetmed.2007.05.019.

Hayama, Y., T. Yamamoto, S. Kobayashi, N. Muroga, and T. Tsutsui (Nov. 1, 2013). "Mathematical model of the 2010 foot-and-mouth disease epidemic in Japan and evaluation of control measures". In: *Preventive Veterinary Medicine* 112.3, pp. 183–193. ISSN: 0167-5877. DOI: 10.1016/j.prevetmed.2013.08.010.

Hayer, S. S. et al. (2018). "Foot-and-mouth disease virus transmission dynamics and persistence in a herd of vaccinated dairy cattle in India". In: *Transboundary and Emerging Diseases* 65.2, e404–e415. ISSN: 1865-1682. DOI: https://doi.org/10.1111/tbed.12774.

Heesterbeek, J. A. P. (Sept. 2002). "A Brief History of R0 and a Recipe for its Calculation". In: *Acta Biotheoretica* 50.3, pp. 189–204. ISSN: 1572-8358. DOI: 10.1023/a:1016599411804.

James, A D and J Rushton (Dec. 2002). "The economics of foot and mouth disease". en. In: *Rev. Sci. Tech.* 21.3, pp. 637–644. DOI: 10.20506/rst.21.3.1356.

Jewell, C. P., M. J. Keeling, and G. O. Roberts (Dec. 6, 2009). "Predicting undetected infections during the 2007 foot-and-mouth disease outbreak". In: *Journal of The Royal Society Interface* 6.41, pp. 1145–1151. ISSN: 1742-5689, 1742-5662. DOI: 10.1098/rsif.2008.0433.

Kamel, Mohamed, Amr El-Sayed, and Hugo Castañeda Vazquez (June 2019). "Foot-and-mouth disease vaccines: recent updates and future perspectives". In:

Archives of Virology 164.6, pp. 1501–1513. ISSN: 0304-8608, 1432-8798. DOI: 10.1007/s00705-019-04216-x.

Kao, Rowland R. (June 2002). "The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK". In: *Trends in Microbiology* 10.6, pp. 279–286. ISSN: 0966842x. DOI: 10.1016/s0966-842x(02)02371-5.

Keeling, M J, M E Woolhouse, D J Shaw, L Matthews, M Chase-Topping, D T Haydon, S J Cornell, J Kappey, J Wilesmith, and B T Grenfell (Oct. 2001). "Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape". en. In: *Science* 294.5543, pp. 813–817. DOI: 10.1126/science.1065973.

Keeling, M. J., M. E. J. Woolhouse, R. M. May, G. Davies, and B. T. Grenfell (Jan. 2003). "Modelling vaccination strategies against foot-and-mouth disease". In: *Nature* 421.6919, pp. 136–142. ISSN: 1476-4687. DOI: 10.1038/nature01343.

Keeling, Matt J (June 2005). "Models of foot-and-mouth disease". en. In: *Proc. Biol. Sci.* 272.1569, pp. 1195–1202. DOI: 10.1098/rspb.2004.3046.

Keeling, Matt J., Edward M. Hill, et al. (Jan. 22, 2021). "Predictions of COVID-19 dynamics in the UK: Short-term forecasting and analysis of potential exit strategies". In: *PLOS Computational Biology* 17.1. Publisher: Public Library of Science, e1008619. ISSN: 1553-7358. DOI: 10.1371/journal.pcbi.1008619.

Keeling, Matt J. and Pejman Rohani (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press. DOI: https://doi.org/10.1515/9781400841035.

Kermack, William Ogilvy, A. G. McKendrick, and Gilbert Thomas Walker (Aug. 1, 1927). "A contribution to the mathematical theory of epidemics". In: *Proceedings of the Royal Society of London. Series A, Containing Papers of a Mathematical and Physical Character* 115.772. Publisher: Royal Society, pp. 700–721. DOI: 10.1098/rspa.1927.0118.

Kim, Hyeyoung, Ningchuan Xiao, Mark Moritz, Rebecca Garabed, and Laura W. Pomeroy (2016). "Simulating the Transmission of Foot-And-Mouth Disease Among Mobile Herds in the Far North Region, Cameroon". In: *Journal of Artificial Societies and Social Simulation* 19.2, p. 6. ISSN: 1460-7425. DOI: 10.18564/jasss.3064.

Kitching, R P, A M Hutber, and M V Thrusfield (Mar. 2005). "A review of foot-and-mouth disease with special consideration for the clinical and epidemiological factors relevant to predictive modelling of the disease". en. In: *Vet. J.* 169.2, pp. 197–209. DOI: 10.1016/j.tvjl.2004.06.001.

Kitching, R. P. and J. S. Salt (Jan. 1, 1995). "The interference by maternally-derived antibody with active immunization of farm animals against foot-and-mouth disease". In: *British Veterinary Journal* 151.4, pp. 379–389. ISSN: 0007-1935. DOI: 10.1016/s0007-1935(95)80127-8.

Knight-Jones, T J D, A N Bulut, S Gubbins, K D C Stärk, D U Pfeiffer, K J Sumption, and D J Paton (Feb. 2015). "Randomised field trial to evaluate serological response after foot-and-mouth disease vaccination in Turkey". en. In: *Vaccine* 33.6, pp. 805–811. DOI: 10.1016/j.vaccine.2014.12.010.

Knight-Jones, T J D, L Robinson, B Charleston, L L Rodriguez, C G Gay, K J Sumption, and W Vosloo (2016). "Global Foot-and-Mouth Disease Research Update and Gap Analysis: 2 – Epidemiology, Wildlife and Economics". In: *Transboundary and Emerging Diseases.*, p. 16. DOI: 10.1111/tbed.12522.

Knight-Jones, T. J. D., S. Gubbins, A. N. Bulut, K. D. C. Stärk, D. U. Pfeiffer, K. J. Sumption, and D. J. Paton (Feb. 2016). "Mass vaccination, immunity and coverage: modelling population protection against foot-and-mouth disease in Turkish cattle". In: *Scientific Reports* 6.1, p. 22121. ISSN: 2045-2322. DOI: 10.1038/srep22121.

Knight-Jones, T. J. D., M. McLaws, and J. Rushton (2017). "Foot-and-Mouth Disease Impact on Smallholders - What Do We Know, What Don't We Know and How Can We Find Out More?" In: *Transboundary and Emerging Diseases* 64.4, pp. 1079–1094. DOI: https://doi.org/10.1111/tbed.12507.

Knight-Jones, T. J. D. and J. Rushton (Nov. 1, 2013). "The economic impacts of foot and mouth disease – What are they, how big are they and where do they occur?" In: *Preventive Veterinary Medicine* 112.3, pp. 161–173. ISSN: 0167-5877. DOI: 10.1016/j.prevetmed.2013.07.013.

Knight-Jones, T.J.D., A.N. Bulut, S. Gubbins, K.D.C. Stärk, D.U. Pfeiffer, K.J. Sumption, and D.J. Paton (2014). "Retrospective evaluation of foot-and-mouth disease vaccine effectiveness in Turkey". In: *Vaccine* 32.16, pp. 1848–1855. ISSN: 0264-410x. DOI: https://doi.org/10.1016/j.vaccine.2014.01.071.

L.M, Mansley, Donaldson A.I., Thrusfield M.V., and Honhold N. (2011). "Destructive tension: mathematics versus experience – the progress and control of the 2001 foot and mouth disease epidemic in Great Britain." In: *Scientific & Technical Review.* 08.1, pp. 483–498. DOI: http://dx.doi.org/10.20506/rst.30.2.2054.

Leforban, Y (Mar. 1999). "Prevention measures against foot-and-mouth disease in Europe in recent years". en. In: *Vaccine* 17.13-14, pp. 1755–1759. DOI: 10.1016/s0264-410x(98)00445-9.

Lyons, Nicholas A. et al. (Feb. 2019). "Considerations for design and implementation of vaccine field trials for novel foot-and-mouth disease vaccines". In: *Vaccine* 37.8, pp. 1007–1015. ISSN: 0264410x. DOI: 10.1016/j.vaccine.2018.12.064.

Mackay, D.K.J., M.A. Forsyth, P.R. Davies, A. Berlinzani, G.J. Belsham, M. Flint, and M.D. Ryan (1998). "Differentiating infection from vaccination in foot-and-mouth disease using a panel of recombinant, non-structural proteins in ELISA". In: *Vaccine* 16.5, pp. 446–459. ISSN: 0264-410X. DOI: https://doi.org/10.1016/S0264-410X(97)00227-2.

Mardones, Fernando, Andrés Perez, Javier Sanchez, Mohammad Alkhamis, and Tim Carpenter (2010). "Parameterization of the duration of infection stages of serotype O foot-and-mouth disease virus: an analytical review and meta-analysis with application to simulation models". In: *Veterinary Research* 41.4. ISSN: 0928-4249. DOI: 10.1051/vetres/2010017.

Maree, Francois F. et al. (Oct. 2014). "Challenges and prospects for the control of foot-and-mouth disease: an African perspective". eng. In: *Veterinary medicine (Auckland, N.Z.)* 5. 32670853[pmid], pp. 119–138. ISSN: 2230-2034. DOI: 10.2147/vmrr.s62607.

Marino, Simeone, Ian B. Hogue, Christian J. Ray, and Denise E. Kirschner (Sept. 2008). "A methodology for performing global uncertainty and sensitivity analysis in systems biology". eng. In: *Journal of Theoretical Biology* 254.1, pp. 178–196. ISSN: 1095-8541. DOI: 10.1016/j.jtbi.2008.04.011.

May, Robert M. and Roy M. Anderson (Aug. 1979). "Population biology of infectious diseases: Part II". In: *Nature* 280.5722, pp. 455–461. ISSN: 1476-4687. DOI: 10.1038/280455a0.

McKinley, Trevelyan, Alex R Cook, and Robert Deardon (Jan. 20, 2009). "Inference in Epidemic Models without Likelihoods". In: *The International Journal of Biostatistics* 5.1. ISSN: 1557-4679. DOI: 10.2202/1557-4679.1171.

McKinley, Trevelyan J., Ian Vernon, Ioannis Andrianakis, Nicky McCreesh, Jeremy E. Oakley, Rebecca N. Nsubuga, Michael Goldstein, and Richard G. White (Feb. 2018). "Approximate Bayesian Computation and Simulation-Based Inference for Complex Stochastic Epidemic Models". In: *Statistical Science* 33.1, pp. 4–18. ISSN: 0883-4237. DOI: 10.1214/17-sts618.

McLachlan, I., G. Marion, I. J. McKendrick, T. Porphyre, I. G. Handel, and B. M. deC Bronsvoort (Nov. 22, 2019). "Endemic foot and mouth disease: pastoral inherd disease dynamics in sub-Saharan Africa". In: *Scientific Reports* 9.1. Number: 1 Publisher: Nature Publishing Group, p. 17349. ISSN: 2045-2322. DOI: 10.1038/s41598-019-53658-5.

Mielke, Sarah R and Rebecca Garabed (Mar. 2020). "Environmental persistence of foot-and-mouth disease virus applied to endemic regions". en. In: *Transbound. Emerg. Dis.* 67.2, pp. 543–554. DOI: 10.1111/tbed.13383.

Minter, Amanda and Renata Retkute (Dec. 2019). "Approximate Bayesian Computation for infectious disease modelling". In: *Epidemics* 29, p. 100368. ISSN: 17554365. DOI: 10.1016/j.epidem.2019.100368.

Moonen, P, L Jacobs, A Crienen, and A Dekker (2004). "Detection of carriers of foot-and-mouth disease virus among vaccinated cattle". In: *Veterinary Microbiology* 103.3, p. 10. DOI: 10.1016/j.vetmic.2004.07.005.

Moonen, P. and R. Schrijver (Oct. 1, 2000). "Carriers of foot-and-mouth disease virus: A review". In: *Veterinary Quarterly* 22.4, pp. 193–197. ISSN: 0165-2176. DOI: 10.1080/01652176.2000.9695056.

Morris, R S, J W Wilesmith, M W Stern, R L Sanson, and M A Stevenson (Aug. 2001). "Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001". en. In: *Vet. Rec.* 149.5, pp. 137–144. DOI: 10.1136/vr.149.5.137.

Munsey, Anna, Frank Norbert Mwiine, Sylvester Ochwo, Lauro Velazquez-Salinas, Zaheer Ahmed, Francois Maree, et al. (2021). "Phylogeographic analysis of foot-and-mouth disease virus serotype O dispersal and associated drivers in East Africa". In: *Molecular Ecology* 30.15, pp. 3815–3825. DOI: https://doi.org/10.1111/mec.15991. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1111/mec.15991.

Munsey, Anna, Frank Norbert Mwiine, Sylvester Ochwo, Lauro Velazquez-Salinas, Zaheer Ahmed, Luis L. Rodriguez, Elizabeth Rieder, Andres Perez, and Kimberly VanderWaal (2022). "Ecological and Anthropogenic Spatial Gradients Shape Patterns of Dispersal of Foot-and-Mouth Disease Virus in Uganda". In: *Pathogens* 11.5. ISSN: 2076-0817. DOI: 10.3390/pathogens11050524.

Myung, In Jae (2003). "Tutorial on maximum likelihood estimation". In: *Journal of Mathematical Psychology* 47.1, pp. 90–100. ISSN: 0022-2496. DOI: https://doi.org/10.1016/S0022-2496(02)00028-7.

Naranjo, José and Ottorino Cosivi (Aug. 5, 2013). "Elimination of foot-and-mouth disease in South America: lessons and challenges". In: *Philosophical Transac-*

tions of the Royal Society B: Biological Sciences 368.1623. ISSN: 0962-8436. DOI: 10.1098/rstb.2012.0381.

Nicholls, M J, L Black, and M M Rweyemamu (1984). "The effect of maternally derived antibodies on the response of calves to vaccination against foot and mouth disease". In: *Journal of Hygiene* 92.1, pp. 105–116. DOI: 10.1017/s0022172400064081.

OIE (2021). *Terrestrial Animal Health Code, Chapter 8.8, Infection with Foot and Mouth Disease Virus.*

Orsel, K, A Dekker, A Bouma, J A Stegeman, and M C M de Jong (Sept. 2005). "Vaccination against foot and mouth disease reduces virus transmission in groups of calves". en. In: *Vaccine* 23.41, pp. 4887–4894. DOI: 10.1016/j.vaccine.2005.05.014.

Orsel, K, M C M de Jong, A Bouma, J A Stegeman, and A Dekker (Jan. 2007). "The effect of vaccination on foot and mouth disease virus transmission among dairy cows". en. In: *Vaccine* 25.2, pp. 327–335. DOI: 10.1016/j.vaccine.2006.07.030.

Ozturk, Nursen, Omur Kocak, and Bouda Vosough Ahmadi (2020). "Economic Analysis of Increasing Foot-and-Mouth Disease Vaccination Frequency: The Case of the Biannual Mass Vaccination Strategy". In: *Frontiers in Veterinary Science* 7. ISSN: 2297-1769. DOI: 10.3389/fvets.2020.557190.

Pacheco, Juan M., Kwang-Nyeong Lee, et al. (Jan. 2016). "Evaluation of Infectivity, Virulence and Transmission of FDMV Field Strains of Serotypes O and A Isolated In 2010 from Outbreaks in the Republic of Korea". In: *PLOS ONE* 11.1, pp. 1–21. DOI: 10.1371/journal.pone.0146445.

Pacheco, Juan M., Meghan Tucker, Ethan Hartwig, Elizabeth Bishop, Jonathan Arzt, and Luis L. Rodriguez (2012). "Direct contact transmission of three different foot-and-mouth disease virus strains in swine demonstrates important strain-specific differences". In: *The Veterinary Journal* 193.2, pp. 456–463. ISSN: 1090-0233. DOI: https://doi.org/10.1016/j.tvjl.2012.01.012.

Parida, Satya (2009). "Vaccination against foot-and-mouth disease virus: strategies and effectiveness". In: *Expert Review Vaccines* 8.3, pp. 347–365. ISSN: 1476-0584. DOI: 10.1586/14760584.8.3.347.

Park, Mi-Young, You Jin Han, Eun-Jin Choi, HeeYeon Kim, Rokeya Pervin, Wonseok Shin, Doheon Kwon, Jae Myoung Kim, and Hyun Mi Pyo (2021). "Post-vaccination Monitoring to Assess Foot-and-Mouth Disease Immunity at Population Level in Korea". In: *Frontiers in Veterinary Science* 8. ISSN: 2297-1769. DOI: 10.3389/fvets.2021.673820.

Parthiban, Aravindh Babu R., Mana Mahapatra, Simon Gubbins, and Satya Parida (June 25, 2015). "Virus Excretion from Foot-And-Mouth Disease Virus Carrier Cattle and Their Potential Role in Causing New Outbreaks". In: *Plos One* 10.6. Publisher: Public Library of Science, e0128815. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0128815.

Paton, D J, J F Valarcher, I Bergmann, O G Matlho, V M Zakharov, E L Palma, and G R Thomson (Dec. 2005). "Selection of foot and mouth disease vaccine strains–a review". en. In: *Rev. Sci. Tech.* 24.3, pp. 981–993. DOI: 10.20506/rst.24.3.1632.

Paton, David J., Keith J. Sumption, and Bryan Charleston (Sept. 2009). "Options for control of foot-and-mouth disease: knowledge, capability and policy". eng. In: *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* 364.1530. 19687036[pmid], pp. 2657–2667. ISSN: 1471-2970. DOI: 10.1098/rstb.2009.0100.

Pomeroy, Laura W, Ottar N Bjørnstad, Hyeyoung Kim, Simon Dickmu Jumbo, Souley Abdoulkadiri, and Rebecca Garabed (2015). "Serotype-Specific Transmission and Waning Immunity of Endemic Foot-and-Mouth Disease Virus in Cameroon". In: *Plos One*, p. 16. DOI: 10.1371/journal.pone.0136642.

Pomeroy, Laura W., Shweta Bansal, Michael Tildesley, Karla I. Moreno Torres, Mark Moritz, Ningchuan Xiao, Tim E. Capenter, and Rebecca B. Garabed (June 2017). "Data-driven models of foot-and-mouth disease dynamics: a review". In: *Transboundary and emerging diseases* 64.3, pp. 716–728. ISSN: 1865-1674. DOI: 10.1111/tbed.12437.

Premashthira, Sith, Mo D. Salman, Ashley E. Hill, Robin M. Reich, and Bruce A. Wagner (2011). "Epidemiological simulation modeling and spatial analysis for foot-and-mouth disease control strategies: a comprehensive review". In: *Animal Health Research Reviews* 12.2, pp. 225–234. DOI: 10.1017/s146625231100017x.

Probert, William J M et al. (July 2018). "Real-time decision-making during emergency disease outbreaks". en. In: *PLoS Comput. Biol.* 14.7, e1006202. DOI: 10.1371/journal.pcbi.1006202.

R Core Team (2020). *R: A Language and Environment for Statistical Computing*. Vienna, Austria.

Ringa, N and C T Bauch (Sept. 2014). "Dynamics and control of foot-and-mouth disease in endemic countries: a pair approximation model". en. In: *J. Theor. Biol.* 357, pp. 150–159. DOI: 10.1016/j.jtbi.2014.05.010.

Rodriguez, Luis L and Marvin J Grubman (Nov. 2009). "Foot and mouth disease virus vaccines". en. In: *Vaccine* 27 Suppl 4, pp. D90–4. DOI: 10.1016/j.vaccine.2009.08.039.

Ross, Ronald (Oct. 1, 1911). "Some Quantitative Studies in Epidemiology". In: *Nature* 87.2188. Number: 2188 Publisher: Nature Publishing Group, pp. 466–467. ISSN: 1476-4687. DOI: 10.1038/087466a0.

Rossi, Gianluigi, Rebecca L. Smith, Stefano Pongolini, and Luca Bolzoni (May 2017). "Modelling farm-to-farm disease transmission through personnel movements: from visits to contacts, and back". In: *Scientific Reports* 7.1, p. 2375. ISSN: 2045-2322. DOI: 10.1038/s41598-017-02567-6.

Rweyemamu, M., P. Roeder, D. Mackay, K. Sumption, J. Brownlie, Y. Leforban, J.-F. Valarcher, N. J. Knowles, and V. Saraiva (2008). "Epidemiological Patterns of Foot-and-Mouth Disease Worldwide". In: *Transboundary and Emerging Diseases* 55.1, pp. 57–72. ISSN: 1865-1682. DOI: https://doi.org/10.1111/j.1865-1682.2007.01013.x.

Sansamur, Chalutwan, Anuwat Wiratsudakul, Arisara Charoenpanyanet, and Veerasak Punyapornwithaya (2020). "Cattle Manure Trade Network Analysis and the Relevant Spatial Pathways in an Endemic Area of Foot and Mouth Disease in Northern Thailand". In: *Veterinary Sciences* 7.3. ISSN: 2306-7381. DOI: 10.3390/vetsci7030138.

Sanson, R.L., G. Struthers, P. King, J.F. Weston, and R.S. Morris (1993). "The potential extent of transmission of foot-and-mouth disease: A study of the movement of animals and materials in Southland, New Zealand". In: *New Zealand Veterinary Journal* 41.1. PMID: 16031690, pp. 21–28. DOI: 10.1080/00480169.1993.35730. eprint: https://doi.org/10.1080/00480169.1993.35730.

El-Sayed, Ehab, Wael Mossad, Samir Mohamed Ali, and Mohamed Shawky (2012). "Studies on the duration of immunity induced in cattle after natural FMD infection and post vaccination with bivalent oil vaccine". In: *Veterinary World* 5, pp. 603–608. DOI: 10.5455/vetworld.2012.603-608.

Schaftenaar, W (Dec. 2002). "Use of vaccination against foot and mouth disease in zoo animals, endangered species and exceptionally valuable animals". en. In: *Rev. Sci. Tech.* 21.3, pp. 613–623. DOI: 10.20506/rst.21.3.1358.

Schley, David, Simon Gubbins, and David J. Paton (May 8, 2009). "Quantifying the Risk of Localised Animal Movement Bans for Foot-and-Mouth Disease". In: *PLoS ONE* 4.5. Ed. by Michael B. Gravenor, e5481. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0005481.

Schnell, Patrick M (2019). "Modeling the role of carrier and mobile herds on foot-and-mouth disease virus endemicity in the Far North Region of Cameroon". In: *Epidemics* 29, p. 7. ISSN: 1755-4365. DOI: https://doi.org/10.1016/j.epidem.2019.100355.

Sellman, Stefan, Kimberly Tsao, Michael J. Tildesley, Peter Brommesson, Colleen T. Webb, Uno Wennergren, Matt J. Keeling, and Tom Lindström (Apr. 6, 2018). "Need for speed: An optimized gridding approach for spatially explicit disease simulations". In: *PLOS Computational Biology* 14.4. Ed. by Mark M. Tanaka, e1006086. ISSN: 1553-7358. DOI: 10.1371/journal.pcbi.1006086.

Senturk, B and C Yalcin (2005). "Economic analysis of foot-and-mouth disease in Turkey-I: Acquisition of required data via Delphi expert opinion survey". In: *Veterinarni Medicina - UZPI* 50.10, pp. 451–460.

Şentürk, Berriṅ and Cengiż Yalçin (Dec. 15, 2008). "Production Losses Due to Endemic Foot-and-Mouth Disease in Cattle in Turkey". In: *Turkish Journal Of Veterinary And Animal Sciences* 32.6, pp. 433–440. ISSN: 1300-0128.

Singh, Raj Kumar, Gaurav Kumar Sharma, Sonalika Mahajan, Kuldeep Dhama, Suresh H. Basagoudanavar, Madhusudan Hosamani, B P Sreenivasa, Wanpen Chaicumpa, Vivek Kumar Gupta, and Aniket Sanyal (2019). "Foot-and-Mouth Disease Virus: Immunobiology, Advances in Vaccines and Vaccination Strategies Addressing Vaccine Failures–An Indian Perspective". In: *Vaccines* 7.3. ISSN: 2076-393x. DOI: 10.3390/vaccines7030090.

Sinkala, Y., M. Simuunza, D. U. Pfeiffer, H. M. Munang'andu, M. Mulumba, C. J. Kasanga, J. B. Muma, and A. S. Mweene (Aug. 2014). "Challenges and Economic Implications in the Control of Foot and Mouth Disease in Sub-Saharan Africa: Lessons from the Zambian Experience". In: *Veterinary Medicine International* 2014, p. 373921. ISSN: 2090-8113. DOI: 10.1155/2014/373921.

Smith, C E (Nov. 1970). "Prospects for the control of infectious disease". en. In: *Proc. R. Soc. Med.* 63.11 Part 2, pp. 1181–1190. DOI: 10.1177/003591577006311P206.

Stenfeldt, C., J. M. Pacheco, G. R. Smoliga, E. Bishop, S. J. Pauszek, E. J. Hartwig, L. L. Rodriguez, and J. Arzt (Apr. 2016). "Detection of Foot-and-mouth Disease Virus RNA and Capsid Protein in Lymphoid Tissues of Convalescent Pigs Does Not Indicate Existence of a Carrier State". In: *Transboundary and Emerging Diseases* 63.2, pp. 152–164. ISSN: 18651674. DOI: 10.1111/tbed.12235.

Stenfeldt, Carolina and Jonathan Arzt (Feb. 28, 2020). "The Carrier Conundrum; A Review of Recent Advances and Persistent Gaps Regarding the Carrier

State of Foot-and-Mouth Disease Virus". In: *Pathogens* 9.3, p. 167. ISSN: 2076-0817. DOI: 10.3390/pathogens9030167.

Stenfeldt, Carolina, Michael Eschbaumer, Steven I. Rekant, Juan M. Pacheco, George R. Smoliga, Ethan J. Hartwig, Luis L. Rodriguez, and Jonathan Arzt (July 15, 2016). "The Foot-and-Mouth Disease Carrier State Divergence in Cattle". In: *Journal of Virology* 90.14. Publisher: American Society for Microbiology Journals Section: Pathogenesis and Immunity, pp. 6344–6364. ISSN: 0022-538x, 1098-5514. DOI: 10.1128/jvi.00388-16.

Stenfeldt, Carolina, Peter MH Heegaard, Anders Stockmarr, Kirsten Tjørnehøj, and Graham J Belsham (2011). "Analysis of the acute phase responses of Serum Amyloid A, Haptoglobin and Type 1 Interferon in cattle experimentally infected with foot-and-mouth disease virus serotype O". In: *Veterinary Research* 42.1, p. 66. ISSN: 0928-4249. DOI: 10.1186/1297-9716-42-66.

Stenfeldt, Carolina, Juan M. Pacheco, Nagendrakumar B. Singanallur, Wilna Vosloo, Luis L. Rodriguez, and Jonathan Arzt (Dec. 2020). "Virulence beneath the fleece; a tale of foot-and-mouth disease virus pathogenesis in sheep". In: *Plos One* 14.12, pp. 1–18. DOI: 10.1371/journal.pone.0227061.

Stevenson, M.A., R.L. Sanson, M.W. Stern, B.D. O'Leary, M. Sujau, N. Moles-Benfell, and R.S. Morris (2013). "InterSpread Plus: a spatial and stochastic simulation model of disease in animal populations". In: *Preventive Veterinary Medicine* 109.1, pp. 10–24. ISSN: 0167-5877. DOI: https://doi.org/10.1016/j.prevetmed.2012.08.015.

Stevenson, Mark et al. (2021). *epiR: Tools for the Analysis of Epidemiological Data.*

Sumption, Keith, Joseph Domenech, and Giancarlo Ferrari (June 2012). "Progressive control of FMD on a global scale". en. In: *Vet. Rec.* 170.25, pp. 637–639. DOI: 10.1136/vr.e4180.

Sutmoller, P. and O. R. Casas (2002). "Unapparent foot and mouth disease infection (subclinical infections and carriers) : implications for control". In: vol. 21, pp. 519–529. DOI: 10.20506/rst.21.3.1366.

Sutmoller, Paul, John W. McVicar, and George E. Cottral (Sept. 1, 1968). "The epizootiological importance of foot-and-mouth disease carriers". In: *Archiv für die gesamte Virusforschung* 23.3, pp. 227–235. ISSN: 1432-8798. DOI: 10.1007/bf01241895.

Tadesse, B., W. Molla, A. Mengsitu, and W. T. Jemberu (2019). "Transmission dynamics of foot and mouth disease in selected outbreak areas of northwest Ethiopia". In: *Epidemiology and Infection* 147, e189. DOI: 10.1017/S0950268819000803.

Tenzin, Aldo Dekker, Hans Vernooij, Annemarie Bouma, and Arjan Stegeman (2008). "Rate of Foot-and-Mouth Disease Virus Transmission by Carriers Quantified from Experimental Data". In: *Risk Analysis* 28.2, p. 7. DOI: 10.1111/j.1539-6924.2008.01020.x.

Tildesley, M. J., S. Brand, E. Brooks Pollock, N. V. Bradbury, M. Werkman, and M. J. Keeling (Sept. 1, 2019). "The role of movement restrictions in limiting the economic impact of livestock infections". In: *Nature Sustainability* 2.9, pp. 834–840. ISSN: 2398-9629. DOI: 10.1038/s41893-019-0356-5.

Tildesley, Michael J, Rob Deardon, Nicholas J Savill, Paul R Bessell, Stephen P Brooks, Mark E J Woolhouse, Bryan T Grenfell, and Matt J Keeling (June 2008). "Accuracy of models for the 2001 foot-and-mouth epidemic". en. In: *Proc. Biol. Sci.* 275.1641, pp. 1459–1468. DOI: 10.1098/rspb.2008.0006.

Tildesley, Michael J, Nicholas J Savill, Darren J Shaw, Rob Deardon, Stephen P Brooks, Mark E J Woolhouse, Bryan T Grenfell, and Matt J Keeling (Mar. 2006). "Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK". en. In: *Nature* 440.7080, pp. 83–86. DOI: 10.1038/nature04324.

Tildesley, Michael J., Gary Smith, and Matt J. Keeling (2012). "Modeling the spread and control of foot-and-mouth disease in Pennsylvania following its discovery and options for control". In: *Preventive Veterinary Medicine* 104.3, pp. 224–239. ISSN: 0167-5877. DOI: https://doi.org/10.1016/j.prevetmed.2011.11.007.

Toni, Tina, David Welch, Natalja Strelkowa, Andreas Ipsen, and Michael P.H Stumpf (Feb. 6, 2009). "Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems". In: *Journal of The Royal Society Interface* 6.31. Publisher: Royal Society, pp. 187–202. ISSN: 1742-5689, 1742-5662. DOI: 10.1098/rsif.2008.0172.

Tsao, Kimberly, Stefan Sellman, Lindsay M Beck-Johnson, Deedra J Murrieta, Clayton Hallman, Tom Lindström, Ryan S Miller, Katie Portacci, Michael J Tildesley, and Colleen T Webb (Feb. 2020). "Effects of regional differences and demography in modelling foot-and-mouth disease in cattle at the national scale". en. In: *Interface Focus* 10.1, p. 20190054. DOI: 10.1098/rsfs.2019.0054.

Wada, M., M. Stevenson, N. Cogger, and T. Carpenter (2017). "Evaluation of the Control Strategy for the 2010 Foot-and-Mouth Disease Outbreak in Japan Using Disease Simulation". In: *Transboundary and Emerging Diseases* 64.3, pp. 978–989. ISSN: 1865-1682. DOI: https://doi.org/10.1111/tbed.12467.

Wickham, Hadley (2016). *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York. ISBN: 978-3-319-24277-4.

Woolhouse, M. E. J., D. T. Haydon, A. Pearson, and R. P. Kitching (June 1996). "Failure of vaccination to prevent outbreaks of foot-and-mouth disease". In: *Epidemiology and Infection* 116.3, pp. 363–371. ISSN: 0950-2688, 1469-4409. DOI: 10.1017/s0950268800052699.

Wu, Jianyong, Radhika Dhingra, Manoj Gambhir, and Justin V Remais (Sept. 2013). "Sensitivity analysis of infectious disease models: methods, advances and their application". en. In: *J. R. Soc. Interface* 10.86, p. 20121018.

Yadav, Shankar, Carolina Stenfeldt, Matthew A. Branan, Karla I. Moreno-Torres, Lindsey K. Holmstrom, Amy H. Delgado, and Jonathan Arzt (2019). "Parameterization of the Durations of Phases of Foot-And-Mouth Disease in Cattle". In: *Frontiers in Veterinary Science* 6.6. Publisher: Frontiers, p. 263. ISSN: 2297-1769. DOI: 10.3389/fvets.2019.00263.

Zaheer, Muhammad Usman, Mo D Salman, Kay K Steneroden, Sheryl L Magzamen, Stephen E Weber, Shaun Case, and Sangeeta Rao (2020a). "Challenges to the Application of Spatially Explicit Stochastic Simulation Models for Foot-and-Mouth Disease Control in Endemic Settings: A Systematic Review". In: *Computational and Mathematical Methods in Medicine*, p. 12. DOI: https://doi.org/10.1155/2020/7841941.

— (Nov. 2020b). "Challenges to the Application of Spatially Explicit Stochastic Simulation Models for Foot-and-Mouth Disease Control in Endemic Settings: A Systematic Review". In: *Computational and Mathematical Methods in Medicine* 2020, p. 7841941. ISSN: 1748-670x. DOI: 10.1155/2020/7841941.