Enhancing an Evidence-Based Decision Making System for Foot-and-Mouth Disease

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Abstract

Foot-and-mouth disease (FMD) is a highly contagious disease with significant economic consequences, for which urgent and rational decisions are essential. It is a great concern for countries worldwide where livestock industries are important, regardless of the current FMD status. This thesis addressed the problems in the existing decision support systems used by the current FMD-free countries, with a particular focus on New Zealand.

Because the exact source of infection is uncertain in the spatially and temporally concentrated focus of an FMD epidemic, it is challenging to predict the behaviour of FMD and determine the best control alternatives within a given susceptible population. The studies proposed a new approach for descriptive spatio-temporal analyses of local spread patterns, which was applied to the data from the FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010). The analyses identified herd-specific risk factors of local spread: size of a susceptible premises, infectious premises with pigs and susceptible premises with cattle were positively associated with hazard of local spread in all the three epidemics. In addition, the adjusted hazard of local spread varied markedly by outbreak. The UK FMD epidemic in 2001 had the highest hazard of local spread. The findings highlight the needs of care in interpolating the local spread probabilities from one epidemic for use of disease modelling for a different susceptible population.

Detailed investigation of the FMD epidemic in Japan in 2010 illustrated a dynamic change in the patterns of local spread during the epidemic prior to emergency vaccination, suggesting contribution of human activities in addition to purely environmental factors to local spread. A stochastic spatial simulation model, using the local spread parameters derived from the analyses showed a high predictive accuracy, in terms of demographical, temporal and spatial patterns of infection. The model indicated that emergency vaccination played an important role in mitigating potentially unwanted outcomes of an epidemic, such as disease spread outside the prefecture. In addition, the model predicted

that both epidemiological and economic consequences of the epidemic could have been reduced by earlier application of vaccination with a smaller vaccination ring for the epidemic in Japan in 2010.

To enhance contingency planning for FMD, a disease simulation modelling system was developed, by adding an economic module to the existing FMD simulation model for New Zealand. The modelling system allowed estimation of the direct and macroeconomic costs of a simulated FMD epidemic. Analyses of data generated by the disease simulation modelling system indicated that vaccinate-to-die was economically preferred to stamping-out alone or vaccinate-to-live, for a simulated FMD epidemic in the Auckland Region with local spread potential similar to that of the Cumbria outbreak in 2001, which had a high potential of developing into a large epidemic, indicated by a high density of premises, a high cumulative number of IPs, or a high estimated dissemination rate, and local spread patterns similar to Cumbria outbreak (2001). Vaccinate-to-live was economically suboptimal under the current OIE standard regarding recovery of FMD-free status. The results were robust to the uncertainty in the resource capacity, vaccination effectiveness, and the early scale of an epidemic, but sensitive to the choice of vaccination radius. VTL was always economically suboptimal under the current OIE code, but would be advantageous if the OIE's waiting period was shortened by 3 months. Using more refined parameters, future work is required to investigate other potentially more advantageous options, such as vaccination applied to specific species or in alternative prioritisation.

The studies presented in this thesis demonstrated that simulation models that incorporated the current best epidemiological and economic knowledge might enhance contingency planning and decision making for the management of FMD. Simulation models could also be used as the quantitative basis of communication with decision makers and stakeholders, which would then encourage informed discussion around disease control measures.

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List of Publications

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Abbreviations

CIP	Cumulative number of infected premises
DEFRA	Department for Environment, Food & Rural Affairs
DIVA	Differentiating infected from vaccinated animals
EDR	Estimated dissemination rate
FAO	Food and Agriculture Organization of the United Nations
FMD	Foot-and-mouth disease
FMDV	Foot-and-mouth disease virus
GAM	Generalised additive model
GDP	Gross domestic product
IP	Infected premises
JA	Japan Agricultural Cooperatives
MPI	Ministry for Primary Industries, New Zealand
NPV	Net present value
NSP	Non-structural protein
OIE	The Office International des Epizooties
RNA	Ribonucleic acid
PRCC	Partial rank correlation coefficient
SAT	South African Territories
SO	Stamping-out alone
SP	Structural protein
VP	Viral protein
VTD	Vaccinate-to-die
VTL	Vaccinate-to-live

1. Introduction

In the current globalised world, the risk of introduction of a new pathogen into a country is particularly high, due to increased opportunities for international trade and individual travel overseas. The reservoirs from which pathogens are transferred to free countries are mainly countries, which do not have enough resources to achieve effective disease control. Foot-and-mouth disease (FMD) is one typical example for such diseases. While developing countries, where the disease continues to circulate, constantly suffer losses due to FMD, many developed countries have eradicated FMD through expensive campaigns and maintained disease freedom through enhanced border security. Despite the efforts to prevent incursion of disease, the risk of entry of FMD and its resulting disastrous impacts are major concerns for those countries. The chance of introduction of FMD is small, but FMD is still highly hazardous, due to the significant consequences that it can cause to the society. The recent, severe impacts of FMD epidemics in previously FMD-free countries (Taiwan in 1997, Argentina in 2000, Uruguay and the UK in 2001, Japan and Republic of Korea in 2010) are still fresh in the memory. Improved preparedness is the key to mitigate such impacts. Being a developed country, New Zealand is relatively unique in that its economic and social wellbeing is highly dependent on the prosperity of its primary industries. However, it has never had an outbreak of FMD, and therefore has no direct experience on which to base policy development. Disease simulation models are powerful decision support tools for such countries, which can be used to explore the potential outcomes of alternative control options without requiring an actual outbreak.

The motivation for the studies of the thesis is to demonstrate how alternative control strategies for FMD can be assessed by using an epidemiological disease spread simulation model. Acknowledging that localised transmission of disease without any traceable movements, 'local spread,' is one of the most influential mechanisms of FMD spread between farms, Chapter 3 describes the spatial and temporal patterns of local spread for the FMD outbreaks in the UK in 2001, Japan in 2010, and Republic of Korea in 2010, by

survival analyses of the empirical outbreak data. Chapter 4 is a case study for the epidemic in Japan in 2010. In this chapter, a set of parameters for a disease simulation model is estimated using an existing spatially-explicit stochastic simulation modelling framework, InterSpread Plus, so that a model represents the FMD epidemic in Japan. The agreement between the spatio-temporal pattern of the actual and simulated epidemics is evaluated. In addition, the study demonstrates retrospective assessment of alternative strategies, for the epidemic in Japan, 2010. The parameters estimated here will be a useful addition to the knowledge base for FMD simulation modelling.

For an incursion of FMD into previously disease-free countries, export bans on animal products are imposed by trading partners for an extended period. For New Zealand, the revenues from the export of agricultural products are important for the national economy. Therefore, contingency planning and decision making for control of FMD should be focused on rapid eradication of disease and prompt recovery of the OIE's FMD-free status, which is an important indicator of the safety of New Zealand's livestock products for trade. In Chapter 5, existing simulation models for FMD in New Zealand termed New Zealand Standard Model are enhanced by adding an economic component so that alternative strategies can be evaluated in economic terms. The study estimates a range of economic parameters, associated with the control efforts and change in the market and production structures for a hypothetical FMD epidemic. Chapter 6 demonstrates an evaluation of three control policies, stamping-out alone, emergency vaccination with subsequent culling, and emergency vaccination without subsequent culling, which are of great interest to policymakers and livestock industries in New Zealand. Chapter 7 provides a more detailed investigation of the optimal control options for a particular epidemic situation in New Zealand, taking a range of epidemiological, economic and logistical uncertainties into consideration. The implications drawn from the studies will inform contingency planning and decision making for New Zealand, while the methodologies developed here can be applied to similar diseases and other countries to enhance their decision making systems.

The thesis is presented as a series of five distinct research papers prepared for publication. At the time of submission of the final version, all chapters have been submitted to peer-reviewed journals and Chapter 4 has been published.

2. Literature Review

2.1. Introduction

Development in veterinary infrastructure and enhanced research has contributed in mitigating the dramatic adverse effects of animal diseases and development in livestock production systems. Today, in developed countries, the majority of dangerous or important animal and zoonotic diseases, such as foot-and-mouth disease (FMD) and classical swine fever (CSF), have been eliminated or brought under control due to continuous efforts by producers and governments (Torgerson, 2013). This is a dramatic change, considering a surprisingly high proportion, 18%, of livestock production in the developed countries was estimated to have been lost due to animal diseases in the 1960s (Pritchard, 1966). These countries are now dealing with less dramatic, yet persistent production diseases such as Johne's disease and bovine tuberculosis, for which there are currently no effective or economically justifiable control strategies. In developing countries, production losses due to livestock disease was much more severe, 35% or more, in the 1960s, with protein malnutrition being a serious health problem for the majority of people (De Onis et al., 1993, Pritchard, 1966). Many pathogens that have been eliminated from the developed countries are still endemic in the developed countries, undermining food safety and economic development. One exception to this is eradication of rinderpest in 2011, which was one of the major successes of veterinary medicine and will bring benefits to those who had been directly affected and deprived of due to presence of disease (Anderson et al., 2011).

For both developing and developed countries, FMD remains as a major concern due to its pathogenicity, high contagiousness and economic importance. On-going efforts have been made for control of FMD in endemic countries, and for prevention and preparedness for a threat of incursion of FMD in countries that have eliminated FMD (Vallat and Lubroth, 2012). The severe social, economic, and political consequences of a large FMD epidemic in the UK in 2001 (Thompson et al., 2002) is a good reference for the time being for what would happen without adequate preparedness. This chapter will

critically review current knowledge about FMD and the methods available for evidence-based decision making for preparedness, control and eradication of FMD for a country previously free from FMD. In Section 2.2, literature related to the epidemiology of FMD is reviewed for the purpose of informing decision making for the management and control of disease. In the subsequent two sections, currently available FMD simulation models (Section 2.3) and economic aspects of FMD (Section 2.4) will be reviewed. The chapter will be concluded by highlighting the current gaps in the literature and describing the aims of this thesis.

2.2. Epidemiology of FMD

In this section, current knowledge and gaps about aetiology (Section 2.2.1), distribution of FMD virus worldwide (Section 2.2.2), host range (Section 2.2.3), clinical aspects (Section 2.2.4), transmission mechanisms (Section 2.2.5) and control measures (Section 2.2.6) for FMD will be briefly described.

2.2.1. Aetiology

FMD is an infectious disease caused by the foot-and-mouth disease virus (FMDV) (Loeffler and Frosch, 1897), which belongs to the genus *Aphthovirus* and the family *Picornaviridae* (Brooksby, 1958). The virus is about 30 nm in diameter and has a capsid containing a single stranded positive sense RNA genome of about 8×10^3 nucleotides, encoding four structural (capsid) proteins (SP), VP1, VP2, VP3, and VP4, and non-structural proteins (NSP) (Jackson et al., 2003, Carrillo et al., 2005, Mahy, 2005). The SP, particularly VP1, is responsible for determining the biological properties of the FMDV, such as attachment and entry of the virus into a host cell, protective immunity in host animals, antigenic specificity, and virus transmission (Jackson et al., 2003).

Seven serotypes of FMDV have been recognised; O, A, C, Asia 1, and South African Territories serotypes SAT 1, SAT 2, and SAT 3 (Vallée and Carré, 1922, Waldmann and Trautwein, 1926, Brooksby and Roger, 1957, Brooksby, 1958). These serotypes are immunologically distinct, that is, immunity against one serotype does not confer protection against another serotype. Further antigenic diversity exists within each FMDV serotype, which necessitates subtyping individual strains. Historically, subtypes were distinguished by difference in the level of immunity conferred between variants of FMDV within the same serotype, using serological tests, with the primary purpose to determine an appropriate vaccine strain that matched the field strain (Kitching et al., 1989). Since the

1980s molecular biological techniques, specifically reverse transcription polymerase chain reaction (RT-PCR) and nucleotide sequencing, have been increasingly used as the definitive method to determine isolate strains, routinely monitor emergence of new field strains, and for tracing virus movements globally (Beck and Strohmaier, 1987, Knowles and Samuel, 2003, Carrillo et al., 2005, Knowles et al., 2005, Samuel and Knowles, 2001, Krebs and Marquardt, 1992, Martinez et al., 1992, Mason et al., 2003). In the OIE/FAO World Reference Laboratory for FMD, Pirbright (UK), a large database for nucleotide sequences of FMDV collected since 1922 has been stored (Samuel and Knowles, 2001).

Like many other RNA viruses, FMDV has a high mutation rate, with an average number of random mutations between 2 – 8 nucleotides per replication cycle (Dopazo et al., 2005). In other words, between 0.025% and 0.100% of the virus genome is mutating every replication cycle. On average, 86% of nucleotide sequences are identical between serotypes, with a substantial variation occurring in the region encoding the SP, namely VP1 (Jackson et al., 2003). The VP1 gene varies between 30 and 50% difference between subtypes (Knowles and Samuel, 2003). Samuel and Knowles (2001) established a new grouping called 'topotype' based on VP1 sequences, in which viruses are categorised in the same topotype if 15 to 20% of their VP1sequences is identical. By analysing topotypes, evolutionary lineages of FMDV and geographical cluster of FMDV became apparent (Knowles and Samuel, 2003).

2.2.2. Global distribution of FMD virus

As of May 2015, 68 countries, or 38% of countries, were listed officially free of FMD (Anonymous, 2015b). The FMD countries are mainly located in Europe, North America and Australasia while those with endemic or sporadic FMD are predominately in Asia, Africa and South America (Kitching et al., 2007). China, Africa and India are estimated to have the greatest number of FMD infected animals (Knight-Jones and Rushton, 2013, Sumption et al., 2008).

Different FMDV serotypes are heterogeneously distributed worldwide. Serotypes O and A are prevalent in the endemic regions worldwide (Knowles et al., 2005, Brito et al., 2015). Serotype Asia 1 used to be restricted to southern Asia, but a novel Asia 1 virus has recently spread into Middle Eastern countries and has been circulating since 2011 (Brito et al., 2015). The three SAT serotypes are typically restricted to Africa, but caused several

outbreaks in the Middle East in 2012 (Brito et al., 2015). Serotype C has not been detected since 2004 (Brito et al., 2015).

FMDV type O strains have been involved in the majority of epidemics in previously disease-free countries (McLaws and Ribble, 2007). Between 2000 and 2004, more than 60% of isolates from disease endemic regions were serotype O (Knowles et al., 2005). Particularly, the FMDV type O PanAsia strain spread from India throughout Asian and Middle Eastern countries in late 1998 – 2000. The PanAsia strain caused explosive epidemics in countries that were previously disease free for many years, including Japan and Republic of Korea in 2000, the UK, Republic of Ireland, France and The Netherlands in 2001 (Knowles et al., 2005). More recently, Japan and Republic of Korea experienced epidemics caused by serotype O FMDV that were circulating the neighbouring Asian countries (Knowles, 2010a, Knowles, 2010b, Brito et al., 2015). For countries striving for eradication of FMD, it is of particular interest to examine how newly emerged virus strain could be introduced into a country, or become established, despite stringent control measures at international borders (Knowles et al., 2005).

2.2.3. Host range

All cloven-hoofed animals are susceptible to FMDV (Thomson et al., 2003). Major domesticated ruminants (e.g., cattle, deer, sheep, goats, and water buffaloes) and pigs, and a wide range of wildlife species were shown to be susceptible to natural or experimental infected of FMD (Weaver et al., 2013, Thomson et al., 2003). With the current knowledge, however, FMD is considered to be a disease exclusive to livestock (Weaver et al., 2013). Cattle are the major livestock species that are affected by FMD (Sumption et al., 2008). The prevalence of FMD in the cattle population worldwide was estimated to be between 2% and 5% globally (Knight-Jones and Rushton, 2013, Sumption et al., 2008).

Knowledge about the role of wildlife populations in maintenance and transmission of FMDV is limited (Thomson et al., 2003). In sub-Saharan Africa, management of FMD is problematic, partly because wild African buffaloes (*Syncerus caffer*) evidently serve as long-term natural maintenance hosts for FMDV SAT serotypes (Condy et al., 1985). Except for this case, however, there is little evidence indicating that wildlife serve as a natural reservoir of FMDV (Weaver et al., 2013). Likewise, it is possible that wildlife (e.g., deer) can play a role in transmission of virus during an epidemic in a previously FMD-free

country, although there has been very few examples to date to support it (Weaver et al., 2013).

2.2.4. Clinical aspects

Host animals typically develop acute vesicles on the feet, in and around the mouth (oral cavity), and on the mammary glands of females, accompanied by fever, anorexia, excessive salivation, and lameness (Alexandersen et al., 2003). The vesicles will rupture and heal in most cases within a few days (Alexandersen et al., 2003). Following the rupture of vesicles, secondary infections may occur on the feet or teats, which delay the healing process (Alexandersen et al., 2003). In dairy cattle, damaged teats due to FMD may result in permanent reduction in milk yields and induction of mastitis (James and Rushton, 2002). Mortality is generally low in adults, but may be high in young animals due to acute myocarditis (Alexandersen et al., 2003). Clinical signs are generally severe in high-yielding dairy cattle and intensively-reared pigs, while they are generally mild, or not apparent in most small ruminants (Geering, 1967, Kitching et al., 2005).

Several other viral vesicular diseases, such as swine vesicular disease (enterovirus), vesicular stomatitis (rhabdovirus) and vesivirus infection show similar clinical signs and as such can be mistaken for FMD (Alexandersen et al., 2003). Therefore, diagnosis of FMD cannot rely solely on clinical aspects and requires laboratory testing.

Some infected animals are known to develop a 'carrier state,' i.e., a state where persistence of FMDV continues in the infected animals for more than 28 days (Barnett et al., 2002, Geale et al., 2015). In general, carrier animals do not show clinical signs, but low level of virus is intermittently excreted, following recovery from the acute clinical stage of infection (Barnett et al., 2002). A significant proportion of infected ruminants develop the carrier state, while pigs do not develop carrier state (Barnett et al., 2002, Kitching, 2002). The carrier state can last over months in sheep and goats, or several years in cattle and buffalo (Barnett et al., 2002). Although carrier animals can potentially transmit FMDV, there is currently little evidence to support carrier livestock act as a source of infection in the field (Paton et al., 2014, Kitching et al., 2007).

2.2.5. Transmission mechanisms

Transmission of FMD occurs through cuts, skin abrasions or mucosae, by inhalation of droplets or droplet-nuclei (aerosols) via the respiratory tract, by ingestion of contaminated milk, meat, organs and offal, and via mechanical contact with contaminated personnel,

vehicles, fomites, and wildlife (e.g., rats, mice and birds) (Sutmoller et al., 2003, Alexandersen et al., 2003). Dependent on the weather conditions, the virus can survive in the environment including carcasses, manure and hay for up to 6 months (Alexandersen et al., 2003). Long-distance windborne spread of over 100 km may occur for some virus strains under a high relative humidity (60% or more) and appropriate wind and topographical conditions, as shown by analyses of past epidemics (Gloster et al., 1982, Sellers and Forman, 1973, Sanson et al., 2011, Donaldson, 1972).

FMDV can initiate infection in susceptible animals with a relatively low dose, although the minimum doses required to infect animals were shown to vary by species (cattle, sheep and pigs) and route of infection (Donaldson and Alexandersen, 2002, Pharo, 2002, Donaldson, 1997). Pigs are susceptible to oral infection but are more resistant to aerosol exposure compared with ruminants (Alexandersen and Donaldson, 2002, Alexandersen et al., 2002). Cattle are typically the most susceptible species by the airborne route, because they can sample more virus from the air with the same concentration of virus due to their size and respiratory tidal volume (Sellers and Parker, 1969).

The virus is excreted in exhaled air, lesions, milk, semen, and blood from infected animals starting from the early stages of disease, possibly before the onset of clinical signs (Charleston et al., 2011, Donaldson and Alexandersen, 2002). Peak of virus production occurs on the onset of clinical signs in cattle and pigs or before the appearance of lesions in sheep, and declines rapidly as suppressed by host immune response (Kitching, 2005). The infectious period at the herd level could extend to weeks or months (Sellers and Daggupaty, 1990). Pigs excrete largest quantities of virus via respiratory tract, compared with ruminants (Sellers and Parker, 1969).

2.2.6. Control measures

FMD control has traditionally been, what is known as 'stamping-out,' that is, prompt culling of all animals in infected herds, followed by destruction of carcasses, cleansing and disinfection (Anonymous, 2014g). Strict movement controls and active surveillance in the high risk places are typically applied in addition to stamping-out measures. In some situations, routine or emergency vaccination may also be applied in addition to stamping-out. Routine vaccination refers to systematic application of standard prophylactic FMD vaccines once or twice a year, whereas emergency vaccination is referred to as the application of high-potency FMD vaccines in the face of an epidemic to rapidly provide

wide spectrum of immunity in the process of eradication (Barnett et al., 2015). Emergency vaccination can be applied either as 'vaccinate-to-live' or 'vaccinate-to-die'. Under vaccinate-to-live all vaccinated animals are kept alive, while vaccinate-to-die involves subsequent destruction of all vaccinated animals.

A country's OIE's disease free status is important for access to the international market, and as such the control strategies are greatly influenced by the regulations of the World Organisation for Animal Health (OIE) (Anonymous, 2014g). The OIE provides two official FMD-free statuses, 'FMD-free where vaccination is not practised' or 'FMD-free where vaccination is practised.' Once FMD has been eradicated from a country previously free of FMD, time to recover 'FMD-free where vaccination is not practised' is either: 3 months after the last case when a stamping-out policy is used, 3 months after the slaughter of the last vaccinated animals under a vaccinate-to-die policy, or 6 months after the last case or the last vaccination (latest event) under a vaccinate-to-live policy (Anonymous, 2014g). When vaccination was practised prior to the outbreak the time to recover 'FMD-free where vaccination is practised' is either: 6 months after the last case for a stamping-out policy, or 18 months after the last case with absence of stamping-out (Anonymous, 2014g).

Time till recognition of FMD freedom varies by types of vaccines used (emergency vaccines or standard vaccines) and presence or absence of vaccinated animals in the country, with emphasis on the risk associated with vaccinated animals. There are two possible reasons. First, improperly inactivated FMD vaccines themselves have historically served as a source of infection, as observed in Europe and South America until the 1980s (Beck and Strohmaier, 1987). Second, vaccinated animals may become asymptomatic carriers that have the potential to transmit FMDV (Barnett et al., 2002, Geale et al., 2015). However, due to the recent improvement in the potency and purity of FMD vaccines, it is becoming less of a problem for substantiating FMD freedom than it used to be (Paton et al., 2014). High potency of vaccines ensures rapid onset of protective immunity. More importantly, high purity enables differentiation between infected and vaccinated animals (DIVA) based on the composition of antibodies against non-structural proteins (NSP) (Barnett et al., 2015). Therefore, the risks of carriers remaining in the populations can be reduced through the use of high-quality vaccines and appropriate serological tests during post-outbreak surveillance (Barnett et al., 2015).

2.3. Infectious disease spread modelling for FMD

Infectious disease spread modelling is an approach to emulate disease spread by some form of mathematical procedure, with the objective of experimenting the effects of alternative control measures and collecting knowledge about mechanisms of disease spread (Miller, 1976). Particularly for FMD-free countries, models are gaining prominence as an essential component of preparedness and decision making for FMD. This is because FMD is distinct from most other diseases in that a wrong decision and an inappropriate control strategy can lead to catastrophic economic consequences for the country. The consequences of a wrong decision may be a long-term damage to livestock industries, permanent loss of trading partners, or an economic recession in the country, as seen in the historical FMD epidemics in the previously FMD-free countries such as Taiwan in 1997 and the UK in 2001 (Yang et al., 1999, Anderson, 2002). To mitigate such consequences, what decision makers and stakeholders can do during the absence of FMD is to develop a 'good-practice' disease model and consider the range of possible scenarios under different disease control options. These results can then be used as the basis of a communication about options with industry and other stakeholders to develop a strategy for response and recovery. If the contingency plans and decision making are made based on the evidence and the stakeholders understand the control measures to be applied, communications between the disease control authority and the stakeholders during an actual outbreak response will become easier, and facilitate a rapid roll-out of control options.

Despite the positives of providing stakeholders and decision makers with modelling results and implications to be used as decision support tools, some caution is advised, or otherwise, models could be misused (Kitching et al., 2006). Those who interpret the models are often not familiar with infectious disease modelling, and decisions can be made without much attention to the assumptions made by modellers, which are often understated, unexplained, or lack transparency. For the control of the FMD epidemic in the UK in 2001, a decision to cull contiguous premises was made based on model predictions (Ferguson et al., 2001), which raised controversy among policy makers. Kitching *et al.* (2005) argued that contiguous culling was 'an economically and socially expensive mistake,' attributing it to use of models based on unjustified assumptions without examining potential variation. The authors debated the necessity of the policy, raising questions regarding whether models considered unique behaviour of the virus strain, the dynamic pattern of movements among the farming community, and potential

overestimation of particular disease transmission parameters (Kitching et al., 2005, Kitching, 2005, Kitching et al., 2006).

In the following, the published literature regarding FMD simulation models developed for policy evaluation will be critically reviewed, with special interest in parameters regarding local spread of FMD, i.e., localised disease transmission without any traceable movements. First, the different types of FMD simulation models will be provided (Section 2.3.1), followed by a critical literature review of the estimation of FMD transmission by local spread (Section 2.3.2). Then, modelling studies for FMD using four prominent simulation modelling frameworks, InterSpread Plus (Section 2.3.3), DADS (Section 2.3.4), NAADSM (Section 2.3.5), and AusSpread (Section 2.3.6), will be reviewed with critical remarks.

2.3.1. Types of FMD simulation models

Models for FMD can be broadly categorised into individual-based models and population-based models (Vynnycky and White, 2014, Bradhurst et al., 2015). Both types of models are used for the same purpose, that is, to explore effectivity of efficiency of alternative control strategies to control an FMD epidemic. The process of modelling is different between individual-based models and population-based models; the former models are formulated from the bottom-up to aggregate individual-level behaviour to describe population-level relationships, while the latter models are formulated from the top-down to apply the population-level relationships to describe individual-level behaviour.

Individual-based models, also called agent-based models, or microsimulation models, explicitly deal with every individual epidemiological unit (i.e., herd/flock, farm, or enterprise) within the population of interest, and simulate changes of state (e.g., at risk, infected, depopulated, vaccinated, etc.) for every individual unit for every time step. The input parameters typically derive from observed distributions representing biological variability, using data derived from the experimental studies, analyses of the field data, or expert opinions. One of the major advantages of individual-based models is their ability to capture explicit location of individual units ('spatially-explicit'). Another feature of individual-based models is its convenience to consider uncertainty in each input variables. For stochastic models, Monte Carlo sampling method is typically used, by which individual results of each process are obtained by randomly drawing observations from

the predefined distributions, representing biological variability, or uncertainty. A probability distribution of outcomes can be obtained after repeated run of simulations (multiple iterations) of stochastic models, presenting the range of outcomes and their associated probability. There are a number of individual-based models for FMD developed for each country, including those for the UK (Morris et al., 2001, Keeling et al., 2001, Tildesley et al., 2006), the Netherlands (Boender et al., 2010), Denmark (Boklund et al., 2013) and Japan (Hayama et al., 2013).Population-based models deal with individuals collectively by dividing the population into subgroups (i.e., 'compartment'), such as susceptible, infectious, and removed. Within the same compartment, individuals are assumed to be alike (i.e., 'homogeneous'). For each time step, models track summary figures (e.g., the number of infected units) based on deterministic mathematical equations, without specifying individuals. The input parameters are estimated so that they represent an 'average' figure for a particular compartment. Unlike microsimulation models, population-based models usually do not have an explicit spatial component, i.e., assumes homogeneous distribution, and often deterministic. Examples of population-based models for FMD include those developed for the UK (Ferguson et al., 2001, Haydon et al., 1997), the Netherlands (Bouma et al., 2003) and Japan, 2010 (Nishiura and Omori, 2010).

While the individual-based approach has an advantage in accounting for individual epidemiological characteristics, it is more computationally intensive than the equation-based approach. The individual-based model requires a larger number of programme steps than a population-based model, and the memory may be insufficient to store large volume of data, which may be the national livestock population data of millions of records. However, it is becoming less problematic than it was ten years ago, due to dramatic advances in computer technology: increase in data storage and an exponential increase in computer processing speed (Moore's Law) (Moore, 1965). A new modelling approach, combining the both advantageous features of population-based model, and individual-based model has recently been developed by Bradhurst *et al.* (Bradhurst et al., 2015).

2.3.2. Estimation of local spread

For transmission of FMD in disease simulation models, those occurring by traceable movements between two units (i.e., source of infection can be identified), and those occurring by untraceable ambiguous contact for which the source of infection cannot be

identified (e.g., unrecorded casual human movements, fomites, wildlife, short distance aerosol and windborne), are usually distinguished. The latter is often called local spread, and its probability is considered to form a shape of a kernel, with a higher probability in the proximity to an infected premises and a lower probability as distance increases (Sanson et al., 2006b, Taylor et al., 2004, Honhold et al., 2004).

In both the large scale FMD outbreaks in the UK in 1967 and 2001, local spread was an important factor, accounting for the majority of disease spread (Gibbens et al., 2001, Sanson et al., 2006a). Unfortunately, parametrisation of local spread in infectious disease modelling is challenging. First, accurate quantifiable information is limited in the field data, because the pattern of spread cannot be estimated by tracing likely contacts from source to recipient. Second, there is wide variation in the pattern of spread due to a combination of factors, such as FMDV strain, geographical features, meteorological conditions and human activities that are specific to a particular epidemic. For example, in the 2001 FMD outbreak in the UK there was variation in local spread patterns across regions, and the stages of the epidemic (Wilesmith et al., 2003). While the importance of local spread is often discussed for some large-scale epidemics, including those in the UK, it may be less important in numerous small-scale outbreaks. For example, an FMD outbreak in Miyazaki in 2001 resulted in 3 IPs (Tsutsui et al., 2003), while that in the same prefecture in 2010 resulted in 292 IPs and the importance of local spread is highlighted (Tsutsui et al., 2003, Muroga et al., 2012, Muroga et al., 2013, Yamane, 2006).

Sanson and Morris (1994) analysed the 1967/68 UK FMD epidemic data to estimate the local spread probabilities. Briefly, the daily probabilities of infection within discrete distance strata (0 – 3 km and 3 – 5 km) were measured by non-parametric survival analysis, based on the data recording time from the onset of clinical signs in the source farm until infection in the susceptible farm or the end of observation. The index farm at the centre of the main cluster of outbreaks was selected as the source of local spread, and all infections that occurred within the cluster in the following 14 days without identified movements were attributed to local spread from the source. Although the approach by Sanson and Morris (1994) was a useful starting point for estimating local spread probabilities from the limited data available at the time of analysis, there are several weaknesses. Firstly, bias could have been introduced by subjectively selecting the source farms and specifying the recipient farms based on the local knowledge. Secondly, the estimates were geographically and temporally restrictive to the local spread foci

investigated. Thirdly, important information could have been lost by use of distance as a categorical variable and averaging what occurred within each distance band irrespective of potential variation in infectivity and susceptibility by animal species and herd size.

More recently, Sanson *et al.* (2006b) analysed the 2001 UK FMD epidemic data to estimate the local spread probabilities with a modified method. An alternative approach was taken to create survival data. Briefly, the source for each new infection was attributed to an IP that had been infected previously and at the latest time, and located closest to the newly infected farm. By systematically allocating the source of local spread and considering the entire population at risk, issues regarding potential biases and limitations in the previous method were solved. However, in this approach distance was still treated as a categorical variable and no effort was made to account for potential risk factors such as species and herd size. Further, when using the new approach, the probabilities would overestimate local spread over shorter distances and/or shorter time periods, and underestimate otherwise.

2.3.3. InterSpread Plus models

2001 UK InterSpread model

A spatial simulation model for the 2001 UK FMD epidemic was developed by Morris *et al.* (2001) using the modelling platform InterSpread. InterSpread was specific for FMD, but later enhanced to model any contagious disease and called InterSpread Plus (Stevenson et al., 2012). The model considered four mechanisms of disease transmission: (i) local spread, (ii) movements of animals or risk materials to other farms or markets, (iii) long-distance windborne spread, and (iv) movements of fixed routes, such as by milk tankers.

Local spread was modelled as infection transferred from a source premises to a neighbouring susceptible premises. All susceptible premises located within the specified maximum local spread range were considered at risk of becoming infected. A daily probability of local spread to each at-risk premises was set according to the distance from the source premises, and adjusted by (i) the susceptibility of the at-risk premises, (ii) the infectivity of the source premises (including the stage of infection), and (iii) any spatial risk level applying to the particular site. If the random number determined that infection would be transferred to a particular at-risk premises on a particular day, then the

susceptible premises was reclassified as infected. Model formulation ensured that local spread occurred in random directions.

Their approach to determine local spread parameters in the initial two weeks of the 2001 epidemic was to adjust the 'default' local spread parameters, representing the 1967/68 UK FMD sub-epidemic, by an appropriate multiplier to obtain agreement between the 2001 observed (in 2001) and simulated epidemic. Although this approach may approximate the overall pattern of local spread, its accuracy depends on correctly capturing potential interaction between the probability of local spread and distance, susceptibility, infectivity, and other risk factors (e.g., species and size).

2002 Republic of Korea InterSpread Plus model

Yoon *et al.* (2006) estimated parameters for a stochastic and spatial simulation model for the 2002 FMD epidemic in the Republic of Korea, using InterSpread Plus (Stevenson et al., 2012). Local spread parameters were assumed to be identical to those of the 2001 UK FMD epidemic model (Morris et al., 2001). Other parameters for disease transmission, i.e., movements and windborne spread, were determined by an ad-hoc methods, i.e., trial-and-error until reasonable agreement between simulated and the actual epidemics was obtained.

The main area of weakness is their assumption that local spread parameters in the FMD epidemic in the Republic of Korea were the same as those of the 2001 UK FMD epidemic because both epidemics were caused by the same serotype (type O). To illustrate the variation in transmission characteristics of different FMD viruses even within a single serotype, the behaviour of the UK type O 2001 strain was characterised by low airborne excretion from infected animals (Donaldson and Alexandersen, 2002), and was distinct from the type O strain responsible for the 1967/68 epidemic (O1 BFS 1860) which was characterised by long-distance airborne (windborne) spread (Sellers and Parker, 1969). The scales of epidemics were shown to vary among different strains of serotype O viruses (range: 1 to 6147 IPs) (McLaws and Ribble, 2007). Although it may be a quick and effective approach to answer a simple question (e.g., whether to use emergency vaccination or not) for the livestock population of interest, more accurate and precise local spread probabilities are required to address more fine-tuned questions (e.g., optimal size of ring vaccination radii).

New Zealand InterSpread Plus model

Sanson *et al.* (2006a) developed an FMD epidemic simulation model for New Zealand to provide decision support that could be used prior to or potentially during an FMD epidemic, using InterSpread Plus (Stevenson et al., 2012). The model is known as the New Zealand standard model (NZSM). The NZSM was similar to that of the 2001 UK FMD model (Morris et al., 2001), except that the model incorporated the pattern of between-herd movement in New Zealand quantified by field surveys (Sanson, 2005), and was simulated using the 2011 New Zealand national livestock population data, AgriBase (Sanson and Pearson, 1997). The movements were specific to the types of livestock premises (beef, dairy, deer, sheep and pigs) and their likely risk. Local spread probabilities were derived from the analysis of the UK 2001 FMD epidemic (Sanson et al., 2006b); later, Owen *et al.* (2011) conducted survival analyses to identify parameters that were influential for the outcomes and needed to be refined. The parameters examined were limited to those regarding movements and surveillance. Although the local spread parameters for the NZSM have been recognised as 'extremely important' (Sanson et al., 2006a) and their uncertainties are expected to be influential for the model outcomes, no sensitivity analysis has been done, or at least appeared in the published literature.

The NZSM has served as an exploratory tool to inform policy development and resourcing needs as a way of investigating potential features of FMD occurrence in a country without any experience of an FMD epidemic, while its weakness is that it is of uncertain validity for an epidemic caused by virus strain unlike the 2001 UK FMDV strain (Anonymous, 2011a). Furthermore, it is based on the assumption that if a virus strain similar to the 2001 UK FMDV strain was introduced in New Zealand, the same local spread patterns would be observed regardless of difference in the populations and environment.

Denmark InterSpread Plus model

Simulation models for FMD in Denmark have been developed using both InterSpread Plus and DADS model (Boklund et al., 2013, Halasa et al., 2014). Their studies will be reviewed in the following subsection for DADS.

2.3.4. Davis Animal Disease Simulation (DADS) models

US DADS model

Bates *et al.* (2003b) developed a spatial stochastic multi-level simulation model, currently known as the Davis Animal Disease Simulation (DADS) model (Carpenter et al., 2011, Hagerman et al., 2012), with the objective of identifying effective eradication strategies for a hypothetical FMD epidemic in the US. The DADS model differs from the InterSpread Plus model in that it simulates individual animals within each herd. Between-herd disease transmission was simulated similarly as the InterSpread Plus models: by (i) direct, (ii) high-risk indirect, and (iii) low-risk indirect contacts considering different types of herds in the US livestock population. The parameters defining contact patterns were derived from surveys in California and expert opinion. Initially, windborne spread and spread by wildlife were not considered. The later versions of the DADS model were modified to incorporate a feature to capture local spread ('local area spread'), representing any mechanisms of spread that were either attributed to these environmental factors or to unrecorded human activities among the farming community (Carpenter, personal communication). The local area spread parameters were derived from the analysis of the 2001 UK FMD epidemic data by Sanson *et al.* (2006b) (Carpenter, personal communication).

Similar to the New Zealand InterSpread Plus model, it is based on the assumption that the local spread patterns would not be affected by difference in the populations and environment from that of the UK, and is specific to the virus strain considered. Addition of sensitivity analyses may be useful for interpretation of the modelling results.

Denmark DADS model

Boklund *et al.* (Boklund et al., 2013) estimated parameters for DADS as well as InterSpread Plus for simulation of FMD epidemics in Denmark. The model modified for Danish livestock population was called DTU-DADS model. Similar local (area) spread parameters as those of Sanson *et al.* (Sanson et al., 2006b) were used, limiting its use to epidemic similar to that in the UK in 2001. The authors examined the effects of doubling and halving the probabilities of local spread. Doubling local spread probabilities increased the total cost of an epidemic by 170%, while halving did not make a significant difference. The local spread parameters were the most influential parameters among 31 parameters examined in the sensitivity analyses.

2.3.5. The North American Animal Disease Model (NAADSM)

The US model by Schoenbaum and Disney

Schoenbaum and Disney (2003) developed a spatial stochastic simulation model framework for a hypothetical FMD epidemic in the US, currently known as the North American Animal Disease Spread Model (NAADSM) (Harvey et al., 2007). The initial model was based on the hypothetical population data without differentiating species, and captured three mechanisms of disease transmission: (i) direct contact, (ii) indirect contact and (iii) airborne spread. The contact patterns were derived from the studies by Bates *et al.* (2001). The model captured local spread by indirect contact and airborne spread. In their paper, airborne spread was not considered important and the scale of airborne spread parameters were determined so that 0.3-0.4% of new infections occurred by the airborne route. The distance of airborne spread was determined based on the 2001 UK FMD InterSpread Plus model (Morris et al., 2001). Like the other simulation models for FMD spread in FMD-free countries, the implications are limited to the particular epidemic scenario considered.

The US NAADSM model

The NAADSM further refined the 'airborne' spread feature (Harvey et al., 2007). The probability of 'airborne' spread was determined as a function of the baseline probability (probability of 'airborne' spread between units of average size 1 km apart), maximum distance of 'airborne' spread, size of source unit and size of recipient unit. Linear decrease in the probability of 'airborne' spread by distance was assumed. The probability of 'airborne' spread considered amount of virus excreted from an infectious herd and minimum infective dose in a susceptible herd.

The areas of weakness are as follows. First, the baseline probability and maximum distance of 'airborne' spread are not provided. Second, linear assumption of a decrease in the probability of 'airborne' spread by distance may be too simplistic. Third, use of herd size as an effect modifier is unverified due to absence of studies quantifying its association in an actual epidemic, and could be incorrect due to existence of other confounders (e.g., biosecurity level, facilities and species). However, there is strong field and experimental evidence that probabilities of airborne spread are influenced by types of livestock enterprises (Alexandersen and Donaldson, 2002, Donaldson and Alexandersen, 2001, Donaldson et al., 2001, Sellers and Parker, 1969).

2.3.6. AusSpread models

Australia AusSpread FMD model

Garner and Lack (1995) developed a regional non-spatial stochastic disease simulation model for Australia, the initial form of AusSpread (Garner and Beckett, 2005). Disease transmission was simulated based on a constant dissemination rate. That is, every uncontrolled IP was assumed to infect a specified number of premises by any mechanisms of spread (movements or windborne) throughout the epidemic. Windborne spread was not considered important in Australia, due to the relatively low livestock densities and climatic conditions, and a dissemination rates lower than those of 1967/68 UK FMD epidemic were used. Dissemination rates were determined for each of the three regions, considering difference in densities, movement patterns and climatic factors. The areas in need of improvement are: lack of the explicit spatial components, and lack of transparency in how the dissemination rates of the 1967/68 UK FMDV epidemic were converted for Australia and how the regional specific dissemination rates were derived.

Later, Garner and Beckett (2005) further elaborated the modelling system with a spatial component and it was named AusSpread. AusSpread simulated disease spread by (i) windborne, (ii) between-herd direct/indirect contact, and (iii) contacts through saleyards. Local spread was therefore captured by either windborne or direct and indirect contact between-herds. The former, windborne spread was simulated from infected pig farms to susceptible farms with the distance and direction adjusted by the weather conditions. The latter, disease spread by direct/indirect contact, was simulated at the spread rate, i.e., the expected number of new infections per infected herd, estimated from the past overseas outbreaks. The rate was modified by herd type, season, and time since infection. Newly infected farms were randomly selected, based on a given distribution of between-farm distance. In more recent study, the model was modified to feature local spread (Garner et al., 2014), and refined movement parameters estimated from production data and animal movement patterns sourced from field studies (Roche et al., 2014, East et al., 2016). The authors estimated the parameters to represent the serotype O (Pan-Asia) strain, although the method of estimating the parameters was not provided.

AusSpread was distinct from other simulation models for FMD described above in terms of use of a rate of infection (which would be dependent on the frequency of contacts) instead of a probability (which would be dependent on the density of susceptible populations), and absence of contact patterns measured from field surveys. Although their

approach was advantageous in terms of less input requirement, use of the spread rate is debatable, because the underlying assumption is that the local movement patterns, and hence the contact rate, were similar to the overseas country that experienced the epidemic, and the local farm densities surrounding the infectious farms would not be explicitly accounted for. The conclusions drawn from the model would be ambiguous, since the parameters regarding the spread rate and distance probability distribution were unexplained and hence unjustified.

US (Texas) AusSpread model

Ward *et al.* (2009) used the AusSpread modelling framework to simulate FMD spread in Texas, USA. Transmission of disease was modelled similarly as that of Garner and Beckett (2005) except that contact (direct/indirect within-herd, and through saleyards) was simulated using the region-specific contact patterns estimated from surveys and expert opinions. The expected dissemination rates at different stages of a hypothetical epidemic in Texas were determined based on the opinions of five experts who had field experience of overseas FMD epidemics.

The study objective was to simulate typical FMD epidemics in Texas. As common for the countries in the absence of the actual data, there are some weakness in the justification of some parameters. The areas of weakness are: potential bias in the dissemination rates determined by expert opinions without quantitative data, lack of reliability in the estimated probability of infection by indirect contact, based on the survey on those without experience of FMD, and absence of explanation in the method of determining distance of between-herd contacts. In addition, the same weakness as that of Garner and Beckett (Garner and Beckett, 2005) can be applied.

2.4. Economic aspects of disease control

Economics in livestock production systems is focused on efficient allocation of limited resources, with the objective of maximising profits, or human welfare. Economic concepts and procedures can be applied to address questions regarding health problems in livestock production systems. Questions raised may address the economic impact of disease, the benefits of current and alternative intervention measures, an optimal level of control measures, and priority setting among multiple existing diseases. This discipline, often called 'animal health economics,' has been increasingly integrated within veterinary epidemiological analyses to support the decision-making processes in management of

animal diseases at the herd, industry, regional, national and even international level (herd/industry/regional/national) (Rushton, 2009, Dijkhuizen and Morris, 1997).

The early economic studies in the 1960s typically estimated substantially high losses due to disease in livestock production systems worldwide, as well as remarkably high return on investments on disease control programmes (Morris, 1999). This is partly because efforts in animal disease control in those days were generally less intensive, and animal health problems which potentially had a high return rate remained unsolved. Those economic studies helped by drawing attention of policy makers and justifying investments in veterinary service infrastructure and research to improve animal health. However, for some diseases, a costly, intensive large-scale disease control or elimination campaign may not be justified for low-input farming systems, or may not be affordable for governments and individuals with the currently available resources, even though positive benefits are expected in long term. For example, some disease control or elimination programmes resulted in costs outweighing the quantifiable benefits (Pritchard, 1966). Furthermore, disease control may results in unanticipated consequences, the dramatic repercussions in the entire society experienced by the UK due to mass culling during the FMD epidemic in 2001 (Thompson et al., 2002). To justify any intervention programme, it is important to critically evaluate the potential benefits of a specific proposed intervention in comparison with the costs, as well as those of the original problem, or other forms of investments (Torgerson, 2013). Although there is a growing literature on animal health economics, there are still many issues concerning economically appropriate disease control strategies which remain unresolved, and decision makers therefore need access to better information on the economic aspects of disease control (Rushton et al., 1999, Rich et al., 2005).

A thorough review for the economic impact of FMD is given by Knight-Jones (2013). In the following subsections, the current methods used to evaluate control of FMD will be reviewed. In the first subsection (Section 2.4.1), a brief explanation of the commonly used evaluation criteria will be provided. Then, the methods for estimating the impact of FMD, in terms of production losses (Section 2.4.2), export loss (Section 2.4.3), and secondary impacts (Section 2.4.4) will be examined. The section will also include reviews of accounting the costs of intervention (Section 2.4.5) and externalities (Section 2.4.6).

2.4.1. Evaluation criteria

In common with many other disease control programmes, interventions for FMD (e.g., prevention, control and eradication) are a long term investment, for which benefits are expected over a number of years. To assess the rationality of a control programme, benefits of a programme over its cost (profitability) needs to be evaluated for the duration when the programme is effective. A cost-benefit analysis is the common method to appraise such control and eradication programmes for FMD (Bates et al., 2003a, Power and Harris, 1973, Berentsen et al., 1992, Barasa et al., 2008). In cost-benefit analyses, the costs and benefits occurring at a later time are converted to present values by a process called discounting (Rushton, 2009). Discounting adjusts for time preference, i.e., investments with returns occurring earlier are generally preferred to those occurring later. A present value (X_0) can be calculated as follows:

$$X_0 = \frac{X_t}{(1+r)^t}$$

where X_t is the value in year t, r is the discount rate, and t is the number of years from the onset of the programme. By discounting, the conclusions of the analyses are more heavily influenced by immediate effects (e.g., stamping-out) than long-term effects that are weighed less (e.g., more trade opportunities). This is because benefits occurring in the short-term are typically preferred to benefits occurring in the long-term. As a discount rate, the rate of return for a competing investment, or the current national interest rate, is typically used. Evaluation criteria for a benefit-cost analysis are typically net present value (NPV), benefit-cost ratio (BCR), and internal rate of return (IRR) (Rushton, 2009). NPV, BCR and IRR for n year projects are calculated as follows:

$$NPV = \sum_{t=0}^{n} \frac{Benefit_t - Cost_t}{(1+r)^t}$$

$$BCR = \frac{\sum_{t=0}^{n} \frac{Benefit_t}{(1+r)^t}}{\sum_{t=0}^{n} \frac{Cost_t}{(1+r)^t}}$$

$$\sum_{t=0}^{n} \frac{Benefit_t - Cost_t}{(1+IRR)^t} = 0$$

where r is the discount rate, and $Benefit_t$ and $Cost_t$ are the undiscounted benefits and costs in year t. An NPV represents an absolute scale of return on investment, while a BCR indicates efficiency of the investment. An IRR is the discount rate where the total discounted benefits and the total discounted costs are breakeven. An IRR indicates the risk of a programme, i.e., higher the IRR, the safer the profitability of the project is, because the conclusion would not be affected by choice of a lower discount rate.

The scale of analyses and suitable approach depend on the nature of the disease and the research questions being considered (Rich et al., 2005). For control of FMD, both the costs and benefits are borne by the tax payer and the private sectors (Knight-Jones and Rushton, 2013). The incentives to control FMD may be more tangible to the commercially-driven industries than small-scale farmers and individuals (Knight-Jones and Rushton, 2013). Irrespective of this variation, FMD would cause significant social repercussions within the whole country, and therefore, national-level economic analyses are suitable. Particularly, the gross benefit of disease control is measured as averted losses, and it requires the measurements for the impact of disease in the whole economy, requiring macroeconomic approaches. To facilitate the estimation process, the impact of disease is often broken down into subcategories, typically a range of production losses in livestock, public health costs, reduction in net export income, and secondary impacts in sectors exogenous to the agriculture sector. The methods of categorisation and terminology may vary by analysis. For example, the economic impact of disease at various scales are referred to as 'consequential costs,' 'direct costs,' 'indirect costs,' and 'secondary costs' by different authors (Knight-Jones and Rushton, 2013, Power and Harris, 1973, Carpenter et al., 2011, Rushton, 2009). Regardless of variation in the accounting process, the purpose is to explicitly and exhaustively account for all economic effects of disease on the stakeholders, without ignoring or double counting any impacts.

2.4.2. Production losses

For FMD, the major losses of production appear as reduction in milk, reduction in meat, mortality, infertility, abortions, and reduction in traction power (Knight-Jones and Rushton, 2013). One way to estimate the production consequences due to FMD at the aggregated level (e.g., regional, national) is to estimate 'unit volume' of products lost due to disease and multiply it by the current unit market price.

The production parameters can be estimated based on an experimental or field study. Tshering (1995) used parameters drawn from previous studies in other countries to estimate the national production loss of FMD in Bhutan. Such an approach is a useful method to obtain an initial estimate of production losses when the field data are not available, but the estimates do not reflect variation by virus strains, affected animal species or breeds, and production systems in the country of interest. The major constraint for collection of field data is that livestock holdings are rarely equipped with extensive computerised systems to record health and productivity, except for intensive enterprises in industrialised countries (Nguyen et al., 2011). Participatory epidemiology (PE) methods and Delphi expert opinion survey (DEOS) methods are practical alternatives when field data are not available. The former was used by Barasa *et al.* (2008) to collect data from livestock owners in villages in Sudan, where infrastructure was extremely poor. The latter was used by Şentürk and Yalcin (2008) to collect data from field-experienced state veterinarians in Turkey. These measurements estimated without quantitative data are, however, less reliable, lack accuracy, and contain bias. Adequate consideration should be given to the uncertainty of estimates in interpreting results.

Although FMD is endemic in two thirds of countries (Anonymous, 2015b) and recognised as an important disease that may result in serious production losses, there are relatively few published studies quantifying the extent of production losses (Knight-Jones and Rushton, 2013). In countries maintaining freedom from FMD and exporting animal products, the question regarding production losses by endemic FMD is never addressed, because the benefits achieved by eradication of FMD for general public, livestock producers, and consumers are felt to be preferable to allowing FMD to become endemic. During the FMD epidemic in the UK in 2001, the same questions were not addressed even though the costs of eradication was extremely high (Rushton, 2009). The common underlying justification of eradication, even for countries that never experienced FMD (e.g., New Zealand), is that long-term costs of production losses and the opportunity cost of trade will always outweigh the eradication costs (James and Rushton, 2002). Nonetheless, for countries with less intensive livestock sectors and low to moderate export potential, production losses due to endemic FMD need much more investigation so that decision is made as the economic rationality of eradicating FMD.

2.4.3. Export loss

Estimation of export loss is not just a matter of measuring the value of products that could be sold in the international markets without export bans. Rather, the estimates should reflect the net impact on the country's economy, after considering changes in supply-demand relationship on the market. In the short term, crude export loss without considering those changes may be sufficient to inform the scale of an economic impact, for instance, an FMD hoax in Waiheke Island in 2005 (Anonymous, 2011a), or the trade disruption of dairy milk powder in New Zealand in 2013 due to fear of *Clostridium botulinum* contamination (Hussain and Dawson, 2013). For FMD, however, export bans could be extended months or years under the current international recognition of risk of FMD. It is likely that the livestock industries will adapt to alternative strategies to mitigate loss, by transforming products into those that have a long shelf life (e.g., powdered milk, butter, and cheese) or reduced risk of FMD (e.g., pasteurised milk, cooked and tinned meat) and explore opportunities in alternative markets within the country or less FMD-sensitive countries.

For countries exporting a high volume of livestock products (e.g., New Zealand and Australia), three key changes in the market are likely to occur: (i) change in accessible markets, (ii) reduction in overall supply, and (iii) change in demand by domestic consumers (Buetre et al., 2013). First, after export bans imposed by FMD-free countries, market access would be limited to domestic and some international markets less sensitive to FMD (i.e., FMD-endemic). The price of livestock products is generally lower in FMD-endemic markets than FMD-free markets. For example, the difference in beef price was estimated to be 15 to 30% (Jarvis et al., 2005). As a result, products that would be exported to FMD-sensitive international markets without an epidemic would be directed to the accessible markets, resulting in increased supply and lower price. Imposition and lifting of export bans is not only influenced by the OIE's ruling, but also by the risk assessments of individual trading partners and complex market reactions, which often lack transparency. The market changes may be irreversible, as competing exporters may take the opportunity. Second, in contrast to the first effect, reduction in overall supply would occur if a large proportion of animals are culled as control measures. Third, besides the two effects, change in demand by domestic consumers may occur if they are concerned about food safety, even though FMD does not affect human health. For example, Taiwan pork industry experienced reduction in the price of pigs to at worst 70% of original values during and after the FMD epidemic in Taiwan in 1997 (Yang et al., 1999).

Hypothetical export losses in FMD-free countries were estimated in several studies for the EU countries (Bergevoet et al., 2009, Mahul and Durand, 2000, Berentsen et al., 1992, Boklund et al., 2013), US (Schoenbaum and Disney, 2003), Australia (Buetre et al., 2013), and New Zealand (Forbes and van Halderen, 2014). In these studies, export losses were typically measured for a few possible scenarios reflecting the reactions of trading partners, based on the current market structure and expert views on what might happen. The estimates of export losses tend to lack accuracy as data are absent and there is a wide range of uncertainties regarding changes in market reactions. The process of thorough sensitivity analyses is also hampered by a lack of linkage between disease simulation models and economic models of export losses, which can make generating estimates labour intensive.

2.4.4. Secondary impacts

Secondary impacts of animal disease may be referred to as 'ripple effects,' or 'spill-over effects.' Ripple effects are those occurring in the upstream and downstream sectors along the market chain, such as feed producers and slaughterhouses, driven by the primary changes in the livestock sector. Spill-over effects are those affecting sectors that are not directly related to livestock sectors, such as tourism, local business and public works (Bergevoet et al., 2009). Secondary impacts of FMD would particularly be high in the current FMD-free countries actively exporting livestock products, while they may be negligible in countries which does not export (Rushton, 2009).

For national level decision making for FMD control in a country where secondary impacts are potentially important, a net economic impact on the whole economy that includes the secondary impacts, rather than the costs on individual economic sector, would be a more appropriate indicator. Although the impact on the agricultural sector may be dramatic, the net impact may be less so. The UK epidemic in 2001 cost agricultural producers GBP 355 million and GBP 2.5 billion for eradication campaign, while the effect on the gross domestic product (GDP) was less than 0.2% (Thompson et al., 2002). This is partially because, from the macroeconomic perspective, the costs to one sector are offset by benefits to other sectors (Anderson, 2002, Berentsen et al., 1992). For example, lower price of products during the export bans is a loss for producers but a benefit for domestic consumers who can obtain livestock at lower prices (Berentsen et al., 1992). Businesses in non-affected urban areas benefit, while rural business in affected

areas is negatively affected due to extensive movement restrictions, as occurred during the FMD epidemic in the UK in 2001 (Thompson et al., 2002).

To estimate secondary impacts, macroeconomic techniques are suitable. While microeconomic approaches deal with economic effects within an individual economic element (e.g., dairy farm) or its aggregation (e.g., dairy industry), macroeconomic approaches can measure cross-sectorial effects considering various economic elements (e.g., agriculture, tourism, transport) in the whole economy that are treated as exogenous to microeconomic models. The commonly used macroeconomic models are input-output (I-O) models (Mahul and Durand, 2000, Garner and Lack, 1995), partial equilibrium models (Carpenter et al., 2011, Hagerman et al., 2012), and computable general equilibrium (CGE) models. Building an extensive macroeconomic model requires heavy data inputs and thus necessitates collaborative multidisciplinary work among epidemiologists, economists, livestock owners, industries and policy makers (Rushton, 2009, Rich et al., 2005). A wide knowledge gap still exists in the macroeconomic impact, and the linkage between an epidemiological and macroeconomic impact (Perry and Sones, 2007, Rich et al., 2005).

2.4.5. Intervention costs

The questions regarding the potential costs of the current and alternative control policies for FMD have often been raised by FMD-free countries, and investigated relatively well compared with other economic impacts. The major studies on the economics of FMD control in FMD-free countries are summarised in Table 2-1. These studies estimated intervention costs using a unit cost approach that involved multiplying the unit costs of control measures by the number of units (e.g., animals, herds or flocks) where control measures are applied (Risk Solutions, 2005).

Table 2-1 Economic studies for assessment of alternative strategies for control and eradication of foot-and-mouth disease (FMD) in FMD-free countries.

Country	Alternative strategies assessed	Reference
Australia	Culling dangerous contacts (DCs), and vaccinate-to-die	Garner and Lack (1995)
Australia	Culling DCs and vaccinate-to-die	Abdalla et al. (2005)
Australia	Culling DCs and vaccinate-to-die	Buetre et al. (2013)
Denmark	Vaccinate-to-die and vaccinate-to-live	Boklund et al. (2013)
France	Culling DCs and vaccinate-to-die	Mahul and Durand (2000)
Netherlands	Routine vaccination	Berentsen et al. (1992)
Netherlands	Contiguous culling and vaccinate-to-die	Bergevoet et al. (2009)
UK	Routine vaccination	Power and Harris (1973)
UK	Culling DCs, contiguous culling, and vaccinate-to-live	Risk Solutions (2005)
US	Vaccinate-to-die	Bates et al. (2003a)
US	Culling DCs, contiguous culling, and vaccinate-to-die	Schoenbaum and Disney (2003)
US	Enhanced surveillance, culling DCs, vaccinate-to-die	Elbakidze et al. (2009)
US	Vaccinate-to-die	Hagerman et al. (2012)

Intervention costs for FMD are typically broken down into the costs of (i) depopulation, (ii) active surveillance, (iii) movement restrictions, and (iv) routine or emergency vaccination. In the process of estimating the unit cost of a particular control measures for countries free of FMD, contingency plans may be insufficient to obtain information on logistics or compensation. Records of a past epidemic in a similar country provide useful information (Anonymous, 2010c, Anderson, 2002, Pluimers et al., 2002). Among all, the uncertainties in the costs of movement restrictions and vaccination are notable.

For uncertainties in the costs of movement restrictions, the impact on livestock production have not been thoroughly investigated although it is potentially important. During the FMD epidemic in the UK in 2001, the prolonged movement restrictions led to delay in sales, overpopulation on farms, lack of feed and increased stress in animals. The net result of these issues was that at least 2.5 million animals culled for welfare reasons (Schley et al., 2009). The previous work typically lacks consideration on such impact of stringent movement restrictions on factors such as animal welfare (Risk Solutions, 2005, Bergevoet et al., 2009, Mahul and Durand, 2000, Boklund et al., 2013).

For the costs of vaccination, variation by policy is expected to be important. For routine vaccination, the cost would be incurred annually or semi-annually every year, while emergency vaccination would be one-off costs. If vaccinate-to-die policy were considered, the costs would depend on how culling would be conducted (on site or slaughterhouses), and whether or not carcasses would be discarded or enter production chains. If vaccinate-to-live was considered, it should account for potential loss of values of vaccinated animals or products deriving from vaccinated animals. Policies regarding FMD vaccination are not founded in FMD-free countries, and these issues have not been well addressed in previous works (Bergevoet et al., 2009, Mahul and Durand, 2000, Hagerman et al., 2012, Elbakidze et al., 2009, Berentsen et al., 1992, Boklund et al., 2013, Buetre et al., 2013, Abdalla et al., 2005).

2.4.6. Externalities

Externalities are either positive or negative effects that affect the party external to the private market transaction considered (Rushton, 2009). The externalities may be excluded from analyses if they are negligible, or due to lack of data and/or difficulty to assign economic values for such effects. For FMD, externalities include psychological distress in livestock owners and field veterinarians directly involved in the culling activities (Van

Haaften et al., 2004, Olff et al., 2005, Peck, 2005, Hannay and Jones, 2002, Hunter, 2001), external value loss from culling pedigree breeding stock that have been genetically selected over many years (Power and Harris, 1973, Nishiura and Omori, 2010), companion animals who had greater values than their market price, environmental pollution due to incineration and burial (Anderson, 2002), and animal welfare. There may be positive externalities, such as improved biosecurity level after repopulation (Power and Harris, 1973). Although externalities may not be included in the analyses, consideration should be given as they may be important for some part of the society.

2.5. Conclusion

This chapter has reviewed the current knowledge about the epidemiology of FMD, and the previous work for disease modelling and economic evaluation for evidence-based decision making for preparedness, control and eradication of FMD, with particular focus on the currently FMD-free countries. Although a number of simulation models for FMD have been developed to support decision making process, they are based on imperfect knowledge. Refining the parameters or considering uncertainty would enhance the validity of these models.

The extent of between-herd transmission of FMD, namely local spread, is likely to be the key in determining a control strategy in the face of an FMD epidemic, and therefore correct understanding is essential. However, there is a wide knowledge gap in the mechanism of local spread. The extent of local spread evidently varies by multiple factors including virus strains, stage of infection, management types, host species, stage of epidemic, and geographical features. Although a number of epidemics have occurred in previously disease-free countries in the last decade, the mechanism of local spread in each epidemic was not thoroughly investigated.

Since the UK FMD epidemic in 2001, computer programmes for spatially-explicit stochastic microsimulation models for FMD, InterSpread Plus, DADS, the NAADSM and AusSpread, have been established or enhanced for the purpose of policy evaluation in the current FMD-free countries. These models accommodate reasonably accurate, detailed national population data, and have flexibility to incorporate more features of epidemiological importance if necessary. However, all the current models are based on local spread parameters that are generally crude and lack justification or extrapolated from the large-scale, overseas epidemics for which data were well recorded, accessible, and well

analysed, namely the 2001 UK FMD epidemic. Hence, the current models have limitations in their implications and would not be appropriate to address detailed questions regarding control strategies. Analyses or reanalyses of the past epidemic data to improve knowledge about a potential range of local spread patterns of FMD would add more validity in the simulation models for FMD.

Although FMD is an economically important disease, the economic aspects of control and eradication strategies for FMD could be refined with further work. The major constraint for economic analyses is that information necessary for estimating the economic inputs may be absent or scarce due to the unprecedented nature of FMD. For the previous work incorporating the economic components with the FMD simulation model, initial input parameters, particularly regarding vaccination, contain a great deal of uncertainty. Thorough sensitivity analyses have yet to be conducted to examine the robustness of the conclusions for each country. In addition, most studies have weakness around the linkage between epidemiological and macroeconomic models. The benefits of controlling FMD will be received by the wider economy that could be better quantified by macroeconomic models. Hence, collaborative work between epidemiologists and economists should be further enhanced.

This thesis firstly aims to address the short comings of the current simulation models for FMD by investigating a transmission mechanism of high importance, local spread, based on available data from different historical FMD epidemics in formerly FMD countries. The second aim of the thesis is to investigate various alternative strategies for control and eradication of FMD in New Zealand, by enhancing the economic components of the previously developed system. The implications drawn from the study will be useful for decision makers, while the approaches can be used for any other infectious disease in New Zealand.

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3. Estimation of the hazard of local spread for foot-and-mouth disease outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010)

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3.1. Abstract

Localised transmission of disease without any traceable contacts is commonly known as local spread, which is an important mechanism of spread for highly contagious livestock diseases such as foot-and-mouth disease (FMD). In the two large-scale FMD epidemics in the UK in 1967/68 and 2001, the majority (> 80%) of farm-to-farm transmissions of infection are attributed to local spread. Despite its importance, the pattern of local spread is not sufficiently understood to extrapolate for external populations. Our approach was to hypothesize occurrence of local spread by randomly allocating a source among spatially and temporally plausible candidate sources for each newly infected premises. A Weibull regression model (i.e., parametric survival model) was fitted to estimate the daily hazard of local spread while accounting for available variables, i.e., country, herd/flock size and species on both infectious and susceptible premises. The method was applied to the first three weeks of the FMD outbreak data from Cumbria (UK, 2001), Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010). Our results showed that the estimated crude daily hazard of local spread in Cumbria (UK, 2001) was at most 4.1 (95% CI: 2.5 to 6.8) per 1,000 susceptible premises on the onset of infectiousness of a source premises, which decreased exponentially by distance and increased as the infection progressed. Given the same density of livestock premises, the crude mean daily hazard of local spread for Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010) was 0.43 (95% CI: 0.25 and 0.74) and 0.28 (95% CI: 0.17 and 0.47) times that of Cumbria (UK, 2001), respectively. The risk factors commonly associated with an increase in the local spread hazard were: larger herd/flock size of a susceptible premises, infectious premises with pigs and susceptible premises with cattle. The estimated daily hazard of local spread will be useful for modelling and decision making for FMD control, while the methodology presented here will be applicable to analyses of other FMD outbreaks, or other contagious diseases with similar characteristics to FMD.

3.2. Introduction

Foot-and-mouth disease (FMD) is a highly contagious viral disease of cloven-hoofed animals. An incursion of FMD into the susceptible population usually results in rapid spread of disease, with a possibility of developing an endemic state, without a prompt and smooth implementation of control measures. An FMD epidemic in a country previously free of FMD causes dramatic economic impacts, arising from the eradication programme, trade bans of livestock and livestock products, and disrupted business in related industries, as highlighted by the UK epidemic in 2001 (Thompson et al., 2002). Since the 2001 UK FMD epidemic, a number of groups around the world have been actively involved in improving the utility of disease simulation models to support decision making (Keeling, 2005). In many disease-free countries, simulation models are an essential component of disease preparedness as they allow policy makers to understand the overall epidemiologic and economic impact of FMD, and provide an evidence-based framework to assess alternative polices when a field experiment is not feasible. However, the predictive ability of a model is strictly limited to the accuracy of prior biological and veterinary knowledge represented in its input parameters. Before drawing any implications from the models, it is important to identify any input parameters, which are uncertain, with their associated distribution of uncertainty, and test their influence on the model outcomes.

Transmission of FMD virus is known to occur typically by contacts between infected and susceptible premises through movements of animals, humans, vehicles, and fomites, or airborne spread (Donaldson et al., 2001). Dissemination of virus without recorded movements from the source of infection over relatively short distances is often called 'local spread.' In practice, local spread is used as a catch-all term to describe any unknown mechanism of disease spread that occurs without any clear linkage other than geographical proximity, which may include not only short distance airborne spread but also through-the-fence contact between animals on contiguous properties, general neighbourly interactions, and mechanical carriage of the agent by wildlife (Sanson et al., 2006a, Sanson, 1994). While movement plays the major role in spreading disease before detection of the index case, local spread is usually the most important mechanism of spread after imposition of strict movement restrictions. For example, greater than 90% of the total number of infected premises (IPs) in the UK 1967/68 FMD epidemic and more than 80% of IPs in the first five months of the UK 2001 FMD epidemic were attributed to local spread (Sanson et al., 2006a, Gibbens et al., 2001, Cottam et al., 2008b). Despite

its importance, the mechanisms and hence the factors influencing the extent of local spread are much less understood in comparison with transmission arising from animal and fomite movement, largely because there is no reliable evidence to link source to recipient premises for local spread, as there is for movement transmission. Genetic data have been demonstrated to provide useful information for determining the likely source of infections within an FMD outbreak (Cottam et al., 2008a, Cottam et al., 2008b). However, collection of samples during the outbreak, maintenance, and generating genome sequences with a sufficiently high resolution for within-epidemic transmission tracing is labour intensive, and may not be feasible.

FMD simulation models generally capture local spread by use of a radial 'transmission kernel' which specifies the probability of infection occurring per unit time at given distance from an infectious unit. The local spread parameter can be one of the most influential parameters in FMD simulation models (Boklund et al., 2013). There are a number of modelling studies where FMD transmission kernels were estimated for the 2001 UK epidemic (Green et al., 2006, Keeling et al., 2003, Sanson et al., 2006a), the 2001 Dutch epidemic (Boender et al., 2010), and the 2010 Japan epidemic (Hayama et al., 2013), with the precise form determined by the observed dynamics (Keeling and Rohani, 2007). Due to absence of experiences or accumulated data, a number of simulation models for FMD, particularly those of countries without recent experience of FMD outbreaks (Sanson et al., 2006a, Carpenter et al., 2011, Boklund et al., 2013), use local spread parameters extrapolated from the 2001 FMD outbreak in Cumbria, UK (Sanson et al., 2006b). Although it goes untested and often unstated, the underlying assumption is that the pattern of future FMD local spread in the population of interest is similar to that of the FMD outbreak in Cumbria (UK, 2001). It should be noted, however, that the extrapolated parameters explicitly represent the overall pattern of local spread in that particular locality (e.g., Cumbria, UK) for that particular epidemic (e.g., 2001 UK FMD epidemic), and is unlikely to replicate that of a future FMD epidemic occurring in a different population with different demographics (e.g., animal species, herd/flock size), production and management systems (e.g., facilities, common grazing, biosecurity practices) and meteorological and geographical conditions, caused by different FMD virus strains. To illustrate this, a substantial difference in the patterns of local spread between Cumbria and Devon during the UK 2001 FMD epidemic was suggested (Wilesmith et al., 2003). However, the current absence of knowledge to differentiate common and epidemic-specific risk factors for FMD local spread makes it difficult to draw generic

implications from the simulation-based studies for policy making and contingency planning.

To address this knowledge gap, the aims of this study were to propose a generic method to quantify the hazard of FMD local spread from typical field data routinely recorded during the course of an outbreak response, compare the patterns of local spread for three FMD outbreaks, Cumbria (UK, 2001), Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010), and examine common and epidemic-specific risk factors for FMD local spread.

3.3. Materials and methods

3.3.1. Epidemic data

Three FMD outbreak datasets were obtained from the Department of Environment, Food and Rural Affairs (DEFRA), United Kingdom, Japan Agricultural Cooperatives (JA) Koyu and Osuzu, and Korean Animal and Plant Quarantine Agency. Analyses were limited to a spatial boundary, which was either an administrative district or a square block, in Cumbria, UK (the number of IPs: n = 182), Miyazaki, Japan (n = 274), and Andong, Republic of Korea (n = 298). In all three boundaries, FMD cases were spatially clustered and local spread was considered to be highly important. Population data, i.e., premises with animals susceptible to FMD, were also available within the spatial boundary. The key demographic features within the study area are shown in Table 3-1. The geographical distributions of cases and susceptible livestock premises are shown in Figure 3-1.

The information used in the analyses were: (i) the geographical location of the centroid of each livestock premises expressed as the easting and northing coordinates, (ii) the dominant species of livestock present on each premises (cattle, pigs, or small ruminants), (iii) total number of FMD susceptible animals present on each premises, and (iv) the infection status of each premises. For premises with FMD, the dates of presumed infection, and the start and the end of an infectious period were required in the following analyses. For the purpose of this study, infection was considered as any event, where any susceptible animals on the premises were exposed to FMD, which was followed by a latent period and a subsequent infectious period. Based on an experimental study reporting airborne excretion of virus typically starting a day prior to the onset of clinical signs (Sellers and Parker, 1969), the duration of a subclinically infectious period was assumed to be one day, followed by immediate detection of disease. The infectious period

was assumed to last till completion of depopulation of the premises. For simplicity, time lag between the onset of clinical signs in infected animals and detection of disease was assumed to be within a day.

For the data for the Republic of Korea, the dates of infection were previously estimated by the authorities considering multiple variables for individual cases (Yoon et al., 2013). For the data for the UK and Japan, the majority of IPs (UK: 175 out of 182 and Japan: 260 out of 274) were missing infection dates, except for important IPs for which infection dates were estimated through epidemiological investigation. For each of these missing data, a value for an interval between infection and detection was randomly sampled from a probability density function derived from kernel smoothing available data (n = 234, UK: 6, Japan: 11 and Republic of Korea: 217) with bandwidth = 0.68. Outliers exceeding 1.5 times the interquartile range (n = 15, UK: 1, Japan: 3 and Republic of Korea: 11) were excluded from the data because they were observed only under specific conditions (e.g., beginning of the epidemic), and unlikely to occur otherwise. The resulting median interval between infection and detection, 8.0 days (5^{th} and 95^{th} percentiles: 1.7 and 14.3 days) was 1 – 2 days longer than the estimated incubation period based on experimental studies (Mardones et al., 2010), which may be due to reporting delay on the field conditions. For the UK data, missing depopulation dates (n = 243 out of 435) were estimated similarly by assigning a random interval between detection and depopulation, using a probability density function derived from kernel smoothing available data (n = 657, UK: 182, Japan: 274 and Republic of Korea: 228), excluding outliers exceeding 1.5 times the interquartile range (n = 27, UK: 0, Japan: 26 and Republic of Korea: 1) with bandwidth = 1.35 (median: 13.5 days, 5^{th} and 95^{th} percentiles: 1.4 and 25.7 days).

Table 3-1 Geographical features of the three areas investigated for foot-and-mouth disease (FMD) outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

	UK	Japan	Republic of Korea
Spatial boundary	A 50 km square, east of Cumbria County	East of Koyu District, Miyazaki Prefecture	Andong City, Gyeongbuk Province
Size of the area (km^2)	2,500	440	1,590
Total number of premises	2,212	880	2,214
-Cattle	1,682	739	2,016
-Small ruminants	530	30	123
-Pigs	0	111	73
Median herd/flock size (5^{th} and 95^{th} percentiles)			
-Cattle	577 (23 and 2685)	8 (1 and 92)	20 (3 and 286)
-Small ruminants	130 (6 and 1538)	7 (1 and 39)	1 (1 and 3)
-Pigs	NA	650 (2 and 9936)	825 (47 and 5902)

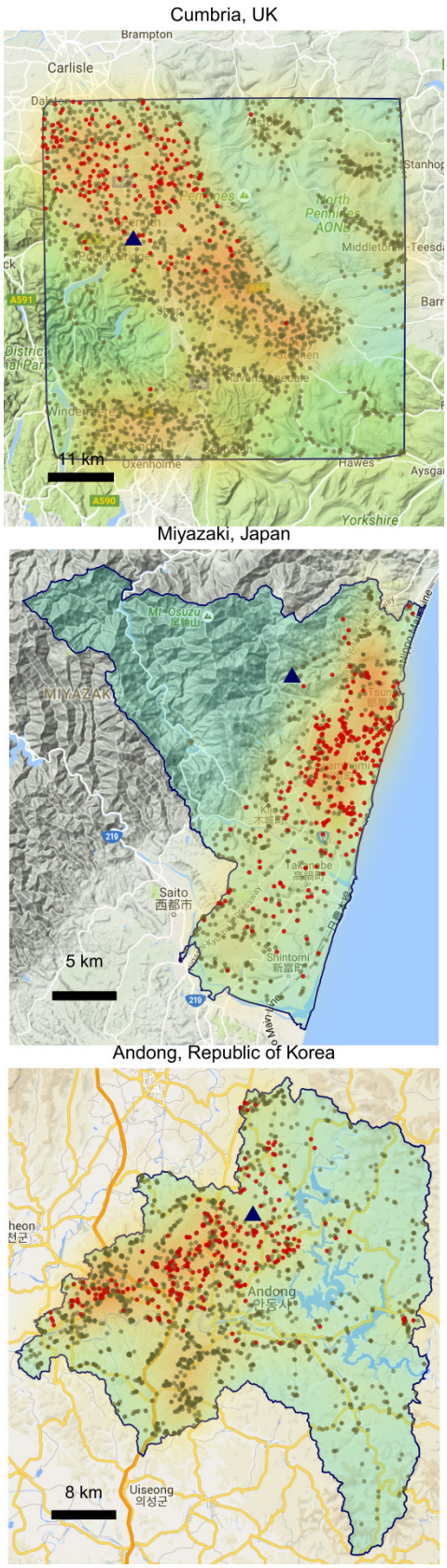

Figure 3-1 Location and infection status of all foot-and-mouth disease (FMD) susceptible livestock premises within the study area (blue triangle: primary case, red: infected, grey: uninfected) for the FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

3.3.2. Creation of survival dataset

For survival analysis, a time-to-event dataset was created from the three outbreak datasets, which observed a pair of an infectious and susceptible premises, with a time of observation starting from the onset of the risk of local spread between the premises pair, and occurrence of local spread (Table 3-2). We limited the period of our analyses to the first three weeks after the first confirmation of disease in each outbreak area, i.e., between 1 and 21 March 2001 (Cumbria, UK), between 20 April and 11 May 2010 (Miyazaki, Japan), and between 28 November and 19 December 2010 (Andong, Republic of Korea), because the course of each epidemic varied substantially after this time.

The first step was to create a pairwise matrix listing all pairs of an infectious and susceptible premises. Premises that became infected within the investigated period were listed as potential source of local spread, and all premises that were susceptible to the infected premises at the beginning of its infectious period (i.e., a day before detection) were listed. Subclinically-infected premises which were pre-emptively culled before becoming infectious were not considered as a potential source. The source of some infections could be attributed to an explicit movement through epidemiological investigation. However, since these data were not available for this study, all infection mechanisms occurring within the defined range was considered as local spread.

The second step was to consider spatial and temporal plausibility of occurrence of local spread for each premises pair. For spatial plausibility, the Euclidian distance (in kilometres) between the centroids of premises pairs was measured, and any pairs where the distance was greater than 10 km were excluded, as hazard of local spread was assumed to be absent beyond 10 km. The choice of 10 km, which was 7 km greater than the commonly used distance, 3 km (Taylor et al., 2004, Gibbens et al., 2001), was considered to be sufficient to encompass all pairs of premises at risk of local spread. Analyses were also conducted for two other cut-off distances, 2.5 and 5.0 km, to test the potential variation in the outcomes. For temporal plausibility, a pair of premises was considered temporally plausible for occurrence of local spread if a susceptible premises became infected before the potential source was culled. It was not considered temporally plausible if a susceptible premises was infected after the potential source was culled.

The third step was to determine the outcome variable, i.e., time-to-event. The time to event was measured as the number of days elapsed since a premises became infectious

until infection occurred on a susceptible premises or the end of the study period, that is, 21 days after the confirmation of the index case in the outbreak area.

The fourth step was to determine occurrence of local spread. For a susceptible premises that became infected and had one or more spatially and temporally plausible sources (which was usually the case), a single source premises responsible for infection was determined as follows. First, the probability of disease transmission was estimated using the distance as a weighting factor. The probability of a potential source (j) being the true source of infection for an arbitrary susceptible premises (i), p_{ij}, was:

$$p_{ij} = \frac{w(d_{ij})}{\sum_{j=1}^{k} w(d_{ij})} \quad (1)$$

where d_{ij} is the distance from a susceptible premises i to the potential source premises j, $w(d_{ij})$ is a weighting function for distance d_{ij}, and k is the total number of plausible sources of infection for the susceptible premises *i*. The weighting function w was represented by the right hand side of the normal distribution function with mean 0 and standard deviation $k/z_{0.975}$, where $z_{0.975}$ is the 97.5 percentile of the standard normal distribution (i.e., 1.96). For *k*, the selected cut-off distance (i.e., 10.0, 5.0 and 2.5 km) was used. The values of p_{ij} sum to 1.0 across all potential source premises. For each newly infected premises, a single source of infection was selected by random sampling on a cumulative step function over the range of 0 and 1 where the steps are equal to the p_{ij} value of each successive potential source premises.

All other pairs considered as possible candidate sources and recipients of local spread were right censored without any positive outcome status. While the resulting dataset usually include a particular premises multiple times either as a susceptible premises or an infectious premises, all the observations of pairs are unique and entered for a single time.

Table 3-2 An example survival dataset, observing 4 pairs of susceptible premises 1 and infectious premises 2 - 5 (observations 1 – 4).

	Susceptible premises			Infectious premises						
Obs.no.	ID	species	size	ID	species	size	Distance (km)	Obs. time (d)	Probability ($p_{i,j}$)	Failure
1	1	cattle	200	2	cattle	220	3.8	4	0.46	1
2	1	cattle	200	3	sheep	420	9.3	3	0.11	0
3	1	cattle	200	4	sheep	800	4.2	2	0.43	0
4	1	cattle	200	5	cattle	1200	13.2	NA	NA	NA

Note that observation 1 has a positive failure status (i.e., local spread occurred from premises 2 to 1) as the distance-weighted probability of premises 2 being the source is the highest among neighbouring infected premises. Observation 4 is excluded from the analyses, because the distance of 13.2 km falls beyond the 10 km cut-off distance.

3.3.3. Survival analyses

In the following survival analyses, an event, or a failure, is defined as occurrence of transmission of disease from an infectious premises to a susceptible premises. An instantaneous hazard of local spread (hereby referred to as hazard), is defined as a daily probability of an occurrence of an event, given the susceptible premises had remained free of infection up the date of interest. All the analyses were conducted using the Survival package (Therneau, 2015) in R, version 3.2.0 (R Development Core Team, 2014).

A Weibull model was chosen to fit the survival data after visually assessing the straightness of a log cumulative hazard plot (Dohoo et al., 2003). Using the Weibull distribution, multivariable regression models incorporating explanatory variables x_i were fitted to describe hazard function $h(t)$ as:

$$h(t) = \lambda_0 s t^{(s-1)} \exp\left(\sum \beta_i x_i\right) \quad (2)$$

where $\lambda_0 = \exp(\beta_0)$ is a scale parameter, s is a shape parameter and β_i is a coefficient. A hazard ratio (HR) was then calculated as $HR = \exp(\beta_i)$. All parameters including the Weibull shape parameter s were fitted using maximum likelihood methods.

Two multivariable Weibull regression models were fitted: a crude model to fit the hazard of a 'typical' pair of premises in the outbreak area, and an adjusted model, which considered the effects of species and herd/flock size for both source and susceptible premises.

The crude model had two explanatory variables selected *a priori*, distance between a potential source premises and a susceptible premises (continuous variable) and the country (categorical variable: UK/ Japan/ Republic of Korea). Polynomial terms for distance were assessed using the log likelihood test statistics. Following this, an interaction between distance and country was added to the model and retained if it was significant with a level $p < 0.05$ using the log likelihood ratio test.

The adjusted model was fitted using six candidate explanatory variables: (i) distance, (ii) country (described above), (iii) species of a potential source premises (categorical variable: cattle, pigs, or small ruminants), (iv) species of a susceptible premises (categorical variable: cattle, pigs, or small ruminants), (v) number of animals in a potential source premises (i.e., herd/flock size), and (vi) number of animals in a susceptible premises (i.e., herd/flock size). An interaction term was added in a stepwise manner and retained if the log

likelihood ratio test had a p-value smaller than 0.05. Once no significant interaction term was found, the adjusted model was evaluated by stepwise elimination process. The final model was used to predict the hazard $h(t)$ of local spread infection (transmission kernel).

3.4. Results

3.4.1. Descriptive statistics

Based on the three FMD outbreak datasets from Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010), 368 unique infectious premises (UK: 81 cattle and 8 small ruminants, Japan: 44 cattle and 33 pigs, Republic of Korea: 191 cattle and 11 pigs) were identified as candidate source premises within the specified three week period, and 3,814 unique susceptible premises (UK: 821 cattle and 193 small ruminant, Japan: 657 cattle, 30 small ruminant and 106 pigs, Republic of Korea: 1,827 cattle, 119 small ruminant and 61 pigs) within 10 km from any of the potential source premises, comprising 168,691 pairs of a potential source and susceptible premises (UK: 12%, Japan: 24%, Republic of Korea: 64%). There were initially 91 (UK: 9, Japan: 12, Republic of Korea: 70) infected premises at the beginning of the study period, and 495 (UK: 134, Japan: 139, Republic of Korea: 222) new infection during the specified period, of which 461 (UK: 118, Japan: 130, Republic of Korea: 213) were attributed to local spread transmission.

The median (minimum and maximum) observation time counting from the onset of infectiousness in the potential source to either infection in the susceptible premises, culling of either premises, or the end of the third week of initial response was 4 (1 – 12), 6 (1 – 12), and 4 (1 – 15) days for the outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010), respectively. The survival function and instantaneous hazard for each of the three outbreaks is shown in Figure 3-2.

There were minor variations in the results by the choice of the cut-off distance of local spread (10.0, 5.0 and 2.5 km). In this paper, only the results of the longest distance, 10.0 km, was presented because local spread occurring beyond 5.0 km was considered important as illustrated in the following sections.

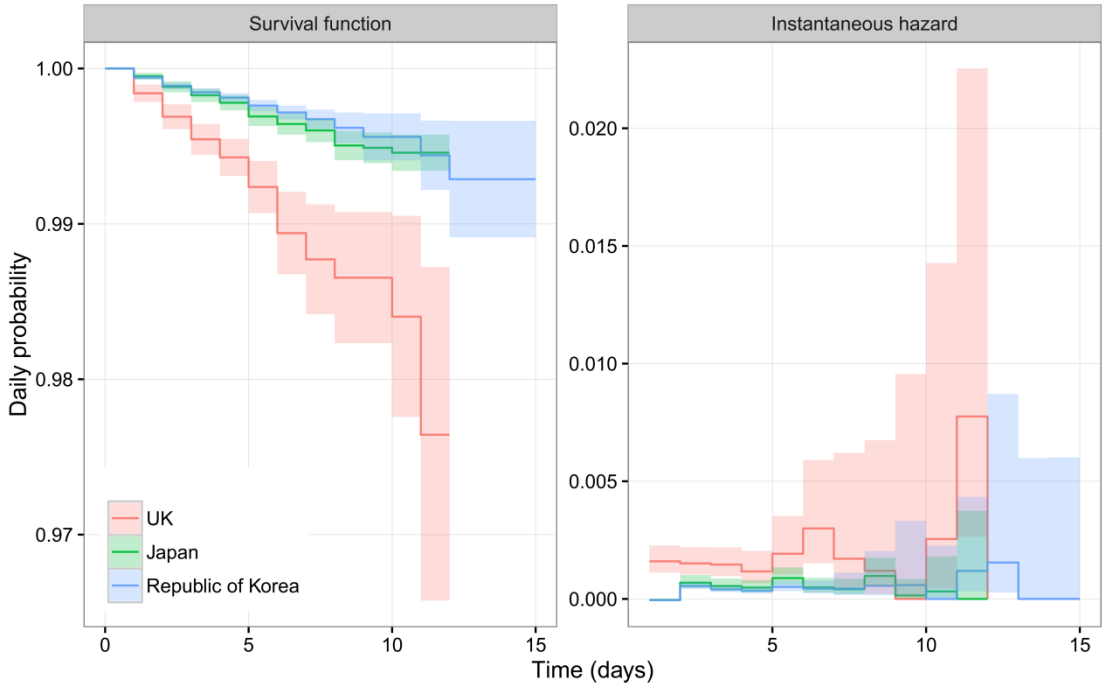

Figure 3-2 Survival function and instantaneous hazard estimated by Kaplan-Meier method (and 95% confidence intervals shown in shade) for local spread infection of foot-and-mouth disease (FMD) since the onset of infectiousness in the potential source premises for the FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

3.4.2. Crude model (typical premises)

The estimated parameters for the best-fit crude Weibull model are shown in Table 3-3. The Weibull shape parameter (s = 1.39) greater than 1 indicated that the hazard of local spread increased as time elapsed since the onset of infectiousness in the potential source premises until the end of observation, up to an observed maximum of 15 days. The association between hazard and distance was significantly greater (i.e., a decrease in hazard by distance was significantly greater) in Miyazaki (Japan, 2010) than that of Cumbria (UK, 2001) and Andong (Republic of Korea, 2010). The hazard ratios of local spread in Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010) were 0.43 and 0.28, respectively, relative to Cumbria (UK, 2001) with a distance of 0 km (i.e., intercept).

The predicted hazard of local spread for varying distances (0 – 10 km) for varying time (0 - 12 days) of infectiousness for Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010) are shown in Figure 3-3. The hazard of local spread between a typical infectious and susceptible premises pair with a distance of 1 km was 3.36 (95% CI: 2.10 to 5.35), 1.25 (0.80 to 1.95), and 0.95 (0.59 to 1.53) per 1,000 premises at risk per day on the first day of infectiousness (i.e., a day prior to the onset of clinical sign) and monotonically increased to 8.76 (5.49 to 13.97), 3.27 (2.10 to 5.10), and 2.48 (1.55 to 3.98) per 1,000 premises at risk per day on the 12th infectious day for the FMD outbreak in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010), respectively (Figure 3-3).

Table 3-3 Estimated hazard ratio (and 95% confidence interval) for local spread infection of foot-and-mouth disease (FMD) for the crude Weibull regression model for FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

Variable	UK	Japan	Republic of Korea
Distance*	0.81 (0.76, 0.88)	0.71 (0.65, 0.78)	0.82 (0.78, 0.87)
Intercept	1.00 (reference)	0.43 (0.25, 0.74)	0.28 (0.17, 0.47)

Weibull shape parameter s = 1.39 and the baseline hazard $\lambda_0 = 2.97 \times 10^{-3}$ (95% CI: 1.79, 4.93×10^{-3})
* Euclidian distance between the centroids of a source and susceptible premises (km). The hazard ratio (HR) of 0.81 for distance can be interpreted that for every 1 km increase in distance from the source farm, the hazard of infection was decreased by a factor of 0.81

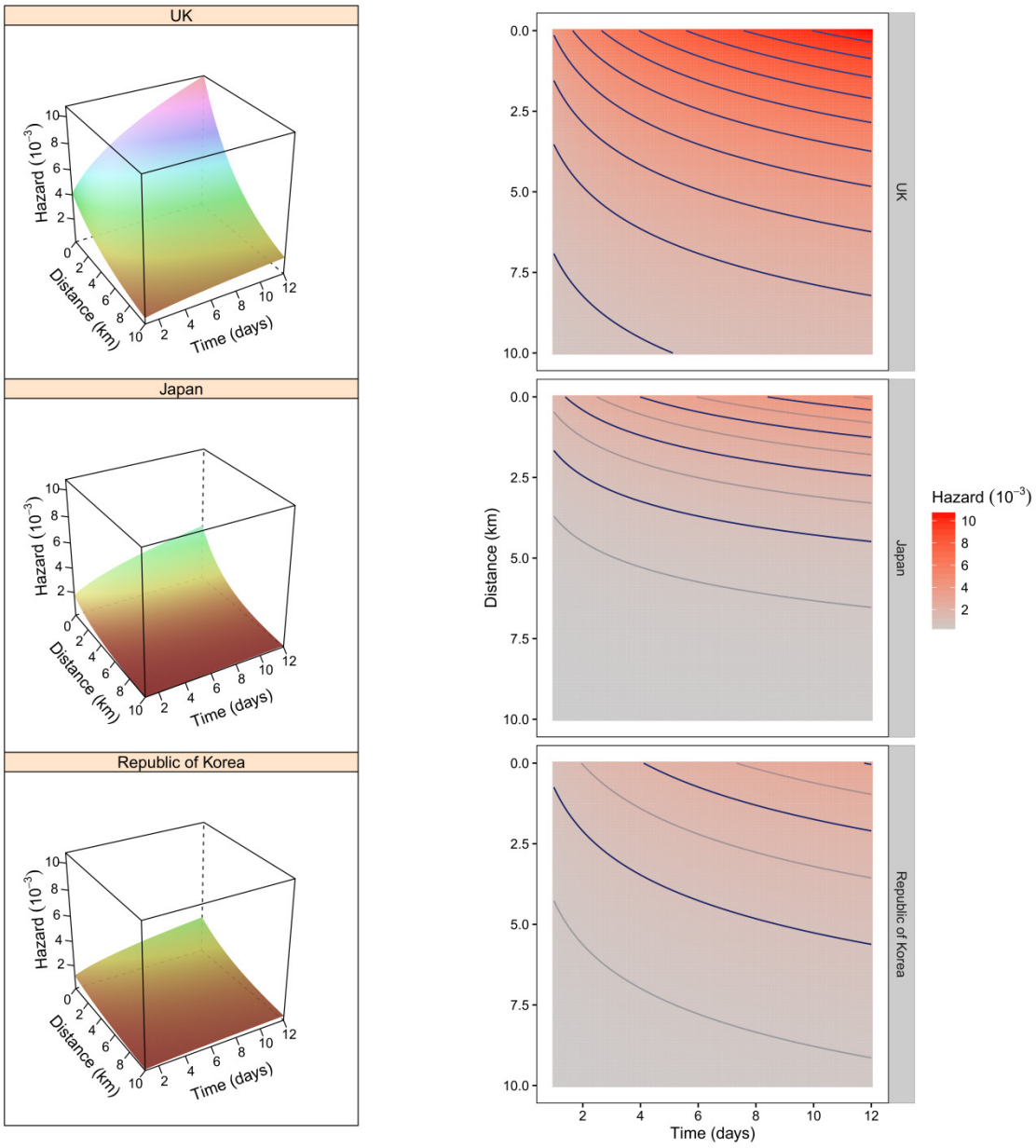

Figure 3-3 Contour plots (top) and perspective plots (bottom) of the predicted daily hazard of local spread of foot-and-mouth disease (FMD) as a function of distance from the potential source premises and the number of days elapsed since the onset of infectiousness for the FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

3.4.3. Adjusted model (adjusted for species and size)

The adjusted Weibull model was fitted using all six explanatory variables (distance, country, herd/flock size of infectious premises, herd/flock size of susceptible premises, source species, and susceptible species) and three interaction terms (distance × source species, susceptible species × country, and herd/flock size of infectious premises × country). The estimated parameters are shown in Table 3-4.

In all of the three outbreaks, the risk factors that were significantly ($p < 0.05$) or marginally significantly ($0.05 \leq p < 0.1$) associated with the hazard of local spread were source species, susceptible species, and herd/flock size on a susceptible premises. For example, if the species of an infectious premises was small ruminants or pigs, the hazard of local spread was 3.23 (95% CI: 0.97 to 10.70) or 4.15 (2.39 to 7.21) times that of cattle (distance: 0 km), respectively. In contrast, the hazard of local spread in a susceptible premises having small ruminants or pigs was 0.09 - 0.47 (95% CI: 0.01 to 1.01) or 0.10 – 0.66 (0.04 to 1.02) times that of cattle, respectively. A 10-fold increase in the herd/flock size on a susceptible premises increased the hazard by 2.81 (95% CI: 2.37 to 3.34) times. Larger herd/flock size on a source premises was associated with a decrease in the hazard (HR: 0.57, 95% CI: 0.35 to 0.94) in Cumbria (UK, 2001), while no significant association was found in Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010).

Using the adjusted model, the adjusted hazard of local spread was predicted for a premises with a median herd/flock size observed in the study area, on the first day of infectiousness for the outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010) (Figure 3-4). The predicted hazard of FMD local spread from small ruminants to cattle in Cumbria (UK, 2001) was 5.80 (95% CI: 1.82 to 18.50) per 1,000 premises at risk at a distance of 1 km on the first day of infectiousness, which was the highest of all pairs of premises in all outbreak area. For Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010), the pairs of premises with the highest hazard were from pigs to pigs and from pigs to cattle, with a hazard of 1.05 (95% CI: 0.52 to 2.12) and 1.23 (0.68 to 2.24) per 1,000 premises at risk at a distance of 1 km on the first day of infectiousness, respectively.

Table 3-4 Estimated hazard ratio (and 95% confidence interval) for local spread infection of foot-and-mouth disease (FMD) for the adjusted Weibull regression model for FMD outbreaks in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010).

Variable	UK	Japan	Republic of Korea
Distance [1]			
-source: cattle	0.84 (0.80, 0.88)	"	"
-source: small ruminants	0.80 (0.64, 1.00)	"	"
-source: pigs	0.72 (0.64, 0.81)	"	"
Source species:			
- Cattle	1.00 (reference)	"	"
- Small ruminants	3.23 (0.97, 10.70)	"	"
- Pigs	4.15 (2.39, 7.21)	"	"
Susceptible species:			
- Cattle	1.00 (reference)	1.00 (reference)	1.00 (reference)
- Small ruminants	0.47 (0.22, 1.01)	NA	0.09 (0.01, 0.65)
- Pigs	NA	0.66 (0.43, 1.02)	0.10 (0.04, 0.23)
Source herd/flock size [2]	0.57 (0.35, 0.94)	0.91 (0.73, 1.15)	1.17 (0.98, 1.41)
Susceptible herd/flock size	2.81 (2.37, 3.34)	"	"
Intercept	1.00 (reference)	0.15 (0.03, 0.68)	0.21 (0.05, 0.90)

Weibull shape parameter s = 1.40 and the baseline hazard λ_0 = 9.07 × 10-4 (95% CI: 1.98, 41.63 × 10-4)
1 Euclidian distance between the centroids of a source and a susceptible premises (km).
2 Measured as log 10 of the number of total animals.
" Same as the estimates for the UK

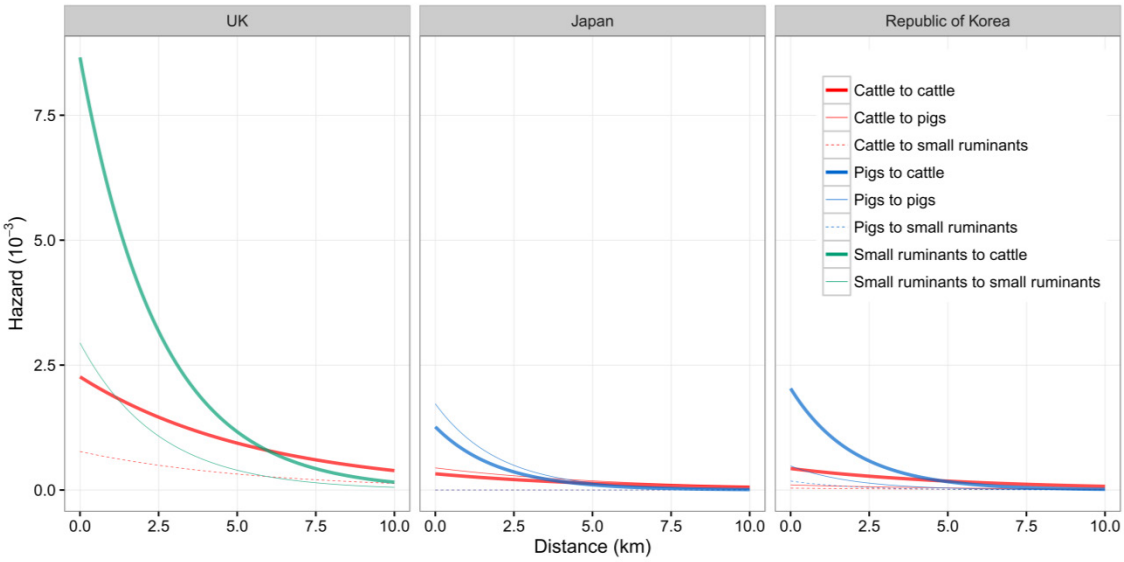

Figure 3-4 Predicted adjusted daily hazard of local spread of foot-and-mouth disease (FMD) on the first day of infectiousness for the FMD outbreak in Cumbria (UK, 2001), Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010).

The herd/flock size was adjusted to the regional median: n = 577 (UK, cattle), 130 (UK, small ruminant), 20 (Japan, cattle), 825 (Japan, pigs), 8 (Republic of Korea, cattle), 650 (Republic of Korea, pigs), and 7 (Republic of Korea, small ruminant).

3.5. Discussion

In this study, FMD transmission kernel, or hazard of local spread, was estimated by fitting presumed time to transmission of infection by potential risk factors (i.e., country, distance, herd/flock size, and species), using Weibull survival models. To date, this is the first study that comparatively described the pattern of local spread from different FMD outbreaks using the same method. Because the mechanism of FMD transmission by local spread is mostly unclear, our approach was to hypothesise occurrence of local spread, considering temporal and spatial plausibility and randomness, with a weight on spatial proximity. Our algorithm for determining the virus transmission pathways may generate errors to an uncertain extent, and was proposed as an alternative to the previous method by which the earliest time of exposure and the shortest distance were used as the deterministic factors (Sanson et al., 2006b). The range of our estimates from the crude Weibull model were comparable to the estimates from previous analyses for Cumbria (UK, 2001) and Miyazaki (Japan, 2010) (Sanson et al., 2006a, Hayama et al., 2013), while this was the first analysis for Andong (Republic of Korea, 2010). Integration of molecular data (Cottam et al., 2008a), or a Bayesian method to use the integrated past and current information (Jewell et al., 2009) could improve determination of transmission pathways, and refine the hazard estimates.

The results presented here illustrated remarkable variations in the patterns of local spread, both within and between FMD outbreaks. Two points should be noted, for making implications for use of FMD simulation models. First, the estimated hazard of local spread is exclusive to the initial three weeks of the outbreak, and within the spatial boundaries defined by the authors. The pattern of local spread in the initial phase of an outbreak is likely to be mixture of artificial and environmental mechanisms. The former may include movements by milk tankers, shared farm personnel, feed trucks, shared farm equipment, and commuting farm personnel (Gibbens et al., 2001, Muroga et al., 2013). These mechanisms of spread would be dynamic, and are likely to be suppressed through the course of an epidemic by implementations of localised movement bans (Schley et al., 2009) or by an increase in the overall efficiency of control measures, as shown for the Miyazaki (Japan, 2010) outbreak (Wada et al., 2016). The latter mechanisms may include airborne spread, mechanical contacts via insects, rodents and birds for animals kept outside or in an open barn. Although it may be influenced by local weather conditions (Donaldson, 1972) or geographical features, the pattern of local spread by the environmental factors is likely to be more static and persist throughout the epidemic.

Prevention of such mechanisms of spread is challenging, and may require installation of physical barriers (e.g., trees or private houses) from the surrounding environment (Muroga et al., 2013), or implementation of expensive and contentious policies, such as emergency vaccination and pre-emptive culling. Second, due to absence of contact data, we relaxed the definition of local spread to encompass any mechanisms of disease transmission (e.g., aerosol dispersion of virus, localised community activities, explicit movements, etc.) occurring within 10 km of a source premises. This should be adjusted for use of some simulation models, which features disease spread by both local spread and explicit between-farm contacts to avoid double counting.

The local spread boundary used in this study is different from the narrower width, i.e., 3 km, commonly used to describe local spread for the 2001 epidemic in the UK (Taylor et al., 2004, Gibbens et al., 2001). This is because previous analyses suggested occurrence of FMD local spread beyond 3 km. During the Cumbria (UK, 2001) outbreak, up to 52% of IPs were shown to have no possible source within 3 km (Taylor et al., 2004), suggesting either local spread or long-distance contact consistently occurring beyond 3 km. The molecular analysis of the outbreak in Durham (UK, 2001) suggested the mean distance of disease transmission, presumably by local spread, was 4.8 km (Cottam et al., 2008a). In addition, since distance was measured between premises centroids, larger premises would generally have longer distance to any other premises, than smaller premises would. Hence, we chose a wider width, 10 km to encompass all mechanisms of disease transmission, which was constrained by the processing capacity of the computers used. The choice of wider bandwidth should not directly affect the intensity of local spread, as the risk of local spread was weighted by shorter distance, and standardised by the density of IPs within the boundary.

Due to absence of precise records regarding the date of infection for individual IPs, or limitation in accessibility to the data, there is a great deal of uncertainty in the dates of infection and the onset of infectiousness. In this study, they were hypothesised by assuming a constant for intervals between the onset of infectiousness and detection (i.e., sum of a subclinical infectious period and detection/reporting delay), and an empirical distribution for incubation period, which were generic to all outbreaks. However, it was evident from a previous analysis of experimental studies that the durations for latent, subclinical, or incubation periods were influenced by multiple factors including virus strain, species, transmission mechanisms and diagnosis method (Mardones et al., 2010).

For example, the pathogenicity of FMD is generally known to be mild for small ruminants (Alexandersen et al., 2003), for which the duration of an incubation period, subclinically-infectious period, and detection delay were typically longer than other species (Mardones et al., 2010, Sellers and Parker, 1969, Gibbens et al., 2001). This means, we could have underestimated the infectious period for small ruminants, which might have contributed to underestimation of the risk of local spread for small ruminants in comparison with other species. Under field conditions, they are further influenced by complex factors, such as enterprise types, stage of the epidemic, region, country, and control strategies. Although it requires further data and may not be possible, adjustment of these factors may refine the effects of species on FMD local spread.

In all of the three outbreaks, a steep increase in the incidence of disease was observed during the initial three weeks after detection of the index case, overwhelming the resource of the disease control authority (Park et al., 2013, Muroga et al., 2012, Gibbens et al., 2001). After accounting for premises density, the estimated crude hazard of local spread for Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010) was significantly lower, less than half the hazard of Cumbria (UK, 2001). This implies that even with a relatively low hazard of local spread, the FMD spread could become overwhelming if it were introduced in an area with high density of livestock premises (as in Japan and Republic of Korea). While the higher crude hazard of local spread in Cumbria (UK, 2001) may be due to unexplained factors such as virus strains, efficiency of control measures, weather conditions, farming practices, or fragmentation of land holdings, it is also possible that confounding risk factors, i.e., dominance of large-sized cattle herds in Cumbria (UK, 2001), also played a role in enhancing the crude hazard of local spread. It emphasises the need for caution when extrapolating the hazard of local spread from foreign outbreaks for use of simulation in a different population, and interpreting the model outputs. More work is required to examine potential variation in the pattern of local spread by various risk factors.

Our results showed that the estimated hazard of local spread increased as the progress of infection during the observed period (10^{th} to 90^{th} percentile: 2 – 8 days). This is biologically plausible, considering that infectiousness at the individual-animal and the herd/flock level would increase as the amount of excreted virus increases. Suppression in virus shedding by the immune response induced in host animals was not apparent by the Weibull model. This is partially because a Weibull survival model could only take into

account either constant or monotonically decreasing or increasing hazard. In terms of the increase in hazard, our result was different from the previous estimates (Sanson et al., 2006b), which showed suppression of hazard after 4 days. Their estimates, particularly those of shorter time, could be overestimated, because infectious premises that became infectious at a later time were given priority in selection of sources.

We anticipated that the hazard of local spread from a large-scale infectious premises would be greater than a small-scale infectious premises, due to its capacity to reproduce and excrete a larger amount of virus in the air, as suggested for the UK 2001 epidemic (Ferguson et al., 2001). However, our results showed that the herd/flock size on a source premises was associated with a decrease in the hazard for Cumbria (UK, 2001), whereas it was not significantly associated with the hazard in Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010). This could be due to presence of unexplained factors confounding the effect of herd/flock size. For example, it was evidently shown that smaller herd size was generally associated with lower level of disease awareness, management and biosecurity practises (e.g., entrance restriction, clothing, disinfection baths, double fencing, etc.) (Noremark et al., 2010, Ribbens et al., 2008, Noremark et al., 2009, Garforth et al., 2013, Oleggini et al., 2001). This may have contributed in negating or reversing the effects of herd/flock size on the infectiousness of premises. In contrast, larger herd/flock size of susceptible premises was strongly associated with an increase in the hazard of local spread. This is consistent with the findings of other studies for the UK (2001) and Japan (2010) epidemics (Hayama et al., 2012, Keeling et al., 2001, Ferguson et al., 2001). It is plausible that the chance of infection at the herd/flock level increases as more animals inhale air contaminated with aerosol containing FMD virus.

The adjusted hazard of local spread from infectious pigs was significantly greater (HR: 4.15, 95% CI 2.39 to 7.21) than that of infectious cattle in all outbreaks where pigs were present, i.e., Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010). This is consistent with previous findings from experimental studies that pigs were the most potent source of airborne virus, excreting 30 - 60 times more virus than cattle or sheep (Donaldson et al., 2001, Sellers and Parker, 1969). A trend of a greater infectivity of a pig herd than a cattle herd is also reported in several studies of the past epidemics (Hayama et al., 2012, Nishiura and Omori, 2010, Ferguson et al., 2001).

The adjusted hazard of local spread for susceptible small ruminants or pigs was less than cattle (small ruminants: HR 0.47, or pigs: 0.10 – 0.66) in all outbreaks where the species

was present. It is reasonable, considering that a large animal with large tidal volume (cattle) is more efficient in inhaling FMD virus than a small animal (sheep, pigs) when they are exposed at the same concentration of virus in the aerosol, as suggested in the experimental studies (1969). Experimental studies have also shown that pigs were more resistant against aerosol infection than cattle and sheep, requiring 30 - 200 times more doses of virus to establish infection via respiratory routes (Donaldson and Alexandersen, 2001, Alexandersen and Donaldson, 2002). However, our results showed no significant difference in the hazard of local spread between susceptible small ruminants and pigs.

3.6. Conclusion

Both the crude and adjusted hazard of local spread in the first three weeks of the FMD were higher in the outbreak in Cumbria (UK, 2001) than that of Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010). Larger herd/flock size of a susceptible premises, infectious premises with pigs, and susceptible premises with cattle were identified as common herd/flock-specific risk factors for local spread of FMD in the outbreak in Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010). The findings highlight the need for precaution in interpolating the local spread hazard from one outbreak for use of disease modelling for a different susceptible population.

3.7. Acknowledgements

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4. Evaluation of the control strategy for the 2010 foot-and-mouth disease outbreak in Japan using disease simulation

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4.1. Abstract

In 2010, Japan experienced a foot-and-mouth disease (FMD) epidemic where 292 premises were infected over a period of 75 days. The epidemic was controlled by stamping-out and vaccination, applied 5 weeks after the first confirmation of disease within a 10 km radius of identified infected premises (IPs). For better preparedness and decision making in future, the aims of this study were to: (i) identify the role of local spread throughout the epidemic and the contribution of emergency vaccination to epidemic control and (ii) assess the impact of alternative vaccination strategies on key outbreak measures including the total number of IPs and epidemic duration using a disease simulation model. Our results indicate that the overall hazard of local spread remained high throughout the silent spread phase and the first two weeks post detection, with significant reduction occurring only from week 3 onwards. The estimated effectiveness of emergency vaccination, quantified as a reduction in the hazard of infection, was at most 81% and 44% for cattle and pig farms, respectively. The vaccination strategy, as applied in the actual epidemic, reduced the simulated median number of IPs by 22%, epidemic duration by 64% and time to complete culling by 52%, but increased the total number of infected or vaccinated premises subject to culling by 144% compared with no vaccination. Our results indicated that an earlier onset of vaccination (3 weeks after first detection instead of 5 weeks) and a smaller vaccination radius (3 km instead of 10 km) would be more cost-effective for eradication of the epidemic, compared with the actually implemented strategy.

4.2. Introduction

In 2010, Japan experienced its first outbreak of foot-and-mouth disease (FMD) in ten years. During 11 weeks (75 days) of the epidemic, a total of 292 infected premises (IPs) were detected in Miyazaki Prefecture (Kyushu Island, in the southwest of Japan), a region in which around 10% of the total number of livestock premises in Japan are located (Anonymous, 2007, 2008, 2009, 2010, 2011, 2012, 2013). The scale of this epidemic was different from the previous FMD epidemic that occurred in Miyazaki and Hokkaido Prefectures in 2000, which in total involved only four infected premises. The primary control strategy in the 2000 epidemics comprised a combination of depopulation of IPs, imposition of movement restrictions, and active surveillance in high-risk premises (Yamane, 2006, Muroga et al., 2012). In the 2010 epidemic, authorities resorted to a vaccinate-to-die policy at 5 weeks after detection of the index case because of failure of the initial response strategy. Japan's OIE disease status, 'FMD-free where vaccination is not practised,' was suspended until February 2011, seven months after the last vaccinated animal was culled, that is, after the stipulated waiting period of three months, and an additional time lag of four months until the next OIE Scientific Commission meeting ratified the change in status.

The 2010 epidemic of FMD in Miyazaki caused significant economic damage to the local economy as livestock industries are a major source of income, with annual gross income from livestock products contributing 7% to the national income from livestock products (Anonymous, 2014h). Further, the culling of bulls of superior genetic merit was estimated to have a negative impact on the regional beef industry for at least five years (Nishiura and Omori, 2010). The national livestock industry, particularly the beef sector, suffered losses due to trade restrictions on the export of wagyu beef. At the time of the outbreak, the cost incurred to the local economy and the livestock industry was estimated to be USD 2.0 billion (JPY 235 billion) over five years (Anonymous, 2010c).

The epidemiological features of the 2010 epidemic of FMD in Miyazaki has been described in several studies (Muroga et al., 2012, Hayama et al., 2012, Nishiura and Omori, 2010). The epidemic was caused by the serotype O virus, which was closely related to the strain that circulated in East Asian regions, such as Hong Kong SAR and The Republic of Korea in early 2010 (Muroga et al., 2012). To date, there is no published study of molecular analyses identifying the route of the FMD incursion into Japan, as was done for the outbreak in the UK in 2007 (Cottam et al., 2008b). Confirmation of disease

occurred on 20 April 2010, which was thought to be at least 20 days after the onset of the clinical signs in the primary case (Muroga et al., 2012). During the period between first incursion and first recognition of disease (i.e., the silent spread phase), at least 10 premises were estimated to have been infected (Muroga et al., 2012). The daily number of detected IPs was relatively low at the early stage of an epidemic, but rapidly increased from week three onwards. Due to a lack of burial sites and a shortage of veterinarians, the rate at which IPs were depopulated did not match the rate of detection for the first five weeks. This resulted in an accumulation of IPs waiting to be culled. During week 5, as the spread of disease increasingly overwhelmed the resource capacity, two notable actions were taken: (1) declaration of the state of emergency, by which local farmers and the general public were encouraged to refrain from unnecessary movements (18 May 2010) and (2) decision to apply emergency vaccination (22 May 2010), by which animals on all susceptible premises within a 10 km radius of detected IPs (1,066 premises: 10% of susceptible livestock premises in the prefecture) were vaccinated, to be subsequently culled. From week 6 onwards, the number of IPs waiting to be depopulated decreased and the epidemic ended with the final case of FMD detected on 4 July 2010.

A number of concerns regarding preparedness and outbreak decision making were raised during and after the 2010 epidemic of FMD in Miyazaki (Anonymous, 2010a). Firstly, the level of awareness by the authorities and stakeholders was not sufficient to manage an incursion of FMD, while there were repeated FMD outbreaks in neighbouring countries. This is illustrated by the lack of a system to facilitate reporting and early detection of disease. In particular, the number of prefectural veterinarians per livestock premises was one-fifth the national average, although the density of livestock premises in Miyazaki is relatively high. In addition, stringent and routine biosecurity measures were not consistently practised on farms (Anonymous, 2010a). The combination of these factors contributed to delay in the first confirmation of disease since the first suspicion of FMD, and failure in the initial response. The cost of failing to promptly detect FMD could be substantial. It was illustrated by a simulation modelling study in the US, which predicted that every additional hour of delay in the onset of controls resulted in the national agriculture losses of USD 565 million (Carpenter et al., 2011). Secondly, the delay in making the decision to implement emergency vaccination likely played a role in increasing the size of the outbreak (Anonymous, 2010a). This might be due to the difficulty of justifying the use of emergency vaccination, in the absence of appropriate decision

support tools and the absence of a vaccination plan with great uncertainty about the efficacy and benefit of emergency vaccination.

There have been two published studies using disease models to evaluate the 2010 FMD epidemic in Japan. Nishiura and Omori (Nishiura and Omori, 2010) examined the temporal pattern of the outbreak and found a decline in the effective reproduction number (R_0) below unity in late May. Hayama *et al.* (2013) developed a microsimulation model incorporating the explicit spatial component, and assessed the effects of alternative control measures. Although the use of emergency vaccination was preferred to stamping-out alone, based on the model prediction, the estimated effect of vaccination might be overestimated due to the following reasons. Firstly, their assumption of 100% effectiveness of vaccination may be optimistic. Secondly, the model did not consider a possible suppression of disease transmission due to reduced human contacts in the later phase, because the pattern of disease spread (transmission kernel) was assumed to be constant.

For FMD, short-distance disease spread without any identified movements ('local spread') has often been reported as an important mechanism of transmission in FMD (Sanson, 1994, Donaldson et al., 2001, Muroga et al., 2013, Gibbens et al., 2001, Sanson et al., 2006a). During the 2010 epidemic of FMD in Miyazaki, human activities as well as environmental factors were found to be a key risk factor for such mechanism of spread (Muroga et al., 2013). In the 2001 epidemic of FMD in the UK, it was shown that local spread risk changed markedly throughout the course of the epidemic (Wilesmith et al., 2003).

In this study, our first aim was to identify the contribution of suppression in local spread and emergency vaccination to the containment of disease for the 2010 Japan epidemic of FMD, considering potential variation in the pattern of local spread over time. A simulation model for the 2010 epidemic of FMD in Japan was developed using InterSpread Plus (Stevenson et al., 2012), a spatially explicit stochastic simulation model platform. Our second aim was to assess the effect of alternative epidemic control measures (i.e., an earlier start of vaccination, use of a smaller vaccination radius, and no vaccination) on predicted numbers of IPs and predicted epidemic duration. Our intention here was to provide a more quantitative basis for decision making concerning the way FMD outbreaks in Miyazaki might be better handled in future.

4.3. Materials and methods

4.3.1. Data

The dataset for the FMD epidemic in Miyazaki (2010) was obtained from Japan Agricultural Cooperatives (JA) in Koyu and Osuzu. The data were comprised of 880 livestock units (premises) with FMD susceptible species, located in five adjacent towns (Tsuno, Kawaminami, Shintomi, Takanabe, and Kijo) in the eastern part of the Koyu District, Miyazaki Prefecture (Figure 4-1). The dataset contained the geographical location of the centroid of premises and the number of animals, by species (cattle, pigs, or small ruminants), present on each premises. In addition, the dates of detection and depopulation were available for FMD cases. Information regarding the presumed source of infection was absent. The dataset included 272 IPs (93% of the total number of IPs in the 2010 outbreak). The other 20 IPs were located outside the investigated area and not included in the analyses, because the spatial livestock population data were absent. Based on these data, a time-to-event (survival) dataset was constructed as described in the previous chapter (3.3.2). The resulting survival data listed all pairs of infectious and susceptible premises located within 10 km of each other, containing the following 8 variables:

(i) the start date of infectiousness of a potential source premises (t_0),
(ii) the end date of infectiousness of the potential source, or the date of infection in the susceptible premises, whichever occurred first (t_1),
(iii) hypothesised occurrence of transmission of disease from the potential source premises to the susceptible premises,
(iv) the Euclidian distance (km) between the centroids of the two premises,
(v) dominant animal species on the infectious premises,
(vi) dominant animal species on the susceptible premises,
(vii) herd size of the infectious premises (presented as log of base 10 of the number of animals present on the premises), and
(viii) herd size of the susceptible premises (presented as log of base 10 of the number of animals present on the premises).

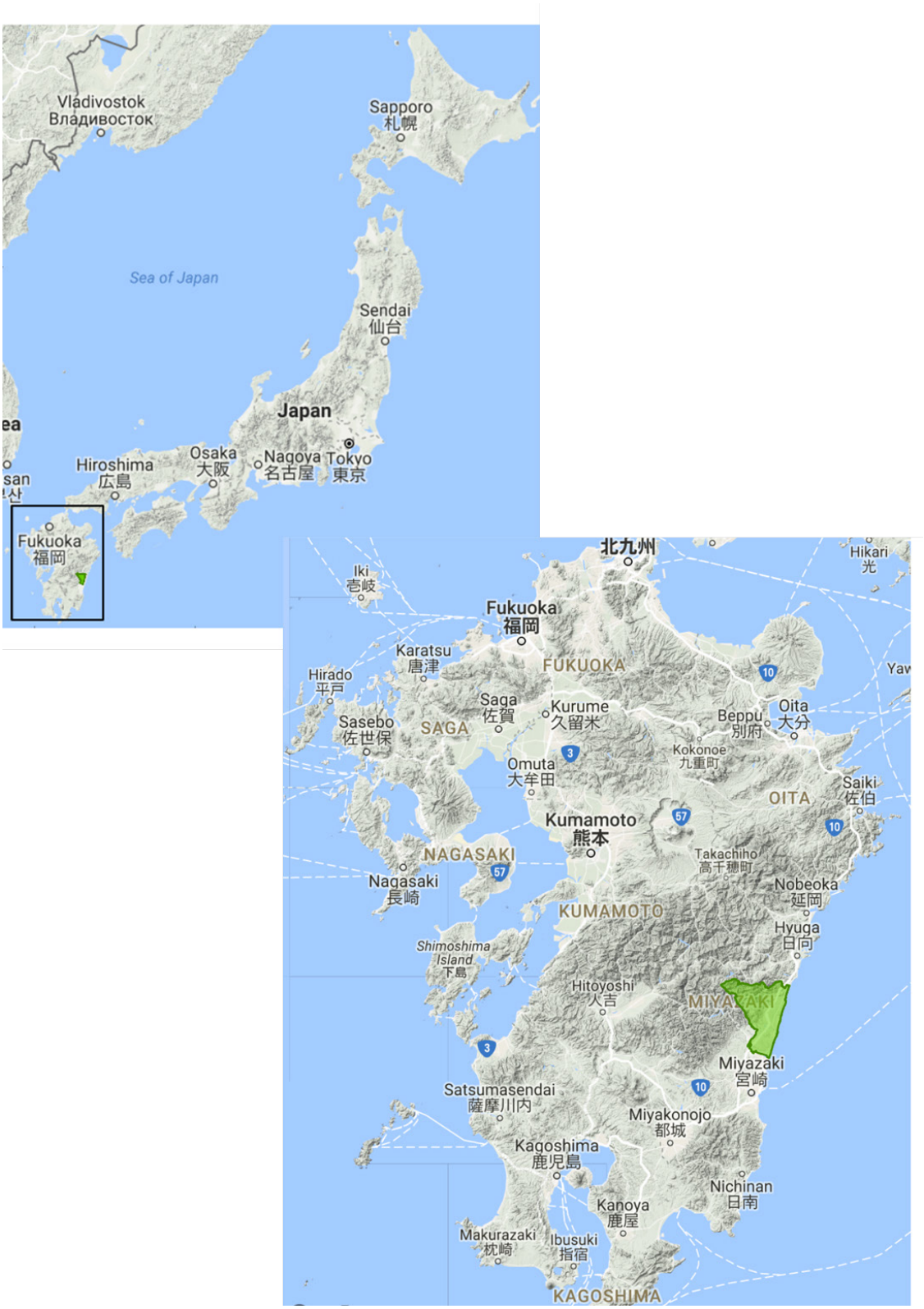

Figure 4-1 A map of Japan [top] and Kyushu Island [bottom], showing the location of the investigated area (in green), where a foot-and-mouth disease (FMD) outbreak occurred in 2010.

4.3.2. Epidemiological phases

Initially, the period between the onset of infectiousness in the primary case (~25 March 2010) and the start of culling of vaccinated animals (7 June 2010) was split into eight phases, based on the calendar time, i.e., the silent spread phase (~25 March – 19 April 2010) and weeks 1 to 7, as shown in Table 4-1. To determine epidemiologically meaningful phases, a crude survival model was fitted using two variables, i.e., calendar-based phases and distance between a potential source and a susceptible premises, as described in the following section. Epidemiological phases were determined by merging adjoining periods if the estimated regression coefficients (β) for the two periods were not significantly ($p < 0.05$) different from each other.

For both calendar and epidemiological phases, the data were structured to allow for a piecewise survival analysis. That is, any pair of infectious and susceptible premises, whose observation period (between t_0 and t_1) extended over two or more phases, was split into multiple phase-wise records. In the restructured data, the first follow-up period ran from the start of infectiousness to the end of the phase, and then the subsequent follow-up period(s) ran from the start of the next phase to the end of the phase or infectiousness.

Table 4-1 The weekly counts and daily rates of detected and depopulated premises during the course of a foot-and-mouth disease (FMD) epidemic in Miyazaki, Japan in 2010.

		Detected premises		Depopulated premises		Cumulative unprocessed IPs
Week	Start date	Count (premises)	Rate (premises/ day)	Count (premises)	Rate (premises/ day)	Count (premises)
1	20 April 2010	8	1.1	4	0.6	4
2	27 April 2010	9	1.3	6	0.9	7
3	4 May 2010	50	7.1	10	1.4	47
4	11 May 2010	59	8.4	29	4.1	77
5	18 May 2010	74	10.6	40	5.7	111
6	25 May 2010	47	6.7	47	6.7	111
7	1 June 2010	29	4.1	75	10.7	65
8	8 June 2010	13	1.9	50	7.1	28
9	15 June 2010	2	0.3	23	3.3	7
10	22 June 2010	0	0.0	7	1.0	0
11	29 June 2010	1	0.1	1	0.1	0

Data source (Anonymous, 2010b)

4.3.3. Parametric survival modelling

The probability of occurrence of disease transmission on day t after the onset of infectiousness, given that the susceptible premises had been uninfected until day t, was represented using a hazard function $h(t)$. A Weibull regression model was fitted as:

$$h(t) = \lambda_0 s t^{(s-1)} \exp\left(\sum \beta_i x_i\right) \quad (1)$$

where s is a shape parameter, λ_0 is a scale parameter (i.e., the hazard when all the explanatory variables are 0), and β_i is the estimated regression coefficient for explanatory variable x_i. Candidate variables were:

(i) distance between a potential source and a susceptible premises,
(ii) species on a potential source premises,
(iii) species on a susceptible premises,
(iv) herd size on a potential source premises,
(v) herd size on a susceptible premises, and
(vi) epidemiological phase.

Any candidate variable was included in the crude model if significance of the log likelihood ratio test statistic were less than 0.10. Based on the fitted multivariable model, inclusion or exclusion of any biologically plausible interaction term was determined based on a likelihood ratio test, with a significance level of $p < 0.05$. The final crude model was evaluated by whether removal of a single term would make a significant deterioration in fit based on a likelihood ratio test by a level of $p < 0.05$.

4.3.4. Parameters of the simulation model

InterSpread Plus version 6.01.6 (EpiSoft NZ) was used as a platform for building simulation models for the FMD epidemic in Japan in 2010.

As parameters for disease transmission, daily probabilities of local spread were predicted using the fitted survival model. The probabilities were estimated for up to 10 km from an infectious premises, counting from the onset of infectiousness, which was assumed to be one day prior to the onset of clinical signs (see previous chapter 3 for justification). Time from infection to the onset of clinical signs was represented by the parameters as an empirical cumulative density distribution, based on the epidemic data, assuming there was no delay in detection after appearance of clinical signs. Variation in local spread patterns

by phase, species and herd size were considered. We then examined whether predicted epidemics temporally and spatially matched that which actually occurred. If necessary, additional parameters for disease transmission by long-distance movements (>10 km) were considered.

The effectiveness of emergency vaccination was determined based on the fitted survival model, assuming a decrease in the hazard in the post-vaccination phase from that of the previous phase was attributable to emergency vaccination. Vaccination was assumed to become effective at the earliest on the 4th day post vaccination and reach maximum effectiveness on the 7th days as reported from experimental studies (Doel et al., 1994, Salt et al., 1998, Barnett et al., 2004). Infectivity of vaccinated infected animals was assumed to be suppressed completely.

Parameters for control measures including depopulation of detected IPs, emergency vaccination, and surveillance were developed to follow what actually occurred during the epidemic. Depopulation was assumed to be conducted on detection of IPs but constrained by the resource capacity as follows: 1 IP per day (week 1 – 3), 5 IPs per day (week 4 – 5), 7 IPs per day (week 6) and 10 IPs per day (week 7 onwards) (Table 4-1). Vaccination was assumed to be applied to animals on apparently uninfected premises within 10 km of detected premises on or after the 32nd day after first confirmation of disease. The resource constraints for vaccination were set as 200 premises per day and premises were processed from outer to inner radius (Muroga et al., 2012). For surveillance, livestock owners were assumed to monitor their animals daily after initial confirmation, and 100% detection and reporting were assumed once clinical signs appeared.

The outcomes of an epidemic were measured as the number of IPs, number of culled premises, epidemic duration, culling duration and infected area. Epidemic duration was defined as the interval from the date of first detection to the date of detection of the last case. Culling duration was defined as time from the first detection to completion of culling of all IPs and vaccinated animals, based on the last date of depopulation of IPs, and time to complete culling of vaccinated premises. We used the observed rate of culling of vaccinated premises, i.e., 26 premises per day. The criteria to start the activity of subsequent culling of vaccinated animals were assumed to be: (i) at least 17 days had elapsed since the onset of vaccination and (ii) the number of premises waiting to be depopulated was less than 60, as what actually occurred (Anonymous, 2010a). Infected

area was measured as the area enclosed by the convex hull of the centroids of all simulated IPs within the investigated area.

4.3.5. Evaluation of alternative control scenarios

The outcomes of four alternative control scenarios were compared against that of the actual control strategy, i.e., 10 km ring vaccination five weeks after first confirmation of disease ('5w10k'), which took place during the epidemic. In the alternative scenarios, emergency vaccination was: (i) applied within a 10 km radius, 3 weeks (21 days) instead of 5 weeks (32 days: actual timing of vaccination) after first confirmation of disease ('3w10k'), (ii) applied within 3 km ring radius (instead of 10 km) 5 weeks after first confirmation of disease ('5w3k'), (iii) applied within 3 km ring radius 3 weeks after first confirmation of disease ('3w3k'), and (iv) never applied throughout the course of the epidemic.

4.4. Results

4.4.1. Epidemiological phases

The hazard ratios for local spread and 95% confidence intervals for each of the calendar-based phases based on the initial survival model are shown in Figure 4-2. Four epidemiological phases were distinguished by a statistically significant difference in the estimated hazard: phase I (the silent spread phase, plus weeks 1 and 2), phase II (week 3), phase III (weeks 4 and 5), and phase IV (weeks 6 and 7). During the four epidemiological phases, there were 202,622 observations (phase I: 7%, phase II: 17%, phase III: 42%, and phase IV: 34%) of unique pairs of a susceptible premises and a potential source of local spread. The number of unique infectious premises for phases I, II, III, and IV were 25 (cattle: 13, pigs: 12), 66 (cattle: 36, pigs: 30), 194 (cattle: 133, small ruminants: 1, pigs: 60), and 186 (cattle: 138, small ruminants: 1, pigs: 47), respectively. It should be noted that a premises that was infectious during two or more phases was recorded as multiple, independent observations. The estimated number of local spread transmissions (and all infections in parentheses) for phase I, II, III, and IV were 73 (74), 61 (63), 110 (110), and 27 (27), respectively.

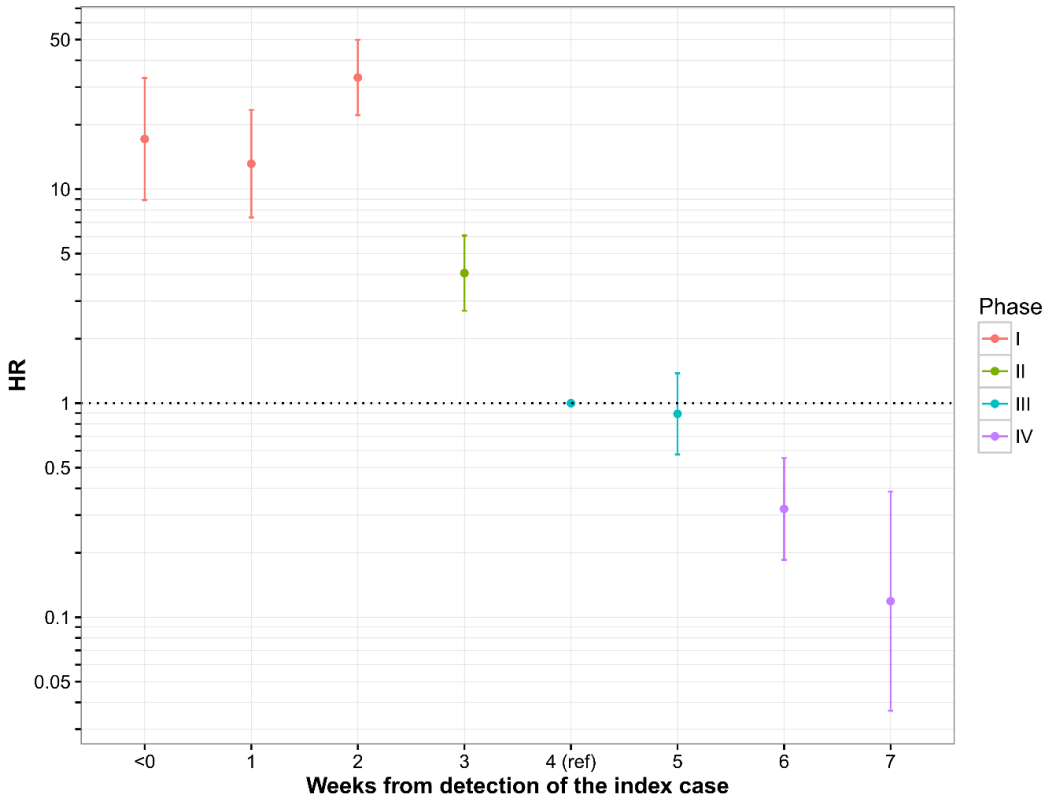

Figure 4-2 Estimated hazard ratio (HR) (points) and 95% confidence intervals (whiskers) of local spread of foot-and-mouth disease (FMD) for seven phases (silent spread phase, and weeks 1, 2, 3, 5, 6, and 7) relative to week 4, i.e., a week prior to application of vaccination (HR = 1: dashed line), for the FMD epidemic in Japan (2010).

4.4.2. Hazard of FMD transmission

A full model was fitted with five explanatory variables (phase, distance, source species, susceptible species, and herd size of susceptible premises) and three interaction terms (phase × distance, phase × susceptible species and distance × source species). The hazard ratios are shown in Table 4-2. Compared with phase III, the adjusted baseline hazard of local spread for a susceptible cattle premises at 0 km distance (intercept) was 19.07 (95% CI: 13.68 to 26.57) and 3.27 (95% CI: 2.26 to 4.74) times greater in phases I and II, respectively. In phase IV, the adjusted hazard for an adjacent susceptible cattle premises decreased to 0.19 (95% CI: 0.12 to 0.32) times that of phase III. Every 1 km increase in distance from an infectious premises was associated with a decrease in hazard by 0.60 to 0.90 (95% CI: 0.56 to 0.98) and 0.49 to 0.73 (95% CI: 0.45 to 0.80) times for cattle and pig sources, respectively. The hazard of local spread to susceptible premises with pigs was 0.38 to 0.52 (95% CI: 0.29 to 0.67) times that of cattle before vaccination (phase I, II and III), whereas it was not significantly different post vaccination (phase IV). The hazard of local spread from an infectious premises with pigs was 2.83 (95% CI: 2.19 to 3.67) times that of cattle. Every 10-fold increase in the herd size of a susceptible premises was associated with a 3.42 increase in hazard (95% CI: 3.10 to 3.77).

Table 4-2 Estimated hazard ratio and 95% condidence intervals (in parenthesis) for the full Weibull regression model for local spread infection for a foot-and-mouth disease (FMD) epidemic in Japan (2010) (n = 202,622).

Parameters	Phase I [1]	Phase II	Phase III	Phase IV
Intercept	19.07	3.27	1.00	0.19
	(13.68, 26.57)	(2.26, 4.74)	(reference)	(0.12, 0.32)
Distance (cattle source) [2]	0.60	0.83	0.90	0.90
	(0.56, 0.64)	(0.78, 0.89)	(0.86, 0.94)	(0.83, 0.98)
Distance (pig source)	0.49	0.68	0.73	0.73
	(0.45, 0.52)	(0.63, 0.72)	(0.69, 0.78)	(0.67, 0.80)
Distance (small ruminant source)	0.32	0.43	0.53	0.49
	(0.00, ∞)	(0.00, ∞)	(0.00, ∞)	(0.00, ∞)
Source species				
- Cattle	1.00	"	"	"
	(reference)			
- Pigs	2.83	"	"	"
	(2.19, 3.67)			
- Small ruminants	0.00	"	"	"
	(0.00, ∞)			
Susceptible species				
- Cattle	1.00	"	"	"
	(reference)			
- Pigs	0.38	0.44	0.52	1.51
	(0.29, 0.51)	(0.32, 0.60)	(0.40, 0.67)	(1.00, 2.28)
- Small ruminants	0.00	0.00	0.82	0.00
	(0.00, ∞)	(0.00, ∞)	(0.30, 2.27)	(0.00, ∞)
Herd size of susceptible premises [3]	3.42	"	"	"
	(3.10, 3.77)			

Weibull shape parameter: 1.22 (95% CI: 1.16 to 1.29), baseline hazard: 2.66 (95% CI: 1.64, 4.33) $\times 10^{-5}$

1 Relative to the first confirmation of disease, phases I (week $\leq$ 2), II (week 3), III (week 4 – 5), and IV (week 6 – 7) (see Table 4-1).

2 Euclidian distance between the centroids of a potential source and a susceptible premises (km).

3 Herd size was measured as $\log_{10}$ of the number of total animals.

" Same as the estimates for phase I.

4.4.3. Simulation model

The epidemiological parameters for the simulation model were determined based on a modified survival model in which the interaction term between distance and source species was removed. This was because multiple, simultaneous local spread patterns were not able to be modelled within the current InterSpread Plus. After removing the interaction term, the estimated coefficients were not greatly different from that of the full model, except for source species; the term for source species was not significant, and thus removed from the modified model. This means, although the estimated hazard of local spread from a premises with pigs was up to 2.83 (95% CI: 2.19 – 3.67) times higher, and more spatially localised than that of cattle (Table 4-2), it was averaged across species in the simulation model. A subset of the local spread parameters used in the model is shown in Figure 4-3. For parsimony, small ruminant farms (n = 30) were classified as cattle, primarily on account of their small numbers, and also their reported similarity in pathogenicity. The estimated epidemiological parameters are shown in Table 4-3.

The degree of agreement between the prediction of the reference model and what was actually observed was evaluated in terms of temporal, spatial and demographical patterns of IPs (Figure 4-4, Figure 4-5 and Figure 4-6). Figure 4-4 shows that the simulated median cumulative epidemic curve was similar to the actual curve, which fell within the 5th and 95th percentile range, except for small overprediction in the first 1.5 weeks. The distributions of the herd size of IPs for simulated epidemics were similar to that of the actual epidemics, with a second peak at 500-1000 animals, whereas that of the total population had only one major peak at 10-50 animals (Figure 4-5). In addition, the percentage of premises with pigs in simulated IPs (median: 28.1%, 5th and 95th percentiles: 24.3 and 34.1%) was higher that of the total population (12.5%), which was similar to that of the actual epidemics (29.9%) (Figure 4-5). The median density of simulated IPs by phase was similar to what was actually observed, in terms of the intensity and the location of the spread (Figure 4-6). Based on these results, our assessment was that the reference model matched reasonably well with what was observed in the actual epidemic, and no post-hoc adjustment in the reference model was made.

Table 4-3 Estimated epidemiological parameters for an InterSpread Plus simulation model for the foot-and-mouth disease (FMD) epidemic in Miyazaki, Japan, in 2010.

	Phase I [1]	Phase II	Phase III & IV
Local spread	See Figure 4-3	"	"
Susceptibility by species			
- Cattle (reference)	1.00	"	"
- Pigs	0.38	0.44	0.51
Susceptibility by herd size [2]	$32.5^{log_{10}(n)}$	"	"
Incubation period (days)	0, 10, 20, 30, 40, 50 60, 70, 80, 90 and 100th percentiles: 2, 5, 5, 6, 7, 8, 8, 9, 10, 11 and 22		
Vaccination effectiveness			
- Cattle (reference)	NA	"	82%
- Pigs	NA	"	47%

1 Relative to the first confirmation of disease, phases I (week < 2), II (week 3), III (week 4 – 5), and IV (week 6 – 7) (see Table 4-1).

2 Risk due to herd size was calculated for all individual premises as $\exp(\beta \times log_{10}(n))$, where β = 3.48 and n is the number of animals on a premises.

" Same as the estimates for phase I

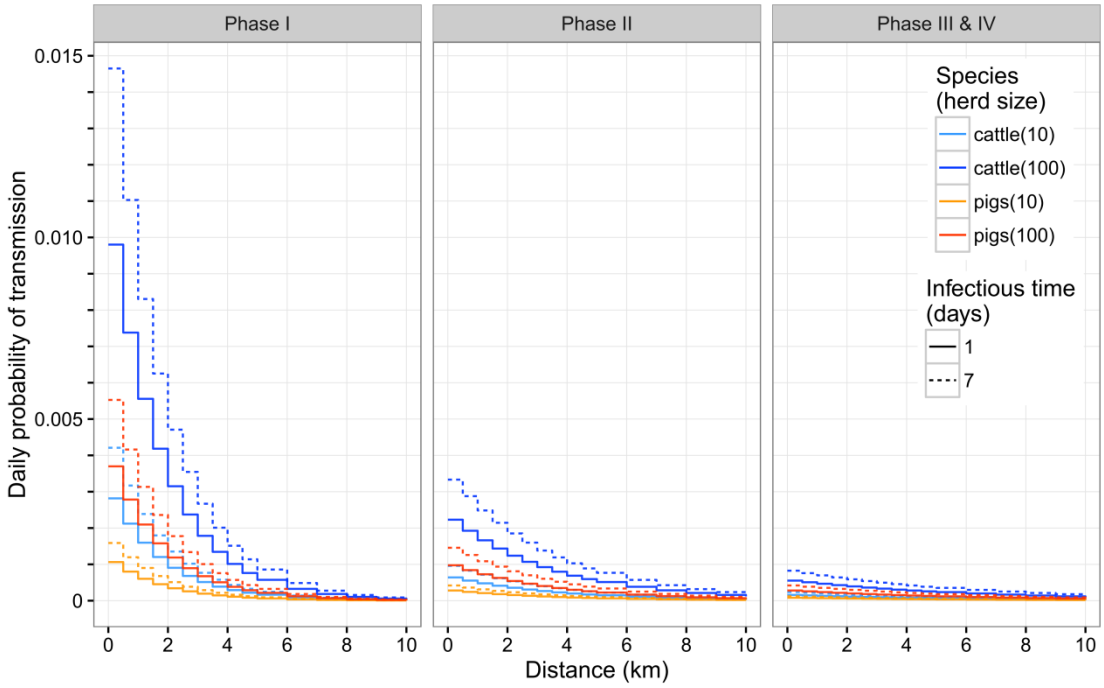

Figure 4-3 Probabilities of local spread of foot-and-mouth disease (FMD) by phase (see section 4.4.1) used in the simulation models for the FMD epidemic in Japan (2010). Four types of susceptible premises (species: cattle or pigs and herd size: n = 10 or 100) on day 1 (straight line) and 7 (dotted line) of infectiousness, are presented.

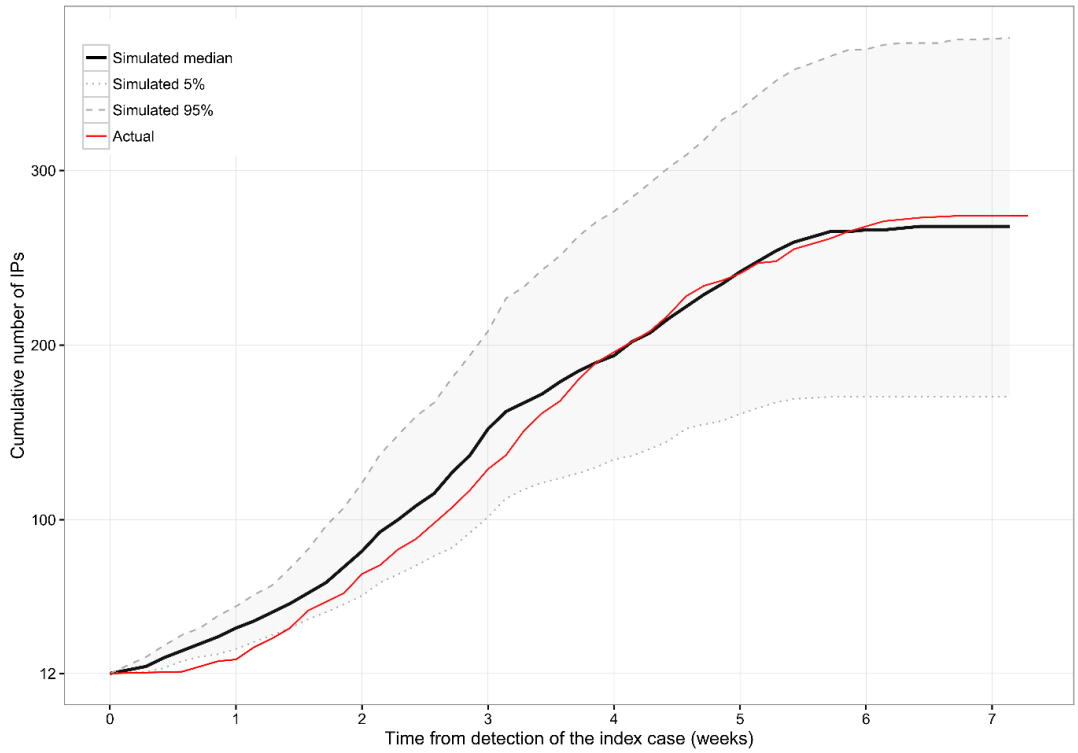

Figure 4-4 Cumulative number of infected premises (IPs) for the actual and simulated epidemics (median and the 5th and 95th percentiles of 100 iterations) for the foot-and-mouth disease (FMD) epidemic in Japan (2010).

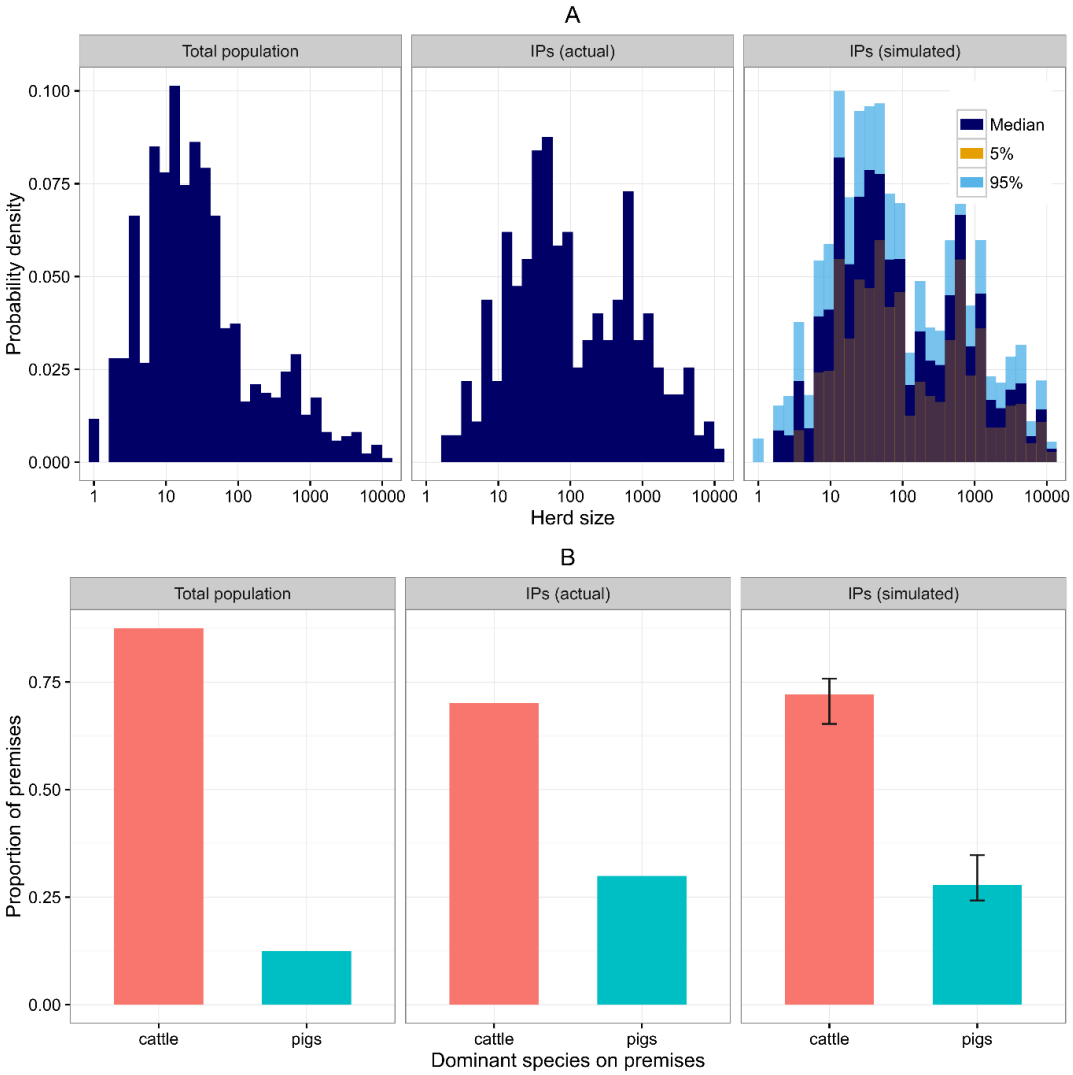

Figure 4-5 Distribution of herd size [A] and proportion of premises by dominant species on premises [B] for the total population, and actual and simulated infected premises (IPs) (median, 5th and 95th percentiles of 100 iterations) for the foot-and-mouth disease (FMD) epidemic in Japan (2010).

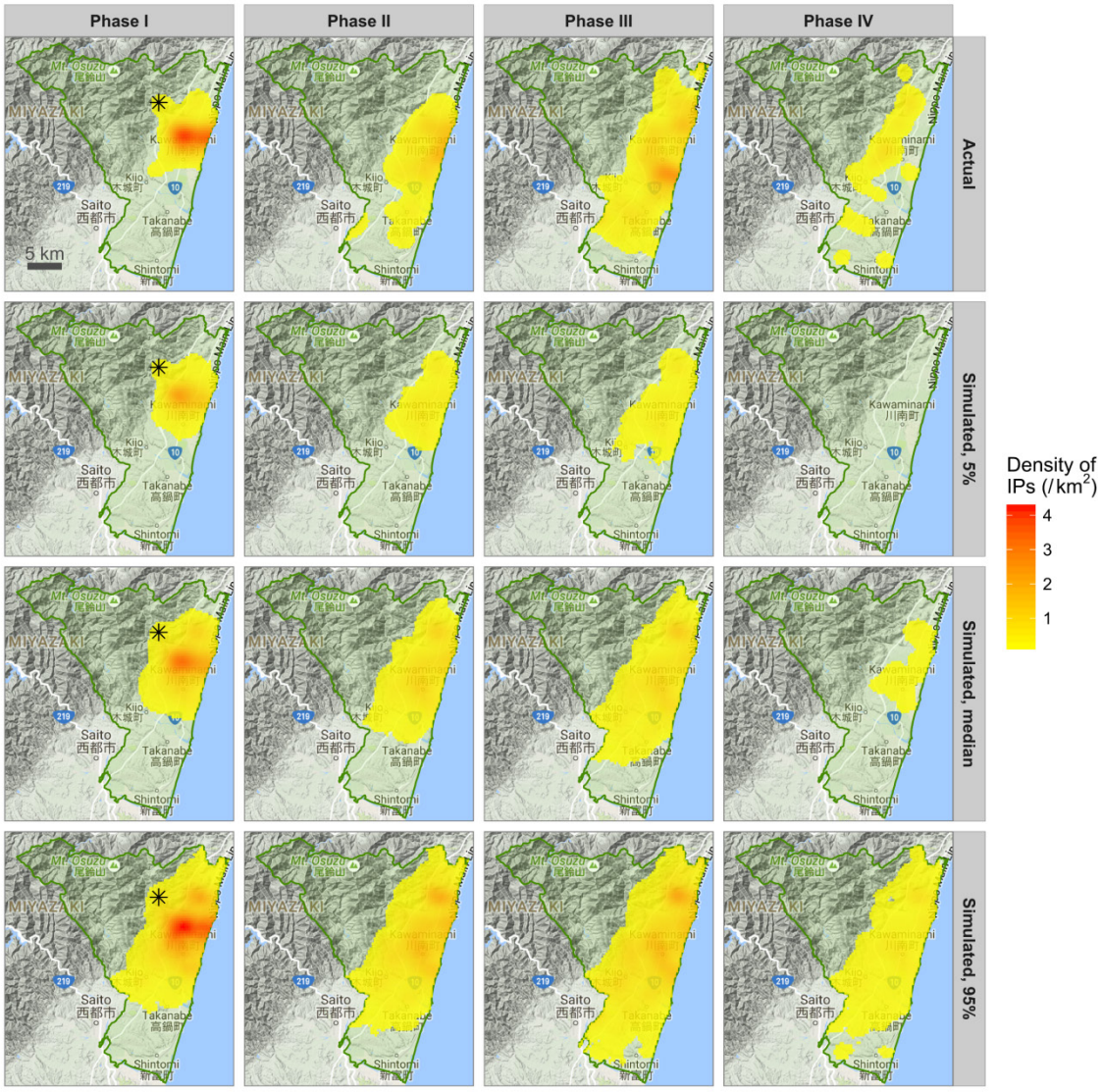

Figure 4-6 Kernel density (bandwidth = 1.00 km) of new cases by phase (see 4.4.1) for the actual and simulated epidemics (median, 5th and 95th percentiles of 100 iterations) for the foot-and-mouth disease (FMD) epidemic in Japan (2010). The asterisk (*) shows the primary case.

4.4.4. Evaluation of alternative control scenarios

The ratios of the predicted epidemic outcomes of the five control scenarios to what was observed in the actual epidemic are shown in Figure 4-7. Vaccination with a smaller radius with the same onset ('5w3k') reduced the predicted number of culled premises and culling duration to a median proportion of 0.87 (5th to 95th percentiles: 0.78 to 0.94) and 0.93 (0.89 to 1.00), respectively. Earlier start vaccination with the same radius ('3w10k') reduced the predicted number of IPs, number of culled premises, epidemic duration, culling duration and infected area to a median proportion of 0.74 (5th to 95th percentiles: 0.49 to 1.00), 0.99 (0.87 to 1.00), 0.84 (0.74 to 0.97), 0.89 (0.83 to 0.96) and 0.81 (0.60 to 0.99), respectively. Earlier vaccination with a smaller vaccination radius ('3w3k') reduced the predicted number of IPs, number of culled premises, and culling duration to a median proportion of 0.72 (5th to 95th percentiles: 0.49 to 0.97), 0.74 (0.64 and 0.81) and 0.80 (0.72 and 0.88), respectively. Stamping-out alone ('novac') reduced the predicted number of culled premises to a median proportion of 0.41 (5th to 95th percentiles: 0.23 to 0.59), but increased the predicted epidemic duration to a median proportion of 2.79 (1.09 to 2.95).

Figure 4-8 shows the simulated range (median, 5th and 95th percentiles) of the density of IPs that were infected 3 weeks after first confirmation of disease for the 5 control scenarios. The density of IPs with a small radius vaccination ('5w3k') was similar to that of the actual strategy ('5w10k'). The infected area and the density of IPs with an early start vaccination ('3w10k' and '3w3k') was smaller than that of later start vaccination. Without vaccination, the infected area extended southwest of the study area by the median and the 95th percentiles, indicating a potential spread of disease to an adjacent area.

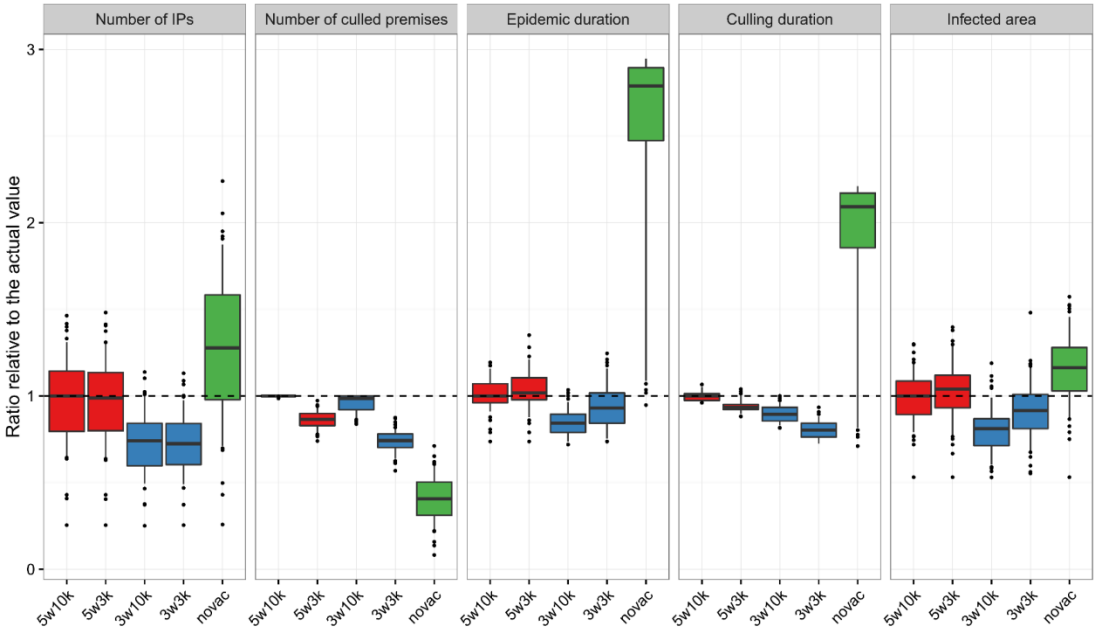

Figure 4-7 Box and whisker plots showing the ratios of the simulated outcomes of an epidemic for the number of infected premises (IPs, reference: 280 IPs), the number of culled (infected or vaccinated) premises (880 premises), epidemic duration (57 days), culling duration (76 days) and the size of the infected area (187 km^2) to the actual values (in parenthesis) for the five control strategies (5w10k, 5w3k, 3w10k, 3w3k and novac: 10 km vaccination in week 5, 3 km vaccination in week 5, 10 km vaccination in week 3, 3 km vaccination in week 3 and no vaccination) for the foot-and-mouth disease (FMD) epidemic in Japan (2010). The box, whisker, and dot represent the interquartile range (IQR), 5th and 95th percentile, and outliers, respectively.

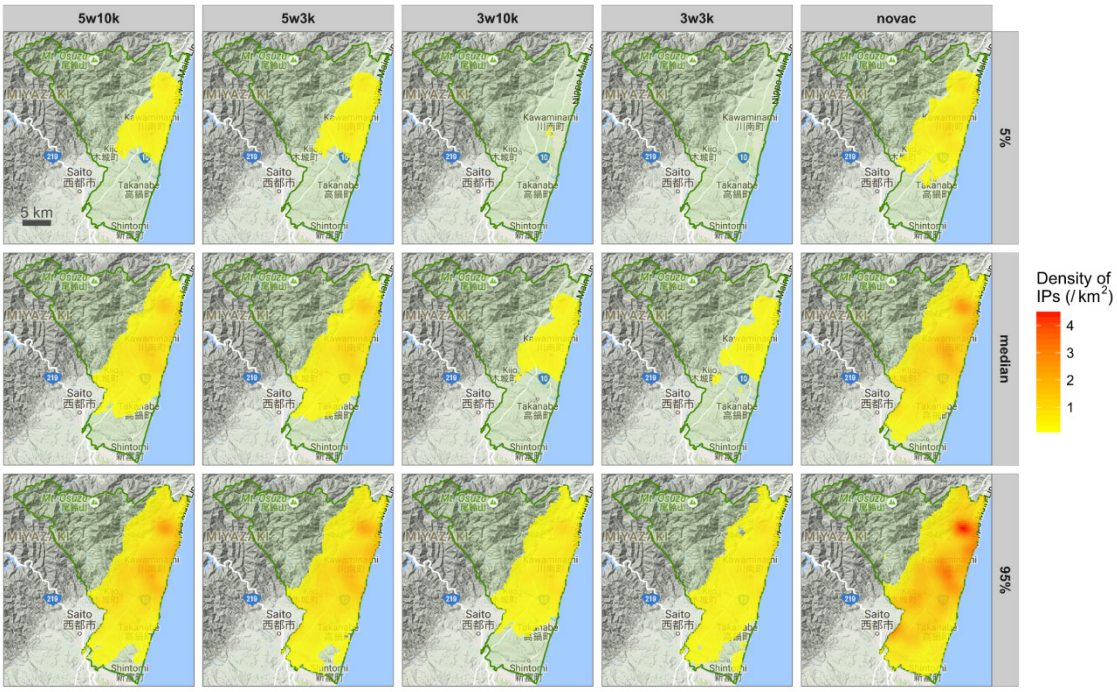

Figure 4-8 Kernel density (bandwidth = 1.00 km) of simulated cases (median, 5th and 95th percentiles of 100 iterations), infected after 21 days onwards since the first confirmation of disease, controlled by the actual (5w10k: 10 km vaccination in week 5) and four alternative strategies (5w3k: 3 km vaccination in week 5, 3w10k: 10 km vaccination in week 3, 3w3k: 3 km vaccination in week 3, novac: no vaccination) for the foot-and-mouth disease (FMD) epidemic in Japan (2010).

4.5. Discussion

In this study, we developed a disease simulation model of the 2010 outbreak of FMD in Miyazaki, Japan, using the disease simulation platform, InterSpread Plus (Stevenson et al., 2012). Alternative control scenarios, where vaccination was targeted to a smaller population (3 km vs 10 km) and/or applied earlier (week 3 vs week 5 post first confirmation), or not applied, were compared with the control scenario that was actually applied (10 km radius vaccination commencing in week 5). Our results showed that all four alternative vaccination strategies reduced the median predicted number of IPs (ratio range: 0.56 to 0.78), epidemic duration (0.30 to 0.37), culling duration (0.38 to 0.48) and infected area (0.70 to 0.90) relative to no vaccination, while the predicted median number of culled premises increased to 1.80 to 2.44 (Figure 4-7). Moreover, our findings indicated that without vaccination, infection was predicted to be more dispersed within the affected area and potentially spread to areas outside the investigated area (Figure 4-8). These results support the use of emergency vaccination as a means to assure containment of disease within an initial infection focus, although additional use of logistical resources could be substantial. It was suggested that earlier start of vaccination (week 3 instead of week 5) would have contributed to reducing the further spread of infection, whereas a smaller vaccination radius (3 km instead of 10 km) would have contributed to a saving in the number of animals to cull and compensate for, and potentially shortening time to recover the OIEs disease free status. In conclusions, earlier vaccination with a smaller vaccination ring ('3w3k') provided the most economically efficient approach of all the alternative vaccination scenarios tested, based on our simulation model results. It should be noted, however, that the risk of disease spreading to the outside of immune belt would be greater with a smaller vaccination radius because of presence of undetected IPs and disease transmission occurring outside the immune belt, as represented in the trend of a larger infected area (Figure 4-7). Moreover, decision making would be more challenging at an earlier timing, when there are less field data to base decisions upon. It is recommended that more simulation studies are done to support the decision making process.

The results of the survival analyses suggested local spread hazard changed significantly throughout the course of an epidemic (Figure 4-2). The results illustrated that a decrease in the hazard of local spread did not occur until the third week after detection of the index case. This was different from our anticipation that the hazard would decrease immediately after the announcement of the first FMD case, because of the caution taken by livestock owners and the general public. Moreover, there was a trend of increase in the

local spread hazard in week 2, which may be due to a lower level of compliance to the control measures to prevent disease spread. A marked reduction in the hazard of local spread before implementation of emergency vaccination (HR: 33.3 to 1.0) might be attributable to the control efforts to suppress human activities responsible for disease spread, such as enhanced biosecurity at the farm level and an increased awareness by livestock owners and the general public. If the local spread probabilities of phase I were replaced with those of phase II, there was a marked reduction in the simulated number of IPs (median: 83 IPs, 5^{th} and 95^{th} percentile: 39 and 177 IPs, results not shown). This would not be sufficient to prevent other environmental mechanisms of transmission (e.g., aerial dissemination of virus, mechanical carriages of virus by wildlife, etc.), necessitating implementation of rigorous measures such as emergency vaccination or contiguous culling. The estimated hazard post-vaccination was 0.19 and 0.56 times that of pre-vaccination for properties with cattle and pigs, respectively. The effectiveness of vaccination was thus estimated as 81% for cattle and 44% for pig enterprises, assuming that the reduction in the hazard of local spread was fully attributable to emergency vaccination. However, this could be overestimated, firstly because the other preventive measures as mentioned above could partially played a role, and secondly, the post-vaccination hazard could have been underestimated as IPs might have been underreported after vaccination due to suppression of clinical signs by vaccination (Nishiura and Omori, 2010). The efficacy of high potency emergency vaccine was reported to be consistent across species (cattle, sheep, goats and pigs) in experimental studies (Barnett et al., 2004), and variations in efficacy by species for emergency vaccine in the field are yet to be clarified.

In this study, we used the method proposed in the previous chapter (section 3.3) for estimating local spread probabilities. We then used these estimates as input parameters for the simulation model. Although there were some minor differences, the temporal and spatial patterns of simulated IPs reasonably matched the actual epidemic (Figure 4-4, Figure 4-5 and Figure 4-6), supporting the validity of our proposed method. The advantage of this approach is that the majority of the model parameters were derived from the actual field data, without having to 'borrow' from other studies of the same or different epidemics.

Two possible reasons were considered for the over prediction in the number of IPs in phase I (Figure 4-4). Firstly, aggregation of epidemic phases (for parsimony) might have

caused overestimation in the local spread parameters in the earlier period of phase I (i.e., week ≤0 and week 1). Secondly, the presumed actual epidemic curve might be biased towards lower value at the beginning of the epidemic, due to an unexplained delay in detection of IPs. The delay may be attributable to lack of information regarding the reporting procedures to livestock owners and field veterinarians, as well as an additional time required for laboratory testing to confirm FMD.

Although long distance, high-risk movements are commonly included in other FMD simulation modelling studies, these movements were not represented in this modelling study primarily because of absence of reliable movement data. For this outbreak, local spread alone with a maximum distance of 10 km was considered sufficient to closely mimic the spread within the relatively small study area (median distance between two premises: 8.6 km, 10 – 90%: 2.8 – 19.1 km, data not shown). Long-distance movement was also excluded in the previous study by Hayama *et al.* (2013). Nonetheless, incorporating long-distance movements in the model is likely to be important, when dealing with populations within a larger area, or investigating the effects of disease spread before imposition of stringent movement restrictions at the beginning of an epidemic.

For an early-start vaccination scenario, we examined the timing of three weeks after first confirmation of disease, allowing sufficient time for antigenic matching, manufacturing and transportation of vaccine. The implications for alternative vaccination strategies are the same as those of Hayama *et al.* (2013), that is, an earlier onset of vaccination (on day 7, or 21 post first confirmation of disease) using a 3 km vaccination radius was more effective in reducing the number of IPs than starting vaccination on day 32 (as actually occurred).

4.6. Conclusion

Emergency vaccination applied during the FMD epidemic in Japan in 2010 reduced the duration of an epidemic to less than 40% of what was simulated to have occurred without vaccination, but resulted in culling more than twice as many animals relative to no vaccination. Our results show that the epidemic could have been contained more effectively by starting vaccination 2 weeks earlier, with a smaller vaccination radius (3 km instead of 10 km). In addition, the hazard of local spread was remarkably high during the initial two weeks after the confirmation of disease. This reinforces the need for rapid deployment of effective control strategies (movement restrictions, enhanced premise-level

biosecurity, rapid detection and quarantine of infected places) within the surrounding high risk areas immediately post detection.

4.7. Acknowledgements

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5. Development of an economic module for a foot-and-mouth disease epidemic in New Zealand

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5.1. Abstract

Introduction of foot-and-mouth disease (FMD) in countries previously FMD-free would result in significant negative economic impacts due to an eradication programme and export bans on animal products imposed by trading partners. In New Zealand, a disease simulation model, termed New Zealand Standard Model (NZSM), has been developed as a decision support tool; but, there is a knowledge gap between model prediction expressed in epidemiological terms and economic inferences made by decision makers, which is perhaps likely to dictate decision making processes. This study describes an analytical approach for quantifying both the short-term direct costs arising from the control and eradication programme and the long-term macroeconomic costs due to export bans and tourism losses for an FMD epidemic. A set of economic parameters specific to an FMD outbreak in New Zealand has been developed, and the direct costs and macroeconomic costs of simulated epidemics were estimated, based on the outputs produced by the NZSM. For an epidemic in Auckland, with a median of 366 (5th and 95th percentiles: 163 and 865) IPs and median epidemic duration (i.e., time from first detection until last depopulation) of 131 (76 and 312) days, the median estimated direct cost and macroeconomic cost were USD 180 (88 and 548) million and USD 11.1 (8.5 and 17.0) billion, respectively, highlighting the relative importance of the macroeconomic cost. The economic module, together with NZSM, produce additional economic outcomes, which may contribute to contingency planning of FMD. The approach presented here may be used as a template for developing simulation modelling systems for other exotic diseases in New Zealand or other countries sharing similar situations, so preparedness is further improved and maintained.

5.2. Introduction

Foot-and-mouth disease (FMD) is widely recognised as the most contagious disease of cloven hoofed animals (Anonymous, 2009). FMD is characterised by development of vesicles on the feet, tongue and buccal mucosa, and the mammary glands of females (Alexandersen et al., 2003), which causes acute milk drop, weight loss, and reduced fertility in infected animals. The mortality rate in adult animals is generally low, but it can be significantly high in young animals due to acute myocarditis (Alexandersen et al., 2003). The direct and indirect losses due to FMD are colossal worldwide, irrespective of the current FMD status (Knight-Jones and Rushton, 2013). Because of its high contagiousness and severe economic impact, FMD is listed as a notifiable disease by the World Organization for Animal Health (OIE) (Anonymous, 2014g). As of May 2016, 67 of 180 member states of the OIE are recognised as FMD-free (Anonymous, 2016). Most high-income countries have eradicated FMD and protect their disease-free status by import controls and continuous screening of in-bound animals, animal products and humans at international borders. FMD-free status ensures access to the widest and most profitable export markets where products can be sold at a premium price.

In countries that have previously been FMD-free without vaccination, introduction of FMD virus usually results in the initiation of an eradication programme. In the typical situation, trading partners apply an immediate ban on importation of animals and animal products from the affected country. The cost of control and eradication and loss of market access result in significant negative economic impacts in the affected country, including livestock owners, government, and food and tourism industries, illustrated by the estimated impacts of USD 12 billion over 4 years, for the 2001 FMD epidemic in the UK (Yang et al., 1999, Thompson et al., 2002). Once disease has been eradicated, there is a lengthy process of 'proving' disease freedom. This includes standard procedure to regain the OIE's official status, 'FMD-free where vaccination is not practised,' and import risk assessments performed by each trading partner to resume trade. This process of market recovery is typically complex and influenced by a number of factors, including the magnitude and the length of disease outbreak, the type and value of products put up for export, the supply of alternative products by competing countries, the credibility of the animal health service of the affected country, political issues and consumer response (Breakwell, 2002). For example, following the 2010 outbreak of FMD in Japan, the duration of bans on importation of Japanese beef after recovery of the official FMD-free status without vaccination were 15, 18, and 37 months, by Canada, the USA, and New

Zealand, respectively (Anonymous, 2014c). Although rules are set out in World Trade Organization (WTO) sanitary and phytosanitary (SPS) measures to ensure health standards based on scientific evidence, these procedures may be lengthy and lack transparency, and the decision if and when to lift a trade ban is entirely at the discretion of importing countries.

New Zealand is a relatively unique country in that its economy has been developed and maintained by the growth of primary industries. The export pattern is unique in terms of its importance in the international markets, as well as the dominance it shares in the total production. The production and manufacturing of meat and dairy products contributed 6% of New Zealand's gross domestic product (GDP) (Anonymous, 2014f). From 2010 to 2013, the average New Zealand share of global export was estimated to be 30%, 6% and 42% for dairy products, beef and lamb/mutton, respectively (Anonymous, 2014d, Anonymous, 2013b, Anonymous, 2012b, Anonymous, 2011b). The majority of the total production, over 95% of dairy products, beef and lamb/mutton meat are exported overseas (Anonymous, 2013c); data (Statistics New Zealand, 2015) . An occurrence of any event that restricts or poses a threat to exports of animal products from New Zealand would have a significant economic impact, all the more because the size of the domestic market is not large enough to absorb the shock. To illustrate, in 2005, an FMD hoax in Waiheke Island activated emergency response systems for 14 days, for which the expenses were estimated to be USD 1.7 million (Anonymous, 2011a). In 2013, an announcement of possible contamination of milk by *Clostridium botulinum* by a leading dairy manufacturer in New Zealand caused a temporary ban on dairy products by major importers, including China. The immediate losses after the announcement were estimated to be more than USD 51 million (Hussain and Dawson, 2013).

There are not many historical examples of an FMD outbreak in a country similar to New Zealand, except for that of Taiwan in 1997 (Yang et al., 1999). Before the epidemic, Taiwan was a major pork exporter, accounting for 15% of the world pork exports (Fuller et al., 1997). In 1996, the value of pork exported from Taiwan was USD 1.6 billion, of which 99% of was exported to Japan (Fuller et al., 1997). Following the FMD outbreak and loss of export markets, the domestic price of pork immediately fell by 69%, and remained at about 25-50% for 1.5 months (Chang et al., 2006, Shieh, 1998).

Disease simulation models can be helpful for enhancing contingency planning in FMD-free countries, as they provide policy makers with a basis to appraise alternative strategies

without the actual experience of an FMD epidemic. Over the last decade, primarily driven by lessons learned from the devastating FMD epidemic in the UK in 2001 (Anderson, 2002), a considerable amount of work has been done to enhance the usability of disease models in FMD-free countries (Sanson et al., 2006a, Bates et al., 2003b, Keeling et al., 2003, Garner and Beckett, 2005, Roche et al., 2014). While such models are extremely useful in terms of providing decision makers with estimates of the scale of epidemic (e.g., the number of infected premises, epidemic duration, etc.), there is a growing demand in expressing model predictions in economic terms, because a decision making process is likely to be dictated by economic rather than epidemiological criteria. A number of economic models have been established and used to address this knowledge gap, for diseases which have substantial impacts on the economy (e.g., FMD, classic swine fever and highly pathogenic avian influenza) (Kobayashi et al., 2007b, Bates et al., 2003a, Schoenbaum and Disney, 2003, Carpenter et al., 2011, Paarlberg, 2008, Tomassen et al., 2002, Backer et al., 2012, Mangen et al., 2004, Mourits et al., 2010). To the best of our knowledge, however, there has been no report of models for New Zealand, which can predict FMD epidemics in economic, as well as epidemiological terms. While a stochastic and spatial FMD simulation model had been developed for New Zealand (Sanson et al., 2006a) using the InterSpread Plus framework (Stevenson et al., 2012), it has no economic components, limiting its inference for evaluation of alternative control strategies. The objective of this study was to develop an economic module to generically compute the costs of simulated FMD epidemics in New Zealand, subjoining to the existing FMD simulation model on InterSpread Plus. The methods of cost estimation were described using simulated epidemics, starting with a hypothetical index case in Auckland Region and controlled by stamping-out policy. Although the description and application of the approach for linking epidemiological and economic modules centres on its use for FMD, the approach used here could be generically used for other countries free of FMD, or other diseases with similar economic influences, such as classical swine fever, equine influenza and highly pathogenic avian influenza.

5.3. Materials and methods

5.3.1. Overview

The costs of FMD, as other animal diseases, typically arise from livestock production losses (e.g., low weight gain, reduced milk yield, deaths, reduced fertility and suboptimal herd structure), additional costs due to the ongoing control programme (e.g., routine

vaccination) or an eradication programme (e.g., quarantine, surveillance, emergency vaccination, and depopulation), negative secondary impacts on the broad economic sectors due to export losses and tourism losses, and negative impacts on the general public (e.g., deterioration of human health, less available livestock products, and restricted movements) (Knight-Jones and Rushton, 2013). The economic module developed in this study aimed at quantifying both the costs of an eradication programme ('direct costs') and the secondary impacts ('macroeconomic costs'), which would be important for countries where FMD is currently absent, and the policy is to eradicate, if there were an introduction of FMD.

In section 5.3.2, an example of the FMD epidemics, simulated to describe the economic module, are illustrated. In sections 5.3.3 and 5.3.4, the methods of estimation of direct costs and macroeconomic costs are described. Section 5.3.5 describes the uncertain analyses. The algorithms were developed using the statistical computing programme R (R Core Team, 2014) and compiled with InterSpread Plus ver. 4.02.17. All monetary values have been converted from New Zealand dollars to US dollars using the June 2014 average currency rate of 1 NZD = 0.8621 USD (Anonymous, 2014b).

5.3.2. Simulation of an FMD epidemic (Auckland incursion)

The FMD simulation model for New Zealand, based on the existing FMD simulation model, New Zealand Standard Model (NZSM) (Sanson et al., 2006a), was used to simulate epidemics using InterSpread Plus ver. 4.02.17. The parameters used in the study are presented in Appendix 5-1. The model accommodated parameters representing: (1) the nature of disease (i.e., incubation period, infectiousness, susceptibility, and local spread), (2) patterns of between-farm movements (i.e., frequency, distance and risk of disease transmission), which would occur without movement restrictions, and (3) the control measures (i.e., zoning, resources, depopulation, surveillance, tracing and movement restrictions) for varying phases of an epidemic. For (1), the parameters for the nature of disease derived from the previous analyses of 2001 UK FMD epidemic caused by FMD virus Type O strain (Sanson et al., 2006b). For (2), parameters representing movement patterns among New Zealand livestock populations derived from the analysis of New Zealand farm survey (Sanson, 2005). For (3), the parameters for the control measures were in accordance with those prescribed in Biosecurity Act 1993 (Anonymous, 1993) and Ministry for Primary Industries (MPI) Biosecurity Response Plan for Foot-and-Mouth Disease (MPI, unpublished).

The national livestock data containing 81,759 records of the geographical location of the premises centroid, counts of animals by species (i.e., beef cattle, dairy cattle, deer, sheep, pigs and goats) and classes of livestock enterprises (e.g., pastoral livestock, dry stock grazing, dairy, etc.) in New Zealand, were obtained from AgriBase (AsureQuality, 2011) (Sanson and Pearson, 1997). For incursion of disease, a lifestyle block (i.e., non-commercial, hobby farm) in the south of Auckland, with 10 sheep, 2 pigs and 1 goat, was chosen as the first infected premises (primary case). While the selection of the primary case was arbitrary, Auckland Region was purposefully chosen, for its proximity of livestock to major ports, a relatively high density of livestock holdings in the country (Figure 5-1), and a high proportion of lifestyle blocks (data not shown). Using the same primary case, disease spread was simulated from incursion until no new infection occurred for 30 days, for 100 iterations, which was arbitrary determined, but based on previous experience believed to be sufficient to produce an adequate outcome distribution.

The simulated epidemics had a median of 366 (5^{th} and 95^{th} percentiles: 163 and 865) IPs, with a median epidemic duration (i.e., time from first detection until last depopulation) of 131 (76 and 312) days. The location of the primary case, and the median and the 5^{th} and the 95^{th} percentiles density of simulated IPs in the Auckland Region are shown in Figure 5-1.

For estimation of the economic impacts, the FMD simulation model was set up so that it recorded the daily counts of premises, which had any of the following six statuses, until the simulated end of outbreak response:

(1) detected
(2) under processing (i.e., suspected, confirmation, slaughter, disposal, and cleaning).
(3) depopulated
(4) empty (i.e., animals were absent)

    Restocking was not modelled by InterSpread Plus. For the economic module, it was assumed premises re-introduce animals after being empty for 21 days after completion of depopulation, considering the New Zealand response plan (MPI, unpublished) and the EU regulations (Anonymous, 2003a).

(5) movement restriction (i.e., located within a 10 km surveillance zone), and
(6) inspected

    Animals on a premises were assumed to be tested serologically or examined clinically, if the premises were (i) suspected of infection, (ii) traced for having

made a high risk contact with any IPs, (iii) located within a 3 km protection zone from any IPs, (iv) had been restocked following depopulation, or (v) sampled for post-outbreak surveillance. Inspection was assumed to occur every 2 days during a follow up period of 14 days, or until infection was detected in the premises, for (i) to (iii), and weekly during a period for up to 28 days after re-introduction of animals for (iv), and once for (v), considering the procedures in the New Zealand response plan (MPI, unpublished) or the EU regulations (Anonymous, 2003a).

The following events were not modelled by InterSpread Plus, and thus, computed externally. For (i), the number of premises that were suspected of infection but diagnosed as negative was calculated based on an assumed ratio of non-infected to infected, i.e., 5:1 (Bingham, unpublished results). For (v), all premises within 3 km protection zones, a sample of premises within 10 km surveillance zones, and a sample of premises within each of the 16 regions of New Zealand were assumed to be tested to prove freedom from FMD. The sample size within each zone/region was determined by a sufficient number of premises to detect at least 1 infected premises with 95 % level of confidence, if the estimated prevalence of the disease were 2% (Anonymous, 2003a). It was calculated as $\left(1-\alpha^{\left(\frac{1}{D}\right)}\right) \times \left(n-\frac{D-1}{2}\right)$ (Dohoo et al., 2003), where α is a significance level of 0.05, n is the total number of premises in the zone/region, D is the estimated minimum number of infected premises in the zone/premises, calculated using a prevalence of 2%. The post outbreak surveillance was assumed to occur immediately after detection of the last case.

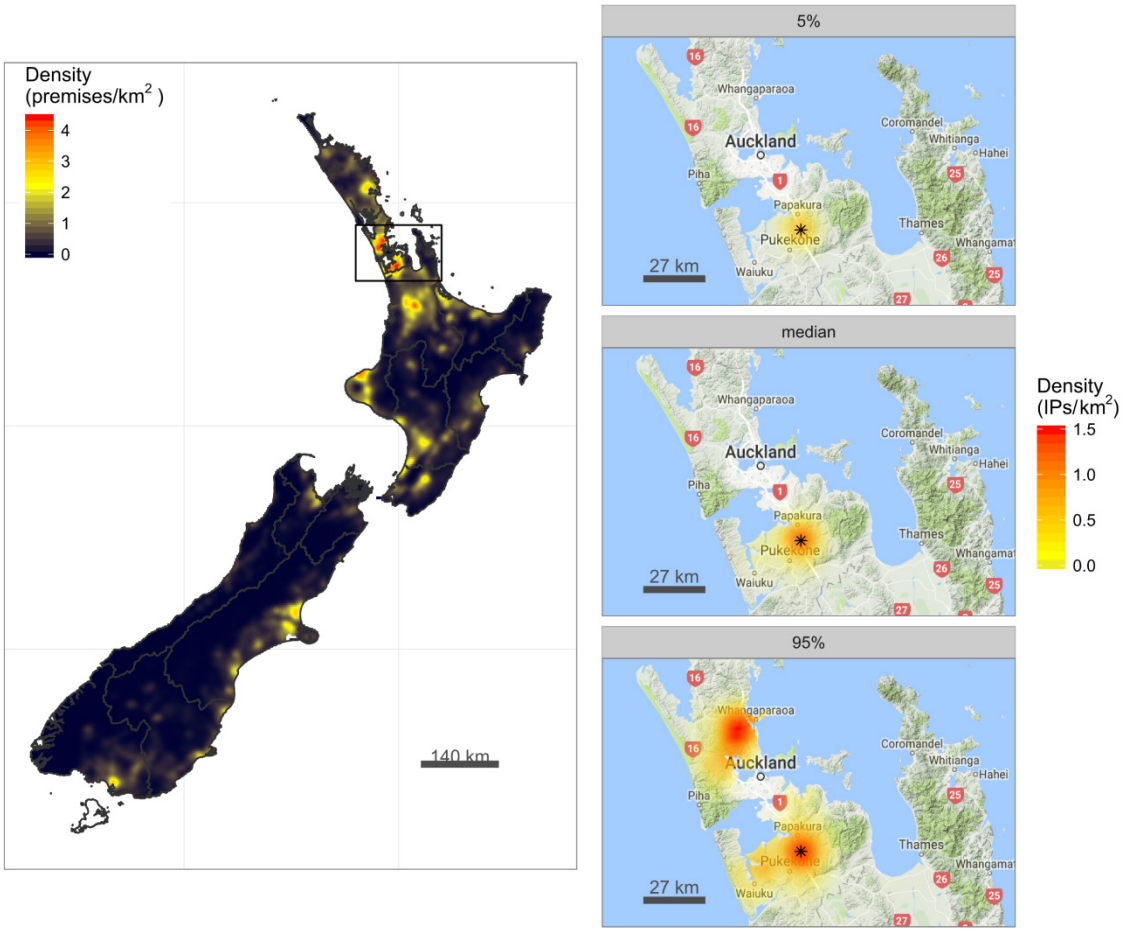

Figure 5-1 [Left] Map of New Zealand, showing the kernel smoothed density of livestock premises (bandwidth = 5.0 km). [B] Enlarged map of Auckland showing the kernel smoothed density of simulated IPs (median and the 5th and the 95th percentiles of 100 iterations, bandwidth = 5.0 km) and the location of the primary case (*).

5.3.3. Estimation of the direct costs

A set of parameters for the direct cost module, closely in line with the MPI's Response Cost Calculator (Bingham, unpublished results, Ansell, unpublished results), was developed. It comprised of a comprehensive list of 113 resources that would be required for each control measure, with the unit cost of each resource and its potential range (Appendix 5-2). For compensation of depopulated animals, 2011 - 2014 national average market values of breeding females for each livestock species (Inland Revenue, 2011, Inland Revenue, 2012a, Inland Revenue, 2013a, Inland Revenue, 2014) were used as the approximate market value of slaughtered animals. In addition, the rate of lost incomes (opportunity cost) per animal species per day in empty premises was estimated from the national average gross margin reported by the relevant industry in the most recent (1 – 4 years) publications available (Solis-ramirez et al., 2012, DairyNZ, 2014, Askin and Askin, 2012, Beef + Lamb New Zealand Economic Service, 2014). To note, the rate of compensation would be determined individually by contracted appraisers in the actual outbreak (Bingham, unpublished results, Ansell, unpublished results). No data were found in the severity of production losses by movement restrictions. It was assumed production losses due to movement restrictions were 5% decrease in daily gross margin per animal.

Based on the simulated outcomes and the estimated cost parameters, the direct cost was calculated as the sum of daily costs, which were calculated by multiplying the amount of each resource by its unit cost for each day, during a period when the outbreak response systems were active. Based on the methods of calculation, the costs were categorised into (i) semi-fixed costs, (ii) variable costs for operation, (iii) variable costs for supplemental staff, (iv) other variable costs, and (v) fixed costs.

(i) Semi-fixed costs

A semi-fixed cost was defined as the cost of a resource that was incurred for a duration, which may vary by the duration of an epidemic, at a rate, which was independent from the daily number of controlled premises (5.3.2). The costs of 42 resources for management activities (e.g., strategic leadership, programme manager, etc.) and 22 resources for operational activities (e.g., operation manager, movement control operation expert, etc.) were categorised in this group. A daily cost for each resource was calculated as a product of the estimated daily amount or workload, and the estimated unit cost (i.e., wage). All the resources for management activities were assumed to be required with 50% workload for 14 weeks post-epidemic. The workload of 46 resources (e.g., fleet management) was

weighted by 0.88% for every increase in the total number of IPs from 280 IPs, to account for increased workload for larger epidemics (Ansell, unpublished results).

(ii) Variable costs for operation

A variable cost for operation was defined as the cost, which varied proportional to daily counts of premises under control, derived from the FMD simulation model (5.3.2). The costs of 16 resources for operational activities (e.g., slaughter, veterinarians' patrol, etc.), value loss and lost incomes by depopulation for 6 animal species, and production loss by movement restrictions for 6 animal species, were categorised in this group. A daily cost for each resource was calculated by multiplying the simulated number of controlled premises, the estimated amount of the resource (i.e., workload or the number of animals) per premises, and the estimated unit cost. The number of animals per premises by species for depopulation and movement restriction derived from the outputs of the simulation model.

(iii) Variable costs for supplemental staff

A variable cost for supplemental staff was defined as an additional cost required for training new personnel to supplement the shortage, if it ever occurred. The costs of 7 resources for operational activities were categorised in this group. A daily cost of these resources was calculated by multiplying the estimated number of staff being trained on that day, the estimated unit workload to train new staff per person, and the estimated unit cost of the trainer (i.e., wage). The number of staff to train was calculated as difference between the number of required workload based on the simulated number of controlled premises (5.3.2), the cumulative number of pre-trained personnel, based on the estimated initial number of personnel available at the beginning of the epidemic, and an estimated training period of 2 days (Bingham, unpublished results).

(iv) Other variable costs

Other variable costs are those that were dependent on the amount of other resources. Four resources were categorised in this group. A daily cost was calculated by multiplying the amount of the dependent resources, the estimated unit amount of the resource, and the estimated unit cost. For example, the cost of employment was based on the number of new staff being employed.

(v) Fixed costs

Any expense incurred by an epidemic at a fixed rate, irrespective of the outcomes of the epidemic, was calculated as a fixed cost (e.g., facility set up cost). Four resources were categorised in this group.

5.3.4. Estimation of the macroeconomic costs

In this study, a macroeconomic cost was calculated as the cumulative net present value reduction in the GDP for 8 years if there were an outbreak compared to the situation where there was no outbreak. The macroeconomic cost was aimed at capturing the long-term effects of disruption in the broad economic sectors within the country, due to shocks from the FMD epidemic, such as export loss, tourism loss, changes in domestic production and consumptions, and exchange rate.

Previously, the macroeconomic costs of 3 hypothetical FMD epidemics were estimated using MONASH-NZ dynamic computable general equilibrium model (CGEM) (Schilling et al., 2014) as part of MPI's FMD Preparedness Programme (Forbes and van Halderen, 2014). The estimated macroeconomic costs were USD 5.3 billion, 6.9 billion, and 14.0 billion in 2010/11 prices with an 8 per cent discount rate, for the three simulated epidemic scenarios: small (1 day and 1 IP), medium (50 days and 52 IPs), and large (191 days and 508 IPs) epidemics (Forbes and van Halderen, 2014). For each of the three scenarios, assumptions on trade resumptions were made for meat and dairy, for trading partners with low/medium/high levels of risk perception, which were described in detail in their report (Forbes and van Halderen, 2014).

Directly linking the CGEM and the FMD simulation model would require multidisciplinary collaboration, which, although desirable, fell out of scope for this study. The alternative approach was to approximate the macroeconomic cost by extrapolation from the previous estimates (Forbes and van Halderen, 2014). Two simplistic assumptions were made to generically compute a macroeconomic cost of any given epidemic. First, considering the importance of the volume of export loss for the economy, which was likely to be proportional to the duration taken to recover OIE's FMD-free status, the macroeconomic cost was assumed to increase linearly by the expected number of days for which OIE's FMD-free status was suspended. Second, potential effects of all the other epidemiological factors (i.e., the number of IPs, geographical distributions of the outbreaks, and eradication strategies) on the macroeconomic cost were ignored.

Prediction of a macroeconomic cost, $f(x)$, was based on the fitted linear regression model:

$$f(x) = \beta_0 + \beta_1 * (x_1 + a)$$

where x_1 is the simulated number of days elapsed since detection of the index case until depopulation of the last case, a is the duration of the waiting period required for recovery of OIE's FMD-free status, i.e., 91 days, the intercept, or the macroeconomic cost of an epidemic, which was contained within a day, was β_0 = 4.9578 (billion USD), and the increment in the macroeconomic cost per additional day required to eradicate was β_1 = 0.0468 (billion USD). The adjusted R-squared of the fitted model was 0.988.

5.3.5. Uncertainty analyses

Uncertainty analyses were conducted to examine the potential ranges in the estimated costs due to uncertainty in the economic parameters. The uncertain ranges of direct costs were calculated, using the minimum and maximum possible rates of each resource (Ansell, unpublished results). For production losses by movement restriction, 1% and 10% decrease in daily gross margins for each animal species were used. The uncertain ranges of the macroeconomic costs were calculated as 95% confidence intervals of prediction, using the fitted linear regression model.

5.4. Results

5.4.1. Simulation of an FMD epidemic

The percentiles of the estimated daily counts of premises that had any of the six statuses (i.e., detected, under processing, depopulated, empty, movement restriction, and inspected) are shown in Figure 5-2. While the median peak incidence was 6 (5^{th} and 95^{th} percentiles: 1 and 17) cases per day, a relatively large number of premises were involved in control measures; at its peak, an estimated median of 22 (6 and 37) premises per day were under processing, 302 (127 and 519) premises per day remained empty, 5200 (3200 and 8900) premises per day were under movement restriction, and 523 (226 and 1206) premises per day were inspected.

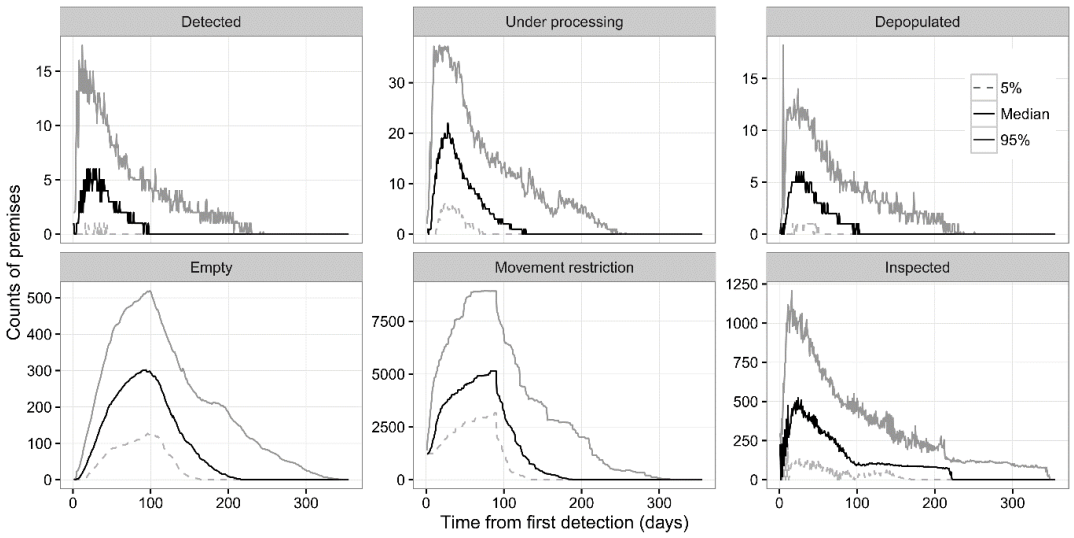

Figure 5-2 Median and the 5th and the 95th percentiles of the estimated number of premises where disease was detected, under processing, depopulated, empty (animals were absent), under movement restriction, and inspected, by time from the first detection for simulated foot-and-mouth disease (FMD) epidemics in Auckland, New Zealand (100 iterations).

5.4.2. Estimation of the costs of an FMD epidemic

Figure 5-3 illustrates the percentiles of the estimated amount of 9 resources for active surveillance (i.e., patrol veterinarians) and depopulation (e.g., slaughterers and disposers), and the estimated number of slaughtered animals, which composed of variable costs for operation. In particular, the peak number of field patrol veterinarians was relatively high, with an estimated median of 262 (5th and 95th percentiles: 113 and 603) persons per day.

Table 5-1 shows the percentiles of the estimated cumulative direct costs and macroeconomic costs with their uncertain ranges. The estimated direct costs (5th and the 95th percentiles: USD 88 and 548 million) were 0.6 to 4.3% of that of the estimated macroeconomic costs (USD 8.5 and 17.0 billion). Based on the uncertain ranges, those direct costs and the macroeconomic costs may be underestimated, or overestimated, by USD 11 - 305 million and USD 4.0 – 14.6 billion, respectively.

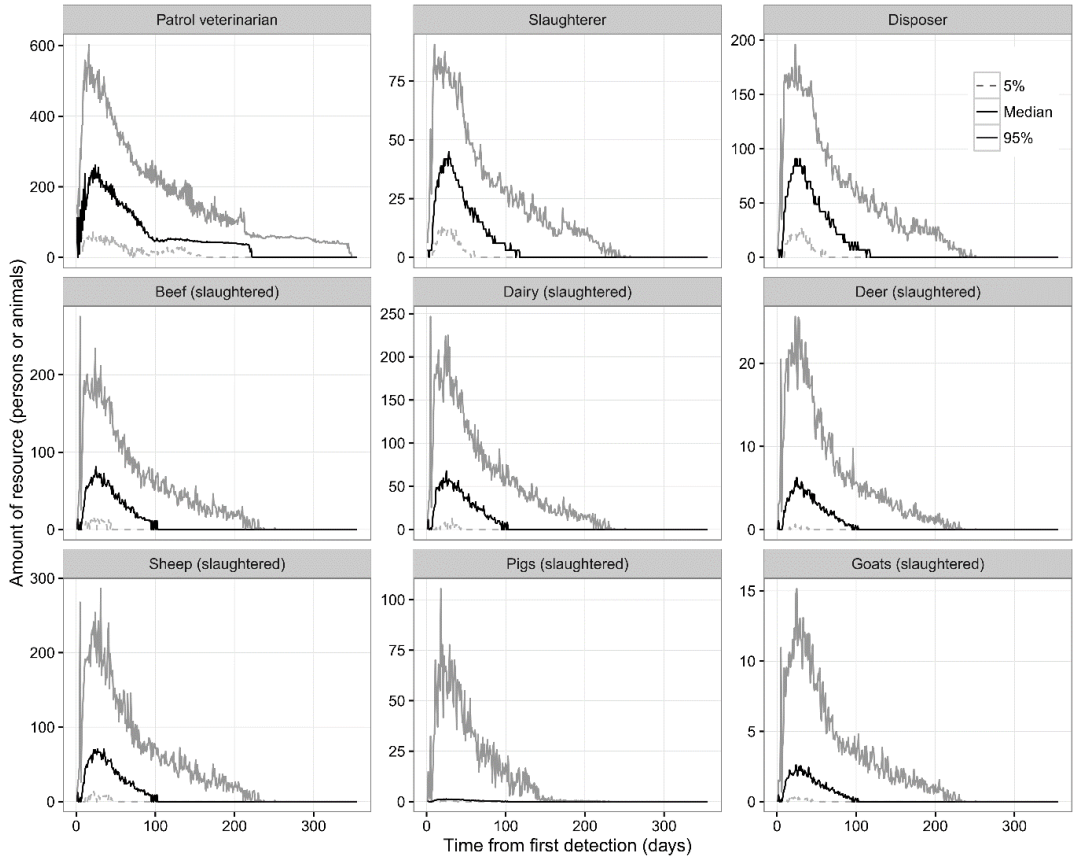

Figure 5-3 Median and the 5th and the 95th percentiles of the estimated amount of selected resources for calculation of the direct costs (variable costs of operation), for simulated foot-and-mouth disease (FMD) epidemics in Auckland, New Zealand (100 iterations).

Table 5-1 Percentiles of the estimated direct costs and macroeconomic costs and their uncertain ranges for simulated foot-and-mouth disease (FMD) epidemics in Auckland, New Zealand (100 iterations)

	Percentile	Estimated value	Uncertain range
Direct costs (USD million)	5%	88	47 to 111
	Median	180	99 to 226
	95%	548	332 to 683
Macroeconomic costs (USD billion)	5%	8.5	4.4 to 12.5
	Median	11.1	6.3 to 15.9
	95%	17.0	7.2 to 26.7

5.5. Discussion

In this study, a generic economic module was developed to iteratively run in conjunction with a spatial and stochastic simulation model of FMD. Economic parameters were estimated to quantify both the direct costs and the macroeconomic costs of any simulated FMD epidemic occurring in New Zealand. Compared with the previous study, carried out to estimate the potential economic impacts of an FMD epidemic for New Zealand (Forbes and van Halderen, 2014, Belton, 2004), this study was aimed at developing a generic module to estimate the costs of any simulated FMD epidemics in New Zealand. The economic module, combined with New Zealand Standard Model (NZSM), may contribute to animal health decision making, particularly around control and eradication of exotic infectious diseases such as FMD. For simulated FMD epidemics in Auckland, the absolute scale of the estimated direct costs (5^{th} and the 95^{th} percentiles: USD 88 to 548 million) and the macroeconomic costs (USD 8.5 to 17.0 billion), was comparable with those of other estimates in FMD-free countries, e.g., US, UK, and Australia (Paarlberg et al., 2002, Thompson et al., 2002, Buetre et al., 2013). The scale of the macroeconomic cost of an epidemic would be equivalent to 3.5 to 7.0% of the New Zealand's GDP in 2015 (MacPherson, 2015), or, 10.8 to 21.7% of the 2016 government budget (English, 2016). The relative scale of the cost of FMD for the country's economy was much greater than what was estimated for other FMD-free countries, i.e., smaller than 1% for the UK, Australia and the US (Paarlberg et al., 2002, Thompson et al., 2002, Buetre et al., 2013).

The main difficulty of the study was dealing with uncertainties in many of the economic parameters, due to the absence of experiences of an FMD outbreak in New Zealand. The greater uncertain ranges of the macroeconomic costs (USD 4.0 – 14.6 billion) compared with the direct costs (USD 11 - 305 million) suggests more efforts should be focused in the macroeconomic area to refine the estimation for future studies. In particular, we propose that more multidisciplinary work is carried out to enhance the linkage between the epidemiological model and the macroeconomic model. In addition, we propose that minimising these uncertainties will simplify the development of contingency plans, in particular, providing greater clarification to stakeholders of the overall objective of an outbreak response.

It should be emphasised that resumptions of trade will be dependent on the risk perceptions by the trading partners, as well as the duration of an epidemic. It would be useful, particularly for a net exporter of livestock products like New Zealand, to make

prior agreements with each of trading partners around resumption of animal product trade in the event of an FMD outbreak. Such agreements exist, for instance, between Canada and the USA, to avoid unnecessary trade disruption while preventing the introduction of highly contagious foreign animal diseases from one country to the other (Anonymous, 2012a). To date, there are no widely recognised FMD-specific trade agreements in which New Zealand participates, but there is little reason why one could not be made with New Zealand's trading partners. In addition, it would be of great use for planning purposes to have some indication of the likely response of trading partners if New Zealand's FMD status were regionalised. For example, in this study, 94% of the simulated FMD epidemics in Auckland were contained within the North Island, while the South Island remained FMD-free. Early resumption of trade from the South Island would reduce the shock of export bans, mitigating the macroeconomic costs. In the absence of clarification around these issues it is likely New Zealand's international market share of agricultural products would be reallocated to competing exporters, and prompt recovery of trade would be difficult.

There were some externalities that were not considered in our economic module due to difficulties in quantifying them in economic terms. For example, although FMD is usually not transmissible to humans, an outbreak itself and the control activities would have a number of serious negative psychological effects, particularly on those directly involved in the response activities (e.g., slaughter), such as stress, depression, isolation, loss of social life and worries about the future, which might be at a clinical level and require professional help (Van Haaften et al., 2004, Olff et al., 2005, Peck, 2005, Hannay and Jones, 2002, Hunter, 2001). Adequate consideration should be given to them by policy makers as they are likely to be important particularly at the individual level. It should also be noted, that the macroeconomic impacts of FMD would not fall evenly across the whole country, but more severely within the regional communities in the infected areas, or in the economic sectors closely associated with the livestock industries.

In conclusion, in this study, we have developed an analytical approach for measuring the economic outcomes of an epidemic of FMD in New Zealand. While the process was necessarily complex and tedious, particularly for estimation of direct epidemic costs, it was important to combine knowledge of disease biology with economics, so that the outcomes can be more readily and effectively interpreted by decision makers. Furthermore, this process was important for structuring our thinking about the problem

at hand and identifying key areas of uncertainty where more effort should be focused. It is suggested that the approach proposed in this study is used effectively as a template for other simulation modelling systems so preparedness for an exotic disease outbreak in countries sharing similar FMD status and policy as New Zealand is further improved and maintained.

5.6. Acknowledgements

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5.7. Supplementary data

Appendix 5-1 Parameters for New Zealand Standard Model (NZSM) for simulation of a foot-and-mouth disease (FMD) epidemic in New Zealand.

Parameters	Values
Disease transmission	
(1) Movements	
(i) Distance probability	
High risk, between-herd	0 to 20 km: 71%, 20 to 40 km: 18%, 40 to 60 km: 3%, 60 to 80 km: 4%, 80 to 100 km: 1%, 100 to 200 km: 2%, and 200 to 1000 km: <1%
Medium risk, between-herd	0 to 20 km: 81%, 20 to 40 km: 12%, 40 to 60 km: 2%, 60 to 80 km: 2%, 80 to 100 km: <1%, 100 to 200 km: 1%, and 200 to 1000 km: 1%
Low risk, between-herd	0 to 20 km: 91%, 20 to 40 km: 5%, 40 to 60 km: 2%, 60 to 80 km: 1%, 80 to 100 km: 0%, 100 to 200 km: <1%, and 200 to 1000 km: <1%
Pastoral livestock, via saleyards	0 to 80 km: 95%, 80 to 120 km: 3%, and 120 to 900 km: 2%
Breeding pigs, via saleyards	0 to 50 km: 69%, 50 to 100 km: 14%, 100 to 150 km: 7%, 150 to 200 km: 6%, 200 to 250 km: 1%, and 250 to 400 km: 2%
(ii) Frequency [1]	
High risk, between-herd	Poisson distribution, λ = 0.03 (PL), 0.04 (DR), 0.11 (GD and PB), and <0.01 (HB)
Medium risk, between-herd	Poisson distribution, λ = 0.47 (PL), 0.88 (DR), 0.91 (GD), 0.33 (PB), 0.29 (PF), and 0.14 (HB)
Low risk, between-herd	Poisson distribution, λ = 0.26
Pastoral livestock, via saleyards	Poisson distribution, λ = 0.01 (PL and DR), <0.01 (GD and HB)
Breeding pigs, via saleyards	Poisson distribution, λ = 0.01 (PB), and <0.01 (HB)
(iii) Transmission probability [2]	
High risk, between-herd	Day 1: 53% (PL and HB), 62% (DR), 67% (GD) and 46% (PB), day 2 to 11: 80%, and day 12 to 16: 100%
Medium risk, between-herd	Day 1: 10%, day 2 to 6: 20%, day 7 to 11: 40%, and day 12 to 16: 50%
Low risk, between-herd	Day 1: 2%, day 2 to 6: 4%, day 7 to 11: 9%, and day 12 to 16: 10%
Pastoral livestock/breeding pigs, via saleyards	Day 1: 46%, day 2 to 11: 78%, and day 12 to 16: 100%
(iv) Number of contacts	
High/medium/low risk, between-herd	Constant, 1.0
Pastoral livestock/breeding pigs, via saleyards	Poisson distribution, λ = 1.9 (PL) and 2.6 (PB)
(2) Local spread	
(i) Transmission probability [3]	
Day -1	0 to 1 km: 0, 1 to 2 km: 0, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 0	0 to 1 km: 7, 1 to 2 km: 2, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 1	0 to 1 km: 12, 1 to 2 km: 3, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 2	0 to 1 km: 12, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 3	0 to 1 km: 9, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
(ii) Adjustment	
Relative susceptibility by species	1.0 (cattle), 0.9 (sheep, goats and deer) and 0.8 (pigs)
Detection status	1.0 (undetected) and 0.5 (detected)

Disease characteristics	
(a) The onset of clinical signs [2]	Day 1: 0%, day 2: 4%, day 3: 16%, day 4: 33%, day 5: 77%, day 6: 79%, day 7: 83%, day 8: 88%, day 9: 91%, day 11: 95%, day 12: 97% and day 16 onwards: 98%
(b) The onset of infectivity [2]	Day 1 to 16: 100%, day 17: 94%, day 18: 88%, day 19: 82%, day 20: 76%, day 21: 71%, day 22: 65%, day 23: 59%, day 24: 53%, day 25: 47%, day 26: 41%, day 27: 35%, day 28: 29%, day 29: 23%, day 30: 17%, day 31: 12%, day 32: 6% and day 33 onwards: 0%
Control measures	
(1) Depopulation	
(i) Start date [4]	Day 0
(ii) Resource [4]	
Day 0 to 4	Day 1: 1, day 2: 2, day 3: 10, and day 4: 20 (premises/day)
Day 5 onwards	Triangular distribution, {minimum, mode, maximum} = {0, 1, 5} (PL), {1, 1, 3} (DR), {0, 1, 4} (GD), {0, 1, 3} (PB/PF), and {0, 0, 1} (HB) (days/premises)
(2) Surveillance	
(i) Detection probability	
Background surveillance (DR, PB and PF)	Day 1: 6%, day 2: 16%, day 3: 21%, day 4: 17%, day 5: 13%, day 6: 9%, day 7: 6%, day 8: 4%, day 9: 3%, day 10: 2%, day 11 to 13: 1%, day 14 onwards: <1%
Background surveillance (PL, GD and HB)	Day 1: 2%, day 2: 6%, day 3 to 5: 9%, day 6: 7%, day 7 to 8: 6%, day 9 to 11: 5%, day 12 to 14: 4%, day 15 to 17: 3%, day 18 to 20: 2%, day 21 to 26: 1%, and day 27 onwards: <1%
Passive surveillance (DR, PB and PF)	Day 1: 7%, day 2: 20%, day 3: 24%, day 4: 17%, day 5: 11%, day 6: 7%, day 7: 5%, day 8: 3%, day 9: 2%, day 10 to 12: 1%, and day 13 onwards: <1%
Passive surveillance (PL, GD and HB)	Day 1: 3%, day 2: 7%, day 3: 10%, day 4: 9%, day 5: 8%, day 6: 7%, day 7: 6%, day 8 to 10: 5%, day 11 to 14: 4%, day 15 to 16: 3%, day 17 to 20: 2%, day 21 to 24: 1%, day 25 onwards: <1%
Patrol visit	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (high risk)	Constantly 100%
Tracing (medium risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (low risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
(ii) Buffer for patrol visit (km)	3
(3) Movement restriction	
(i) Restriction probability	
First 14 days (initial standstill)	High risk: 91%, medium risk: 60%, and low risk: 24%
Day 15 onwards: inside 3 km infected zone	High risk: 94%, medium risk: 80%, and low risk: 39%
Day 15 onwards: inside 10 km surveillance zone	High risk: 95%, medium risk: 85%, and low risk: 52%
Day 15 onwards: outside 50 km control area	High risk: 100%, medium risk: 90%, and low risk: 80%

1 Classification of New Zealand livestock premises: PL (pastoral livestock enterprise), DR (dairy enterprise), GD (dry grazing enterprise), PB (breeding pig enterprise), PF (finishing pig enterprise) and HB (hobby farms).
2 Relative to the date of infection.
3 Relative to the onset of clinical signs.
4 Relative to the date of detection of the index case.
5 Relative to the date of application of vaccination.

Appendix 5-2 Input parameters for estimation of the direct costs for a foot-and-mouth disease (FMD) epidemic in New Zealand.

ID	Resources	Source[1]	Category[2]	Unit amount (AU)[3]	Unit cost (USD/AU)	Initial amount
	Management					
	General					
1	Response strategic leadership	a	(i)	1.4	1,600	
2	Response programme manager	a	(i)	0.6	1,600	
3	Spokesperson	a	(i)	0.6	860	
	Planning & Intelligence					
4	Workstream lead	a	(i)	0.4	860	
5	Team members	a	(i)	17.1	860	
	Liaison - domestic					
6	Workstream lead	a	(i)	0.4	860	
7	Team members	a	(i)	2.9	690	
	Liaison - international					
8	Market access risk mitigation lead	a	(i)	0.4	860	
9	Team members	a	(i)	12.9	690	
	Communications					
10	Workstream lead	a	(i)	0.1	860	
11	Team members	a	(i)	6.4	690	
	Logistics - human resources					
12	Staff recruitment and induction	a	(i)[w]	3.0	690	
13	Travel and accommodation	a	(i)[w]	0.4	690	
14	Record of hours worked	a	(i)[w]	0.2	690	
15	Remuneration	a	(i)[w]	0.2	690	
	Logistics - equipment					
16	Purchasing, rental and asset management	a	(i)[w]	0.4	690	
17	Fleet management	a	(i)[w]	0.3	690	
18	Equipment storage and maintenance	a	(i)[w]	0.1	690	
19	Inventory	a	(i)[w]	0.1	690	
20	Personal equipment issuance and return	a	(i)[w]	0.3	690	
	Logistics - centre est., field headquarters etc.					
21	Centre establishment	a	(i)[w]	0.6	690	
22	Centre management	a	(i)[w]	0.3	690	
23	Centre biosecurity	a	(i)[w]	0.3	690	
24	Building management	a	(i)[w]	0.3	690	
25	IT management	a	(i)[w]	0.7	690	
26	Reception and switchboard	a	(i)[w]	0.7	690	
27	Fax management	a	(i)[w]	0.3	690	
28	Laundry	a	(i)[w]	0.3	690	
29	Cleaning and waste disposal	a	(i)[w]	0.3	690	
30	Office equipment	a	(i)[w]	0.3	690	
31	Mail management, couriers	a	(i)[w]	0.4	690	
32	File management	a	(i)[w]	0.6	690	
33	Occupational health and safety	a	(i)[w]	0.1	690	
34	Visitor management	a	(i)[w]	0.3	690	
35	Group managers	a	(i)[w]	2.3	690	
	Logistics - financial					
36	Financial authorisation, delegations	a	(i)[w]	0.3	690	
37	Contract management	a	(i)[w]	0.3	690	
38	Accounting	a	(i)[w]	0.6	690	
39	Financial reporting	a	(i)[w]	0.6	690	
40	Accounts payable	a	(i)[w]	0.1	690	
41	Debtors and creditors	a	(i)[w]	0.1	690	
	Other expenses					
42	Travel & accommodation of management personnel	a	(i)[w]	7.1	520	

	Operation					
	General					
43	Operations manager	a	(i)	0.3	1,600	
44	Employer	a	(iv)	0.1	1,600	
45	Supervisor manager	a	(iv)	0.1	1,600	
	Movement control					
46	Restricted place manager (supervisor)	a	(ii)	0.3	1,600	
47	Restricted place manager (trainer)	a	(iii)	0.1	1,400	
48	Restricted place manager (field personnel)	a	(ii)	2.0	1,600	70
49	Movement control operations expert	a	(i)	0.3	1,400	
50	**Liaison with police, transit NZ, local authority**		(i)	0.1	1,600	
51	Security officer (supervisor)	a	(ii)	0.3	830	
52	Security officer (trainer)	a	(iii)	0.1	1,400	
53	Security officer (field personnel)	a	(ii)	2.0	830	60
54	Controlled areas maintenance	a	(i)[w]	0.3	830	
55	Perimeter controls	a	(i)[w]	114.7	830	
56	Data input	a	(i)[w]	0.4	560	
57	Regionalisation internal border security	a	(i)[w]	5.9	830	
58	Movement permit management	a	(i)[w]	1.4	830	
59	Training	a	(i)[w]	0.3	830	
60	Conveyance decontamination	a	(i)[w]	6.0	1,400	
61	Reporting and liaison	a	(i)[w]	0.3	830	
62	Investigation of breaches of the Act	a	(i)[w]	0.3	830	
	Mapping					
63	GIS mapping experts	a	(i)	0.7	1,400	
	Tracing					
64	tracing	a	(i)[w]	5.1	860	
	Monitoring (surveillance)					
65	surveillance ops expert (surveillance)	a	(i)	0.3	1,400	
66	Patrol veterinarian (supervisor)	a	(ii)	0.1	1,600	
67	Patrol veterinarian (trainer)	a	(iii)	0.1	1,400	
68	Patrol veterinarian (field personnel)	a	(ii)	0.5	1,400	100
	Diagnostics					
69	Diagnostician (field personnel)	a	(ii)	1.0	860	
70	Diagnostics managers - for liaison	a	(i)[w]	0.6	860	
71	Identification costs - diagnosticians in containment	a	(i)[w]	28.6	860	
72	Data management staff for test results	a	(i)[w]	8.6	860	
73	Non containment lab support staff	a	(i)[w]	11.4	860	
74	Lab logistics support staff	a	(i)[w]	8.6	860	
	Depopulation					
75	Manager	a	(i)	0.3	1,600	
76	Organism management expert	a	(i)	0.3	1,600	
77	Slaughterer (supervisor)	a	(ii)	0.4	1,600	
78	Slaughterer (trainer)	a	(iii)	0.1	1,400	
79	Slaughterer (field personnel)	a	(ii)	3.0	1,400	0
80	Disposer (supervisor)	a	(ii)	1.0	1,600	
81	Disposer (trainer)	a	(iii)	0.1	1,400	
82	Disposer (field personnel)	a	(ii)	7.0	1,400	0
83	Cleaner (supervisor)	a	(ii)	1.0	1,600	
84	Cleaner (trainer)	a	(iii)	0.1	1,400	
85	Cleaner (field personnel)	a	(ii)	7.0	1,400	0
86	Appraiser (supervisor)	a	(ii)	0.1	1,600	
87	Appraiser (trainer)	a	(iii)	0.1	1,400	
88	Appraiser (field personnel)	a	(ii)	1.0	1,400	0
	Other expenses					
89	Decontamination	a	(ii)	1.0	39,000	
90	Travel & accommodation of operation personnel	a	(iv)	1.0	62	
91	Facilities, equipment & teleco costs of operation personnel	a	(iv)	1.0	25	

	Compensation				
92	Compensation (beef)	b	(ii)	x[3]	840
93	Compensation (dairy)	b	(ii)	x	1,700
94	Compensation (deer)	b	(ii)	x	370
95	Compensation (sheep)	b	(ii)	x	410
96	Compensation (pigs)	b	(ii)	x	220
97	Compensation (goats)	b	(ii)	x	110
98	Empty housing (beef)	c	(ii)	x	0.81
99	Empty housing (dairy)	d	(ii)	x	1.9
100	Empty housing (deer)	c	(ii)	x	0.27
101	Empty housing (sheep)	c	(ii)	x	0.19
102	Empty housing (pigs)	e	(ii)	x	0.40
103	Empty housing (goats)	f	(ii)	x	0.74
104	Production loss (beef)	c	(ii)	x	0.081
105	Production loss (dairy)	d	(ii)	x	0.19
106	Production loss (deer)	c	(ii)	x	0.027
107	Production loss (sheep)	c	(ii)	x	0.019
108	Production loss (pigs)	e	(ii)	x	0.040
109	Production loss (goats)	f	(ii)	x	0.074
	Others				
110	Facility set-up	a	(v)	1.0	170,000
111	Technical Advisory Group - teleconference	a	(v)	1.0	430
112	Factsheet production	a	(v)	1.0	860,000
113	Research	a	(v)	1.0	1,700,000

1 a (Ansell, unpublished results, Bingham, unpublished results), b(Inland Revenue, 2011, Inland Revenue, 2012b, Inland Revenue, 2012a, Inland Revenue, 2013a, Inland Revenue, 2013b, Inland Revenue, 2014), c(Beef + Lamb New Zealand Economic Service, 2014), d(DairyNZ, 2014), e(Askin and Askin, 2012) and f(Solis-ramirez et al., 2012)

2 (i) semi-fixed costs, (i)[w] semi-fixed costs weighted by the epidemic scale, (ii) variable costs for operation, (iii) variable costs for supplemental staff, (iv) other variable costs, and (v) fixed costs (see 5.3.3).

3 Amount per day for (i), per premises for (ii), per personnel for (iii), and per unit of other resources for (iv). The unit is full-time equivalent (FTE) for workload, and animals for resources related with compensation and production losses. One FTE was equivalent to labour of one person of one day.

4 The average number of animals per premises by species, derived from the outputs of the simulation model.

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6. Economic assessment of alternative eradication strategies against foot-and-mouth disease in New Zealand

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6.1. Abstract

The alternative vaccination policies for eradication of foot-and-mouth disease (FMD) epidemics for New Zealand were assessed based on an existing simulation model, with an addition of an economic component. Infection was seeded in a randomly chosen livestock premises in two regions, with a high and low density of susceptible premises (i.e., Auckland and Otago, respectively). The outcomes of FMD epidemics controlled by stamping-out alone (SO), and addition of 3 km ring vaccination, with or without subsequent culling (VTD and VTL) on day 21, were compared. In addition, the effects of three epidemiological indicators: density, the cumulative number of infected premises on day 14 (*CIP*) and a crude estimated dissemination rate (*EDR'*) on day 14 to 21, on the epidemic outcomes were examined. The results showed that the effectiveness of emergency vaccination in terms of median reduction in the simulated total number of IPs, time to eradication, direct costs and macroeconomic costs, was generally greater for the high density region, higher *CIP*, or higher *EDR'*. In terms of reduction in the macroeconomic costs, VTD was preferred to SO by $\leq$USD 4.5 billion, for an epidemic in the high density region with higher *CIP* and *EDR'*, and SO was preferred otherwise. VTL was not economically advantageous, in terms of the macroeconomic impacts under the current OIE's standard, but could become the preferred policy if the OIE's waiting period were 3 months. It is suggested that contingency planning and preparedness for FMD in New Zealand could be enhanced by using the simulation modelling system demonstrated for other possible epidemiological and/or economic scenarios.

6.2. Introduction

Foot-and-mouth disease (FMD) is a highly infectious disease of cloven-hoofed animals, which causes severe production loss in infected livestock (Alexandersen et al., 2003). As of May 2016, more than one-third of the member states of the World Organisation for Animal Health (OIE) were recognised as FMD-free (66 countries without vaccination, 1 with vaccination) (Anonymous, 2016). The status of FMD-free without vaccination ensures access to the widest and most profitable export markets where products can be sold at a premium price. New Zealand is among those with this status and, as such, an FMD outbreak would result in trade bans on livestock and livestock product for potentially a prolonged period by current trading partners. New Zealand's economy is heavily dependent on the export of agricultural products. Therefore, if New Zealand were to experience an outbreak of FMD the policy will likely be one of eradication.

Historically, the primary approach for eradication of FMD in previously FMD-free countries was 'stamping-out' (SO), which involved immediate slaughter of all susceptible animals on infected premises (IPs), followed by disposal, disinfection, cleaning and quarantine (Haydon et al., 2004, Radostits et al., 2007, Geering and Lubroth, 2002). In some situations, however, stamping-out alone may not effectively contain the epidemic, due to a combination of epidemiological and logistic factors. Once the speed of disease spread overwhelms the available resources for stamping-out activities, it is likely that infection would spread to extended geographical areas, making it more costly and lengthy to eradicate. The resulting epidemic would be prolonged and involve more number of infected premises. To illustrate, a stamping-out approach was adopted by the UK during the 2001 epidemic of FMD, which lasted for 221 days and resulted in the culling of at least 6.5 million animals and a total (direct and indirect) costs of approximately USD 12 billion (£ 8 billion) over 4 years (Anderson, 2002, Thompson et al., 2002). The stamping-out approach used in the UK and elsewhere has also raised concerns about animal welfare, environmental problems and the overall efficiency of the policy.

The devastating consequences of stamping-out alone draw controversy among policymakers as to whether supplemental strategies (i.e., emergency vaccination) should be implemented. Emergency vaccination provides rapid protection from clinical disease in susceptible animals and dramatically reduces virus shedding in animals that are already infected (Golde et al., 2005, Barnett et al., 2004, Cox et al., 1999, Doel et al., 1994, Salt et al., 1998, Orsel and Bouma, 2009). Large numbers of animals can be vaccinated quickly

using relatively fewer resources, compared with depopulation that requires more specialised personnel and equipment. Emergency vaccination has been used to control outbreaks, where the primary eradication strategy was initially stamping-out, in Taiwan, 1997 (Yang et al., 1999), the Republic of Korea, 2000 and 2010 (Park et al., 2004, Park et al., 2013), Argentina, 2001-2002 (Mattion et al., 2004), Uruguay, 2001 (Anonymous, 2001b, Anonymous, 2001a, Rivas et al., 2004), the Netherlands, 2001 (Pluimers et al., 2002), and Japan, 2010 (Muroga et al., 2012). Supported by these experiences, combined with a shift in public perception, emergency vaccination is beginning to be accepted as an important component of contingency plans by a number of FMD-free countries (Anonymous, 2014e, Anonymous, 2014a, Anonymous, 2003a). In 2013 the New Zealand Ministry for Primary Industries initiated a review of its FMD preparedness and response arrangements particularly around the use of emergency vaccination (Anonymous, 2013a).

Rational decision making regarding use of emergency vaccination is challenging, as the extra costs for substantiating FMD freedom need to be compared with the expected epidemiological benefits. This is because vaccinated animals can become sub-clinically infected and develop an asymptomatic carrier state (Barnett and Carabin, 2002). For differentiation of infected from vaccinated animals (DIVA), an intensive post-epidemic surveillance is required to prove absence of virus within a vaccinated population (Paton et al., 2014, Barnett et al., 2015, Geale et al., 2015). To address this issue, the OIE's recognition of FMD-freedom with presence of vaccinated animals ('vaccinate-to-live') requires an additional three months compared with stamping-out alone (Anonymous, 2014g). Although recently there are discussions around shortening the OIE's waiting period by 3 months (Barnett et al., 2015, Geale et al., 2015), it has not been realised as of September 2016. To avoid the extra waiting period, vaccinated animals may be subsequently culled after achieving disease eradication ('vaccinate-to-die') (Anonymous, 2014g). Although it is possible to cull vaccinated animals efficiently in slaughterhouses and process meat for domestic consumptions, it may not be feasible in the actual outbreak situation if there is no specific plan well discussed in advance with all stakeholders. To illustrate, carcasses of vaccinated animals were destroyed in the epidemics in the Netherlands, 2001 (Pluimers et al., 2002) or Japan, 2010 (Muroga et al., 2012). In addition, culling a large number of vaccinated animals could cause disruption in the related industries, due to long term imbalance between supply and demand. There is a potential loss of perceived product value due to consumer fear towards animals treated with new

and unfamiliar vaccines (Scudamore, 2007). Culling healthy, uninfected, vaccinated animals may not be well accepted by the producers as well as general public.

Disease simulation models are increasingly used for enhancing contingency planning in FMD-free countries, as they provide policy makers with basis to appraise alternative strategies without actual experience of an FMD epidemic (Hagerman et al., 2012, Halasa et al., 2013, Garner et al., 2014). Because the rational strategy will vary by the circumstances surrounding the outbreak, it is important to test alternative control strategies for a variety of conditions, informing the complete range of advantages and disadvantages of one strategy over another to decision makers and stakeholders.

This study aimed at estimating the relative benefits of two alternative FMD control policies, vaccinate-to-die and vaccinate-to-live over stamping-out alone to control an FMD epidemic in New Zealand, and identifying factors, which may indicate the benefits of the alternatives policies at the time of decision making, such as the density of livestock premises in the incursion site and the number of IPs at the initial stage of an epidemic, using the predeveloped FMD simulation modelling system.

6.3. Materials and methods

6.3.1. Epidemic simulation

FMD epidemics were simulated by InterSpread Plus (Stevenson et al., 2012) ver. 4.02.17, using the predeveloped parameters, New Zealand Standard Model (NZSM) (Sanson et al., 2006a). The parameters used in the study are presented in Appendix 6-1. Data of livestock enterprises in New Zealand were obtained from AgriBase 2011 (AsureQuality), the national spatial farm database, which records the enterprise class (e.g., dairy, pastoral livestock, etc.), counts of FMD-susceptible animals by species (beef, dairy, deer, sheep, pigs and goats), and the easting and northing coordinates of the centroids of premises (Sanson and Pearson, 1997).

Two regions were selected for incursion of FMD: Auckland and Otago (Figure 6-1). Auckland region was chosen for its relatively high density of livestock premises (mean density: 1.7 premises/km^2 or 135 animals/km^2), with a high proportion of small-scale livestock enterprises (mean number of animals per premises: n = 85), with 29% beef, 17% dairy, 2% deer, 49% sheep, <2% pigs and <2% goats. Otago region was chosen for its relatively low density of livestock premises (mean density: 0.1 premises/km^2 or 214

animals/km^2), with a high proportion of large-scale livestock enterprises (mean number of animals per premises: n = 1447), with 5% beef, <4% dairy, <3% deer, 89% sheep, <1% pigs, and <1% goats. In the following, Auckland and Otago regions are referred to as high and low density regions, respectively.

Initially, epidemics with a stamping-out only (SO) policy were simulated by seeding FMD into randomly selected premises in the two regions. For epidemics that continued for longer than 21 days (i.e., at least one new case was detected on the 21st day or later, counting from detection of the index case) with SO, another epidemic was simulated with all the same conditions except for additional application of emergency vaccination, as described in section 6.3.3. Simulation was repeatedly conducted until a sufficient number of data were obtained for the analyses, as described in section 6.3.4.

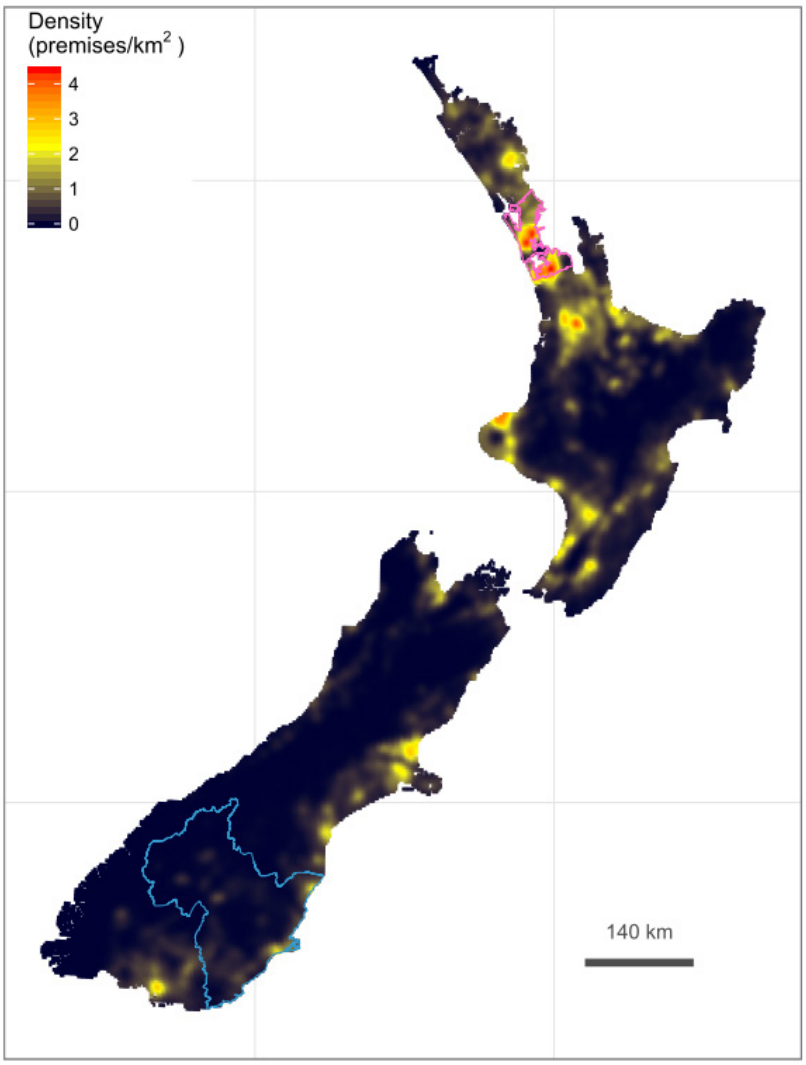

Figure 6-1 Kernel smoothed density of livestock premises (bandwidth = 5.0 km) susceptible to foot-and-mouth disease (FMD), and the location of Auckland (pink) and Otago (blue) regions, in which hypothetical primary cases were selected for FMD simulation.

6.3.2. Estimation of the costs of an FMD epidemic

The direct costs and the macroeconomic costs of the simulated epidemics were estimated, using the economic module described in Chapter 5. Some modifications were made to account for the costs of emergency vaccination, which is described in the following section.

6.3.3. Assumptions for emergency vaccination

If the epidemic lasted longer than 21 days, application of emergency vaccination, that is, 3-km ring vaccination, starting from the beginning of the 3rd week (21st day) after the first detection, was examined. A period of 3 weeks was considered to be sufficient for matching vaccine strains, manufacturing vaccines and transport from the overseas vaccine bank (Owen, personal communication). The effectiveness of vaccination, as measured as percentage of premises protected from infection, was assumed to be 0%, 50%, 75%, and 100%, on day $\leq$3, 4, 5 and $\geq$6 after application of vaccination, respectively. Subclinical infection, and subsequent virus shedding, in vaccinated animals was not considered.

The following parameters for vaccination resources were added to the direct cost module (see section 5.3.3), for vaccinate-to-die (VTD) and vaccinate-to-live (VTL). For both policies, vaccination activities were assumed to require veterinarians for vaccine administration (1 full time equivalent per premises) and appraisers (1 full time equivalent per premises). For VTD, culling of vaccinated animals was assumed to occur in designated slaughterhouses located in the same region as the vaccinated zone. There is currently no stipulated plan for New Zealand regarding processing of products from FMD-vaccinated animals (Thomson, unpublished). While products from vaccinated animals can enter the food chain, provided they are processed separately from non-vaccinated animals and receive prescribed treatments (Anonymous, 2003a), there would be an uncertain degree of value loss due to complex factors including excessive supply, restricted markets, and perceived value loss. As aggregated costs of culling, processing and lost values of products from vaccinated animals, the market value of vaccinated animals was added to the cost of VTD. In addition, the additional gross margin of vaccinated animals during a period between vaccination and restocking was added as an opportunity cost. To note, these costs are likely to be borne by the government, as subsidies to the slaughterhouses and compensation to the producer (Thomson, unpublished). For VTL, serological testing of all vaccinated animals would be required as part of post-epidemic surveillance to prove freedom of disease (Paton et al., 2014). The resources for post-

epidemic surveillance on vaccinated premises were assumed to be 10 times that of other premises where samples of animals would be tested. This is was based on the calculated mean ratio of the total number of animals per premises to the minimum number of animals per premises to test to detect disease with 95% confidence, assuming 5% animal-level prevalence (Mackereth and Kittelberger, 2008). The minimum number of animals to test was calculated by: $\left(1-\alpha^{\left(\frac{1}{D}\right)}\right)\times\left(n-\frac{D-1}{2}\right)$, where α is 0.05, n is the total number of animals per premises, and D is the expected diseased animals, n * 5% (Dohoo et al., 2003). For VTL, no reduction in the market value and no production loss were assumed for vaccinated animals, although there would be, to an unknown degree, due to likely changes in consumers' perception, and restrictions in the movements of vaccinated animals throughout their lives.

The macroeconomic cost of an epidemic controlled by emergency vaccination was estimated using the macroeconomic module described in section 5.3.4. For VTD, the coefficient for duration was determined as the simulated number of days elapsed since detection of the index case until depopulation of the last case, or until completion of subsequent culling of vaccinated animals, whichever was the greater, considering the current OIE's standard (Anonymous, 2014g). Time to complete culling was estimated by dividing the simulated number of vaccinated animals by an assumed culling capacity of 8,200 animals per day, which was equivalent to 2010-2014 average peak regional rate of culling in New Zealand (Statistics New Zealand, 2015), starting 14 days after the last vaccination (i.e., no more infection occurred outside the current vaccination zone), considering the Netherlands' experience in 2001 (Pluimers et al., 2002). For VTL, the coefficient for duration was determined as the simulated number of days since detection of the index case until depopulation of the last case or last vaccination, whichever was greater. For VTL, the waiting period required for recovery of OIE's FMD-free status was assumed to be 183 days, in accordance with the OIE's standard (Anonymous, 2014g). In addition, the macroeconomic cost with VTL with a hypothetical shortened waiting period of 3 months (91 days) (VTL*) was also examined, considering the discussion around aligning the waiting period for VTL with that of SO or VTD (Barnett et al., 2015, Geale et al., 2015).

6.3.4. Non-parametric data analyses

For each unique incursion scenario (i.e., primary case) and for each vaccination policy (VTD/VTL/VTL*), the effectiveness of the vaccination policy was measured as

reduction in the overall epidemic outcomes from that of SO. Four epidemic outcome variables for each simulated epidemic were recorded for analyses. The outcomes were two epidemiological variables, i.e., total number of IPs and time to eradication, as measured by the number of days elapsed from detection of the index case until depopulation of the last case, and two economic variables, i.e., direct costs and macroeconomic costs.

In addition, three explanatory variables were recorded for each unique incursion scenario (i.e., primary case): region of the primary case (*region*), cumulative number of IPs on day 14 after detection of the index case (*CIP*), and the crude estimated dissemination rate (*EDR'*) (Miller, 1976) on day 21, calculated as the rate of change of CIPs (slope of epidemic curve) during the first 14 days divided by the rate of change of CIPs the next 7 days (Figure 6-2). *EDR'* > 1 (Figure 6-2A) or < 1 (Figure 6-2B) indicates whether disease is spreading at an increasing rate (a growing epidemic) or decreasing rate (a diminishing epidemic) (Miller, 1976). *EDR'* was converted into a dichotomous variable based on the criterion value of 1.

Non-parametric methods were used because distributions were highly skewed, and the assumptions for parametric methods to estimate were violated. The median values and their 95% confidence intervals for the outcome values were computed based on the non-parametric bootstrap method as described by Efron and Tibshirani (1993). Preliminary, precisions of the estimates, or widths of confidence intervals (upper/lower confidence limit – median) for varying sizes of bootstrap samples were evaluated by plotting the width of the confidence intervals by sample size. The optimal number of iterations was determined as the point above which addition of iterations would not greatly improve the precision of the estimate, by visually evaluating the plots. A new categorical variable, *qCIP* was created, based on the quantiles of *CIP* with the levels that satisfied the sample size criteria. Within each group, categorised by region, *EDR'* and *qCIP*, the estimated median values of the simulated outcomes were computed by the bootstrap method, and evaluated.

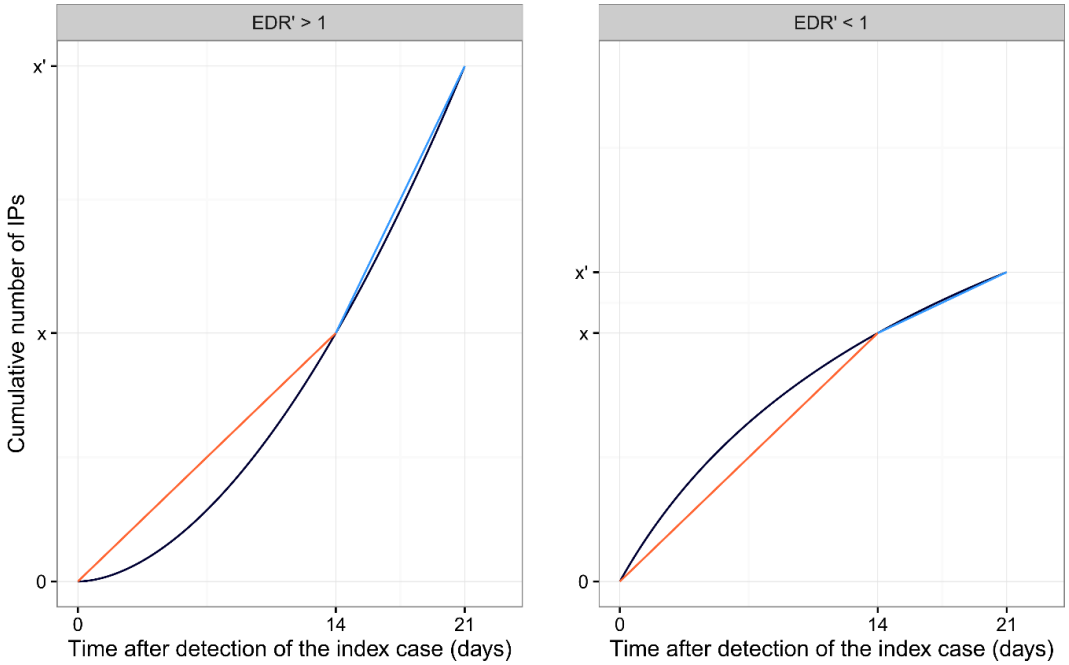

Figure 6-2 Cumulative epidemic curves with a crude estimated dissemination rate (*EDR'*) greater than 1 [left] and smaller than 1 [right], representing a growing epidemic and a diminishing epidemic. *EDR'* is calculated as the slope of line between days 14 and 21 (blue) divided by that of days 0 and 14 (orange).

6.4. Results

6.4.1. Descriptive statistics of the simulated epidemics

In total, 1,284 and 2,055 epidemics were simulated using unique seed premises, of which 90 (7.0%) and 100 (4.9%) died off without any cases being detected and 181 (14.1%) and 1,133 (55.1%) were controlled within 21 days by SO, for high and low density regions, respectively. The following analyses used the remaining 1,013 (78.9%) and 822 (40.0%) simulated epidemics, which lasted for longer than 21 days by SO, for high and low density regions, respectively.

The cumulative density functions of the two epidemiological outcomes in the high and low density regions are shown in Figure 6-3 A and B. In the high density region, simulated epidemics lasting for $\geq$21 days and controlled by SO resulted in a median of 207 (5^{th} and 95^{th} percentiles: 11 and 718) IPs and 116 (29 and 276) days till eradication, which was reduced by emergency vaccination to a median of 57 (10 and 226) IPs and 46 (29 and 74) days till eradication. In contrast, in the low density region, the scale of the epidemic was relatively small with SO, i.e., a median of 18 (5^{th} and 95^{th} percentiles: 6 and 75) IPs and 39 (25 and 87) days till eradication, which was similar to the results of emergency vaccination, i.e., 17 (5^{th} and 95^{th} percentiles: 6 and 62) IPs and 36 (25 and 60) days. The percentages of epidemic outcomes with emergency vaccination smaller than that of SO were 95.4% and 93.6% for the total number of IPs and time to eradication in the high density region, while these percentages were reduced to 72.5% and 76.0% in the low density region.

The cumulative density functions of the two economic outcomes in the high and low density regions are shown in Figure 6-3 C and D. The estimated direct costs by SO were a median of USD 119 (5^{th} and 95^{th} percentiles: 32 and 504) million and USD 45 (5^{th} and 95^{th} percentiles: 31 and 84) million, for the high and low density region, respectively. The percentages of the estimated direct costs smaller than that of SO was 64.1% (VTD) and 84.3% (VTL/VTL*) in the high density region. In the low density region, the direct costs by VTL/VTL* were similar to that of SO, while the direct costs by VTD was always higher than that of SO.

The estimated macroeconomic costs by SO were a median of USD 10.3 (6.3 and 17.9) billion and USD 6.7 (6.1 and 9.0) billion, for the high and low density region, respectively. The percentages of the estimated macroeconomic costs smaller than that of SO were

77.5% (VTD), 40.3% (VTL) and 93.6% (VTL*) in the high density region, and 16.5% (VTD), 0.2% (VTL) and 76.0% (VTL*) in the low density region.

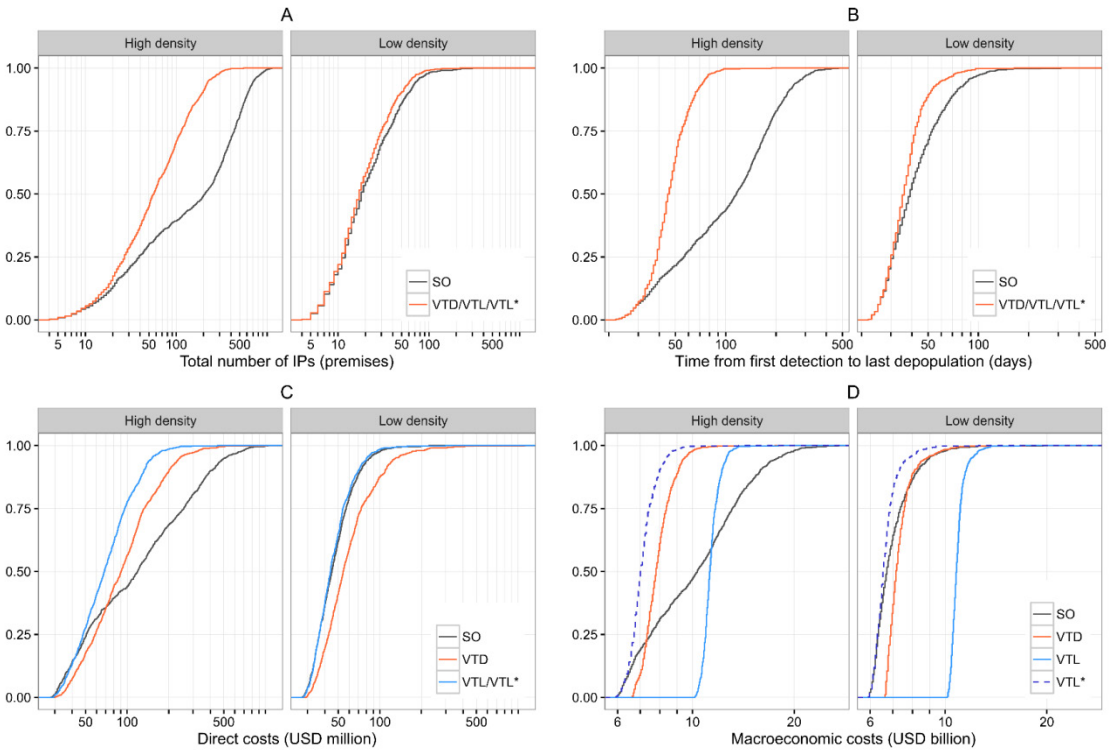

Figure 6-3 Cumulative distribution functions of the [A] total number of infected premises (IPs), [B] time till eradication, [C] direct costs and [D] macroeconomic costs for simulated foot-and-mouth disease (FMD) epidemics lasting for ≥21 days in the high and low density regions in New Zealand, controlled by stamping-out (SO), vaccinate-to-die (VTD), vaccinate-to-live (VTL), and vaccinate-to-live with 3 month waiting period (VTL*) (1,013 and 822 iterations for high and low density regions).

6.4.2. Non-parametric data analyses

The variability in the estimated median values for varying size of bootstrap samples is illustrated in Figure 6-4. The precision of the estimates improved to a relatively greater extent with an increase in the sample size from 0 to ~75 and from 0 to ~50 for high and low density region, respectively. The variability in the estimates was rather constant regardless of an increase in the sample size greater than these numbers. The optimal number of samples was thus determined as 75 and 50 for high and low density regions, respectively. The absolute scale of the variability in the estimates for high density region was always greater than that of low density region.

The effectiveness of vaccination policy, measured by median reduction in the simulated total number of IPs and time till eradication, is presented in Figure 6-5. In the high density region, there was a trend of a greater reduction in the total number of IPs by vaccination, with an increase in *CIP* measured on day 14. This reduction was in general greater with $EDR' > 1$ than $EDR' \leq 1$ measured on day 21 (Figure 6-5A, left). In the low density region, the median reduction in the total number of IPs was minimal and occurred only when $EDR' > 1$ and $CIP \geq 8$ (60% percentile), or $EDR' \leq 1$ and $CIP \geq 25$ (86% percentile) (Figure 6-5A, right). Similar trend was observed for reduction in time till eradication (Figure 6-5B).

Figure 6-6 shows the median reduction in the estimated direct costs by VTD or VTL/VTL*. The median reduction in the direct costs was always greater with VTL/VTL* than with VTD. In the high density region, the median reduction in the direct costs for VTL/VTL* was greater than 0 when $EDR' > 1$ with any values of *CIP*, or $EDR' \leq 1$ and $CIP \geq 15$ (60% percentile), while it was such for VTD when $EDR' > 1$ and $CIP \geq 12$ (38% percentile) or $EDR' \leq 1$ and $CIP > 27$ (80% percentile). In the high density region, there was an increasing trend in the median reduction in direct costs with an increase in *CIP,* reaching USD 71.7 - 140.0 million and USD 24.5 - 74.6 million for VTL/VTL* and VTD, respectively (Figure 6-6, top). In the low density region, the median reduction in direct costs by VTL/VTL* was consistently around USD 0 million, while that of VTD was always negative and decreased with an increase in *CIP*, reaching -USD 23.7 - -25.1 million (Figure 6-6, bottom).

Figure 6-7 shows the median reduction in the estimated macroeconomic costs by VTD, VTL or VTL*. The median reduction in the direct costs was always greater with and in the order of, VTL*, VTD and VTL. In the high density region, the median reduction in

the macroeconomic costs was always greater than 0 except for *EDR'* $\leq$ 1 and *CIP* < 9 (20% percentile) with VTL*, always greater than 0 except for *EDR'* $\leq$ 1 and *CIP* < 15 (40% percentile) with VTD, and marginally greater than 0 ($\leq$ USD 0.3 billion) when *EDR'* > 1 and *CIP* $\geq$ 32 (75% percentile) with VTL. In the high density region, the median reduction in macroeconomic costs was at most USD 4.5 billion, USD 3.2 billion and USD 0.3 billion with VTL*, VTD and VTL, respectively (Figure 6-7, top). In the low density region, the median reduction in macroeconomic costs was at most USD 0.3 billion, -USD 0.5 billion, and -USD 3.9 billion for VTL*, VTD and VTL, respectively. The median reduction in macroeconomic costs by VTD and VTL was always negative, while it was greater than 0 for VTL* when *EDR'* > 1 and *CIP* > 12 (80% percentile) or when *EDR'* $\leq$ 1 and *CIP* > 19 (75% percentile) (Figure 6-7, bottom).

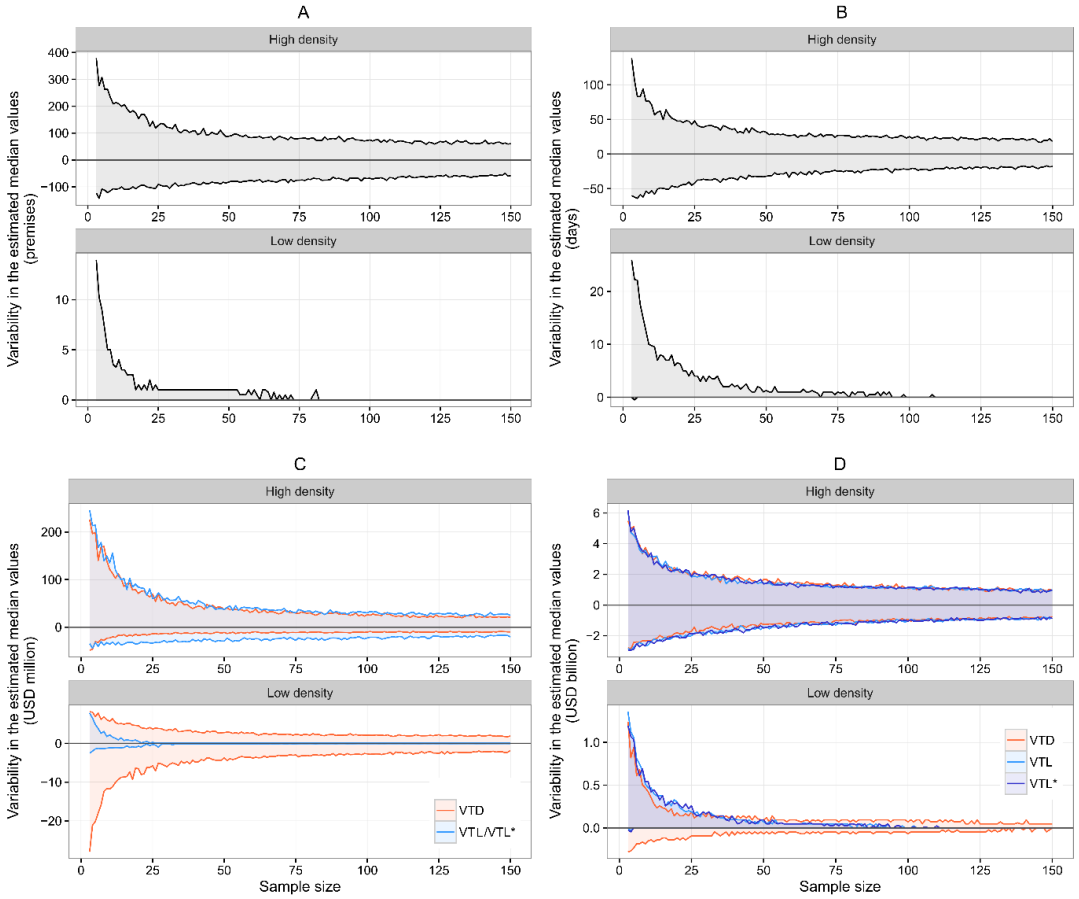

Figure 6-4 Variability in the estimated median values, measured by upper/lower 95% confidence limits minus median, for varying sizes of bootstrap samples, for simulated four outcome variables: reduction in the total number of infected premises (IPs) [A], time to eradication [B], direct costs [C] and macroeconomic costs [D] by region (high/low density) and control policy (vaccinate-to-die: VTD and vaccinate-to-live: VTL and VTL*).

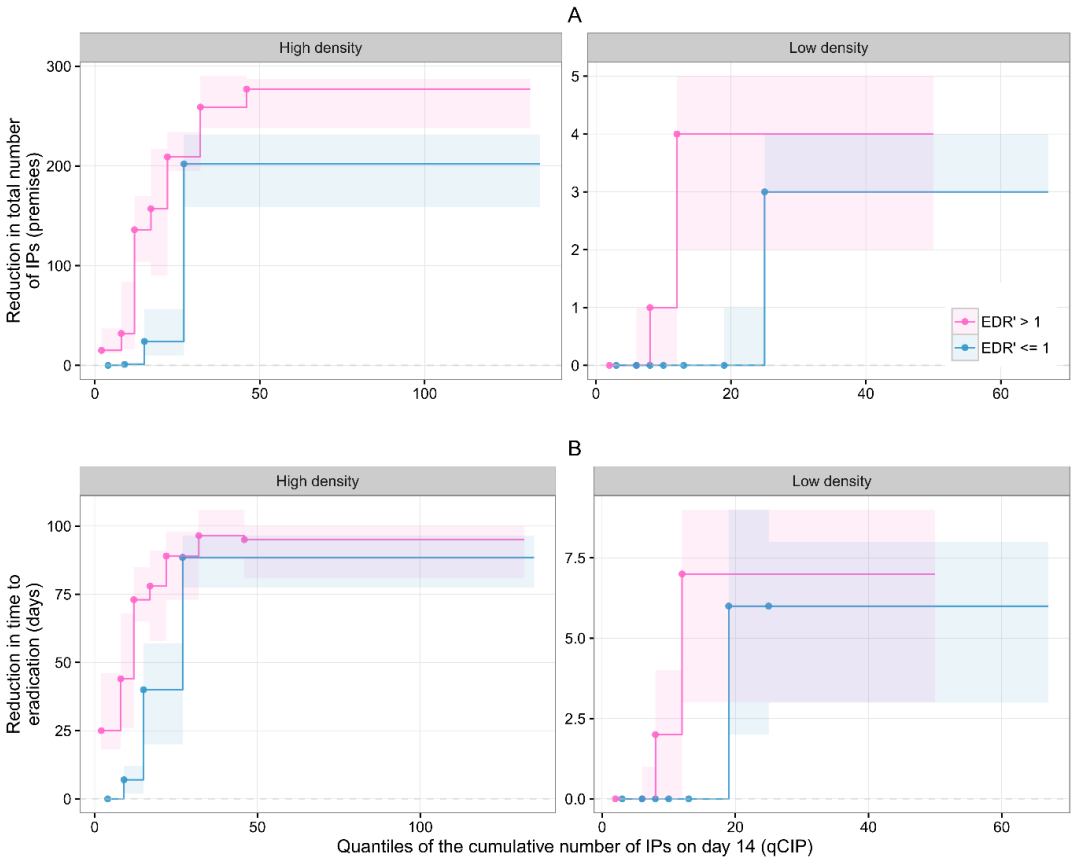

Figure 6-5 Effectiveness of vaccination policy (3-km ring vaccination starting on day 21 after detection of the primary case) in reduction of the total number of IPs [A] and time to eradication [B], presented as bootstrap median values (points) with their 95% CI (shade) by the region of incursion (*region*), estimated dissemination rate ≤ 1 or > 1 (*EDR'*) and the lower limits of the quantiles of the cumulative number of infected premises (IPs) on day 14 (*qCIP*) for simulated foot-and-mouth disease (FMD) epidemics lasting for ≥ 21 days in New Zealand (n = 42 - 113).

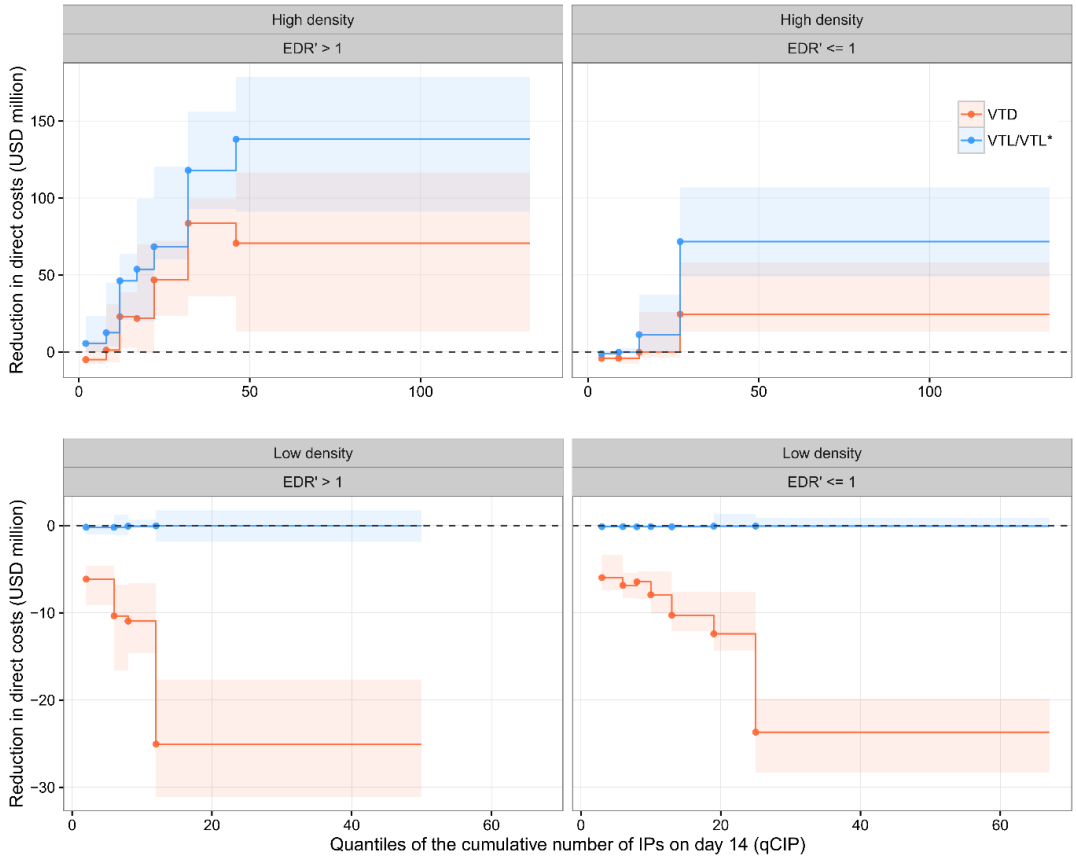

Figure 6-6 Effectiveness of vaccination policy (vaccinate-to-die: VTD and vaccinate-to-live: VTL/VTL*, both applied within 3 km on day 21 onwards after detection of the primary case) in reduction of the direct costs, presented as bootstrap median values (points) with their 95% CI (shade) by the region of incursion (*region*), estimated dissemination rate ≤ 1 or > 1 (*EDR'*) and the lower limits of the quantiles of the cumulative number of infected premises (IPs) on day 14 (*qCIP*) for simulated foot-and-mouth disease (FMD) epidemics lasting for ≥ 21 days in New Zealand (n = 42 - 113).

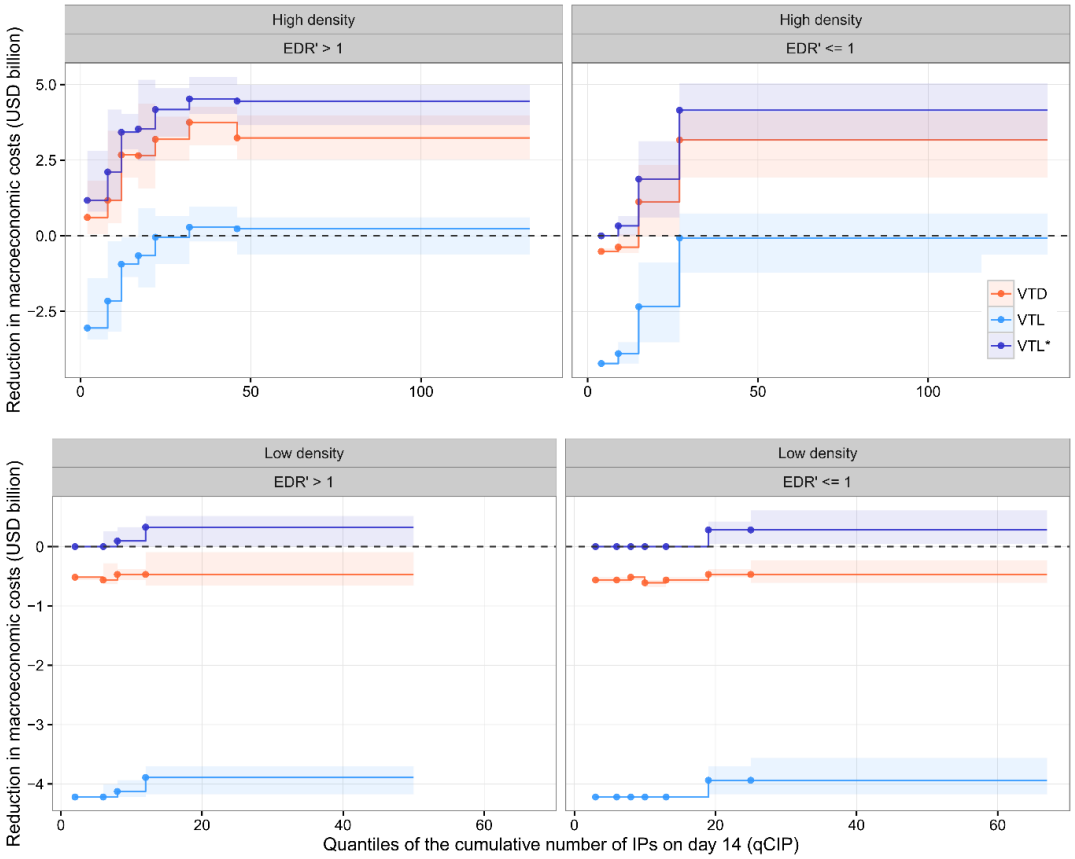

Figure 6-7 Effectiveness of vaccination policy (vaccinate-to-die: VTD and vaccinate-to-live with or without an additional 3-month waiting period: VTL/VTL*, all applied within 3 km on day 21 onwards after detection of the primary case) in reduction of the macroeconomic costs, presented as bootstrap median values (points) with their 95% CI (shade) by the region of incursion (*region*), estimated dissemination rate ≤ 1 or > 1 (*EDR'*) and the lower limits of the quantiles of the cumulative number of infected premises (IPs) on day 14 (*qCIP*) for simulated foot-and-mouth disease (FMD) epidemics lasting for ≥ 21 days in New Zealand (n = 42 - 113).

6.5. Discussion

For countries such as New Zealand, which rely heavily on export of animal products, making a rational decision regarding use of emergency vaccination in the face of an FMD outbreak is crucial for mitigating the potentially devastating impacts of trade bans due to FMD. This study demonstrated an approach to inform decision making using simulation modelling, whereby the epidemiological and economic effectiveness of alternative vaccination policies were evaluated for a range of epidemiological situations. The results indicated that addition of VTD to SO could be the most beneficial option compared with SO alone or VTL under the current OIE ruling, in terms of greater savings in the macroeconomic costs (median: <USD 4.5 billion) and direct costs (<USD 74.6 million), in a high livestock premises density area, and a greater number of IPs or dissemination rate > 1 at the initial phase of an epidemic. Otherwise, addition of emergency vaccination could increase the direct costs (<USD 22.2 million) and macroeconomic costs (<USD 4.2 billion) of an epidemic, relative to that of SO alone. These implications were intuitive and in line with the findings in other studies, in that the probability of an extreme outbreak was reduced with emergency vaccination (Hagerman et al., 2012) and the benefit of emergency vaccination was maximal in large epidemics with resource constraints (Kobayashi et al., 2007a). It should be noted, however, that these implications would be subject to the assumptions made on the efficacy, costs or value loss, and application (e.g., radius and timing) of vaccination, the scale and the extent of disease spread (e.g., local spread and movement patterns), efficiency of the baseline control measures (e.g., resource constraints for stamping-out activities and compliance to movement restrictions), and macroeconomic shock assumptions (e.g., trading partner reactions).

The effectiveness of emergency vaccination was sensitive to the proposed three epidemiological variables, i.e., density of the region of FMD incursion, the cumulative number of IPs and an EDR, which were quantifiable during 2 – 3 weeks of the initial response phase, suggesting they could be useful indicators for decision making regarding whether or not to use emergency vaccination. A higher value for each of these variables would indicate a large-scale, long-lasting epidemic, as suggested by their correlations with the total number of IPs (0.28 - 0.54) and time to eradication (0.27 - 0.59), contributing to greater savings in the direct costs or macroeconomic costs by emergency vaccination. Similarly, other studies (Halasa et al., 2013, Hutber et al., 2006) demonstrated an effective use of quantifiable information available early in the epidemic (i.e., cumulative number of

IPs and area of the detected area) to determine whether vaccination would be economically viable.

This study examined only application of emergency vaccination to all animal species in a 3-km ring radius of an IP on day 21 after detection. While the timing to start emergency vaccination would be constrained by a logistic delay for preparing vaccines, it is possible that the implications would be influenced by changes in the application of vaccination. More simulation studies, as done by Tildesley *et al.* (2006) should be conducted to determine optimal vaccination strategies.

There are great uncertainties regarding value losses of vaccinated animals for both VTD and VTL, due to absence of experiences in New Zealand. For VTD, there is currently no stipulated plan agreed by the stakeholders regarding the methods of culling, processing and marketing. Although in this study the whole market values of vaccinated animals were assumed as the cost of culling and partial value loss, the direct costs for VTD could be lower, if there were a higher salvage value in vaccinated animals by processing them into products with long shelf life, and expanding accessible markets under such situations. Also, the direct costs for VTD could be higher, if vaccinated animals were culled and disposed of on premises, as occurred in Japan in 2010(Muroga et al., 2012). There should be more discussions around these issues among trading partners and stakeholders, to save avoidable costs and loss due to culling vaccinate animals by VTD policy. For VTL, while this study made an optimistic assumptions of no value loss in vaccinated animals, there may be reduction in the value of products from vaccinated animals (and potentially products originating from non-vaccinated animals) due to limited access to both domestic and international markets, under the current standards of OIE (Anonymous, 2014g), which may influence the long-term production and macroeconomic impacts. These uncertainties, which may increase the direct and macroeconomic costs for VTL, were not considered in this study, because VTL was not preferred in terms of no reduction in the macroeconomic costs, with the optimistic assumptions. However, it is likely to be an important issue, which will influence the attractiveness of this policy, if, for example, the waiting period was aligned with other policies in the OIE code, or VTL was preferred by the stakeholders based on other criteria, which were not quantified in this study. Particularly, there is a recent shift in international attitudes toward VTL policies, due to the improvement in technologies to differentiate infected from vaccinated animals by DIVA tests (Paton et al., 2014, Geale et al., 2015, Barnett et al., 2015). If alignment of

waiting periods for a VTL and VTD policies were justified and the OIE code were changed, the use of a VTL policy would become a strong alternative strategy for the control of an FMD outbreak, which would bring benefits in terms of mitigating risks, reducing direct costs, minimising the damage of livestock industries and the impact on the country's economy.

At an early phase of an epidemic, animal health decision makers are under enormous pressure to bring an outbreak under control. It is reasonable to assume that disease control measures will not be met with universal approval from all stakeholder groups. At this time arguments among stakeholders concerning the appropriateness of different control measures (SO alone vs VTD vs VTL) often tend to be counter-productive and serve to undermine the general level of confidence in the ability of the animal health authority to bring the situation under control (Kahn, 2009). In this regard, the Government Industry Agreements (GIA) for biosecurity readiness and response in New Zealand are being set up, which will provide joint and informed decision making and manage relationships between industries and government, to achieve favourable outcomes (Anonymous, 2015a).

It is proposed that the analyses presented in this paper provide a useful starting point to encourage informed discussion around disease control measures that would be appropriate for a range of incursion scenarios, such as an interactive industry workshop where researchers, industries, and policy makers exchange ideas about an FMD outbreak. What is meant by 'interactive' in this context is that participants would be presented with a set of model outputs and, following discussion of the results, further simulations might be carried out to allow them to better understand the relationship between the onset of controls and epidemic outcomes. If this process were carried out well in advance of an outbreak, an animal health authority could do a much better job 'preparing' industry groups for unfavourable control measures, which would help eliminate counter-productive public argument during an outbreak, allowing disease control measures to be applied with minimum delay. In addition, it would serve as an important reminder to stakeholder groups of the importance of early detection and prompt application of, and strict adherence to, control measures. It should be noted, however, that the whole approach used in this study is predicated on the only important aspect represented by economic terms. It is entirely possible that other stakeholders, particularly those who are not directly involved in the peace time discussion, will value other aspects (animal welfare,

environmental issues, business continuity, human welfare, etc.) more than the economic criteria.

6.6. Conclusion

This study demonstrated that the effectiveness of emergency vaccination generally increased by density of livestock premises, an estimated dissemination rate (EDR) and the cumulative number of IPs in the initial 2 – 3 weeks of an epidemic. In terms of the macroeconomic costs, vaccinate-to-die was preferred under the current OIE's rulings with a maximum median reduction of USD 4.5 billion, if an outbreak occurred in the high density region, and EDR and the cumulative number of IPs in the early phase were relatively high. Otherwise, stamping-out alone was preferred. Vaccinate-to-live would be potentially advantageous in terms of reduction in the macroeconomic costs, if the waiting period were aligned with other policies.

6.7. Acknowledgements

This study was partially funded by Hokkaido University International Training Program, Massey University Doctoral scholarship, and the Morris Trust. We thank Dr Robert Sanson for his work on NZSM, Bryan O'Leary, Masood Sujau, and Simon Verschaffelt for their support in simulation, Ashley Lienert for his advice on macroeconomics and Rod Forbes, Andre van Halderen, Paul Bingham, Katie Hickey, Bex Ansell, Katie Owen and Thomas Rawdon at MPI for their assistance while developing the economic parameters.

6.8. Supplementary data

Appendix 6-1 Parameters for New Zealand Standard Model (NZSM) for simulation of a foot-and-mouth disease (FMD) epidemic

Parameters	Values
Disease transmission	
(1) Movements	
(i) Distance probability	
High risk, between-herd	0 to 20 km: 71%, 20 to 40 km: 18%, 40 to 60 km: 3%, 60 to 80 km: 4%, 80 to 100 km: 1%, 100 to 200 km: 2%, and 200 to 1000 km: <1%
Medium risk, between-herd	0 to 20 km: 81%, 20 to 40 km: 12%, 40 to 60 km: 2%, 60 to 80 km: 2%, 80 to 100 km: <1%, 100 to 200 km: 1%, and 200 to 1000 km: 1%
Low risk, between-herd	0 to 20 km: 91%, 20 to 40 km: 5%, 40 to 60 km: 2%, 60 to 80 km: 1%, 80 to 100 km: 0%, 100 to 200 km: <1%, and 200 to 1000 km: <1%
Pastoral livestock, via saleyards	0 to 80 km: 95%, 80 to 120 km: 3%, and 120 to 900 km: 2%
Breeding pigs, via saleyards	0 to 50 km: 69%, 50 to 100 km: 14%, 100 to 150 km: 7%, 150 to 200 km: 6%, 200 to 250 km: 1%, and 250 to 400 km: 2%
(ii) Frequency [1]	
High risk, between-herd	Poisson distribution, λ = 0.03 (PL), 0.04 (DR), 0.11 (GD and PB), and <0.01 (HB)
Medium risk, between-herd	Poisson distribution, λ = 0.47 (PL), 0.88 (DR), 0.91 (GD), 0.33 (PB), 0.29 (PF), and 0.14 (HB)
Low risk, between-herd	Poisson distribution, λ = 0.26
Pastoral livestock, via saleyards	Poisson distribution, λ = 0.01 (PL and DR), <0.01 (GD and HB)
Breeding pigs, via saleyards	Poisson distribution, λ = 0.01 (PB), and <0.01 (HB)
(iii) Transmission probability [2]	
High risk, between-herd	Day 1: 53% (PL and HB), 62% (DR), 67% (GD) and 46% (PB), day 2 to 11: 80%, and day 12 to 16: 100%
Medium risk, between-herd	Day 1: 10%, day 2 to 6: 20%, day 7 to 11: 40%, and day 12 to 16: 50%
Low risk, between-herd	Day 1: 2%, day 2 to 6: 4%, day 7 to 11: 9%, and day 12 to 16: 10%
Pastoral livestock/breeding pigs, via saleyards	Day 1: 46%, day 2 to 11: 78%, and day 12 to 16: 100%
(iv) Number of contacts	
High/medium/low risk, between-herd	Constant, 1.0
Pastoral livestock/breeding pigs, via saleyards	Poisson distribution, λ = 1.9 (PL) and 2.6 (PB)
(2) Local spread	
(i) Transmission probability [3]	
Day -1	0 to 1 km: 0, 1 to 2 km: 0, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 0	0 to 1 km: 7, 1 to 2 km: 2, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 1	0 to 1 km: 12, 1 to 2 km: 3, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 2	0 to 1 km: 12, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 3	0 to 1 km: 9, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
(ii) Adjustment	
Relative susceptibility by species	1.0 (cattle), 0.9 (sheep, goats and deer) and 0.8 (pigs)
Detection status	1.0 (undetected) and 0.5 (detected)

Disease characteristics	
(1) The onset of clinical signs	Day*2 1: 0%, day 2: 4%, day 3: 16%, day 4: 33%, day 5: 77%, day 6: 79%, day 7: 83%, day 8: 88%, day 9: 91%, day 11: 95%, day 12: 97% and day 16 onwards: 98%
(2) The onset of infectivity	Day*2 1 to 16: 100%, day 17: 94%, day 18: 88%, day 19: 82%, day 20: 76%, day 21: 71%, day 22: 65%, day 23: 59%, day 24: 53%, day 25: 47%, day 26: 41%, day 27: 35%, day 28: 29%, day 29: 23%, day 30: 17%, day 31: 12%, day 32: 6% and day 33 onwards: 0%
Control measures	
(1) Depopulation	
(i) Start date [4]	Day 0
(ii) Resource [4]	
Day 0 to 4	Day 1: 1, day 2: 2, day 3: 10, and day 4: 20 (premises/day)
Day 5 onwards	Triangular distribution, {minimum, mode, maximum} = {0, 4, 8} (PL), {1, 4, 7} (DR), {0, 4, 7} (GD), {0, 4, 7} (PB/PF), and {0, 1, 2} (HB) (days/premises)
(2) Vaccination	
(i) Start date [4]	Day 21
(ii) Radius	3 (km)
(iii) Resource	200 (premises/day)
(iv) Suppression in infectivity [5]	Day 4 onwards: 50%
(v) Efficacy [5]	Day 1 to 3: 0%, day 4: 50%, day 5: 75%, and day 6: 100%
(3) Surveillance	
(i) Detection probability	
Background surveillance (DR, PB and PF)	Day 1: 6%, day 2: 16%, day 3: 21%, day 4: 17%, day 5: 13%, day 6: 9%, day 7: 6%, day 8: 4%, day 9: 3%, day 10: 2%, day 11 to 13: 1%, day 14 onwards: <1%
Background surveillance (PL, GD and HB)	Day 1: 2%, day 2: 6%, day 3 to 5: 9%, day 6: 7%, day 7 to 8: 6%, day 9 to 11: 5%, day 12 to 14: 4%, day 15 to 17: 3%, day 18 to 20: 2%, day 21 to 26: 1%, and day 27 onwards: <1%
Passive surveillance (DR, PB and PF)	Day 1: 7%, day 2: 20%, day 3: 24%, day 4: 17%, day 5: 11%, day 6: 7%, day 7: 5%, day 8: 3%, day 9: 2%, day 10 to 12: 1%, and day 13 onwards: <1%
Passive surveillance (PL, GD and HB)	Day 1: 3%, day 2: 7%, day 3: 10%, day 4: 9%, day 5: 8%, day 6: 7%, day 7: 6%, day 8 to 10: 5%, day 11 to 14: 4%, day 15 to 16: 3%, day 17 to 20: 2%, day 21 to 24: 1%, day 25 onwards: <1%
Patrol visit	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (high risk)	Constantly 100%
Tracing (medium risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (low risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
(ii) Buffer for patrol visit (km)	3
(4) Movement restriction	
(i) Restriction probability	
First 14 days (initial standstill)	High risk: 91%, medium risk: 60%, and low risk: 24%
Day 15 onwards: inside 3 km infected zone	High risk: 94%, medium risk: 80%, and low risk: 39%
Day 15 onwards: inside 10 km surveillance zone	High risk: 95%, medium risk: 85%, and low risk: 52%
Day 15 onwards: outside 50 km control area	High risk: 100%, medium risk: 90%, and low risk: 80%

1 Classification of New Zealand livestock premises: PL (pastoral livestock enterprise), DR (dairy enterprise), GD (dry grazing enterprise), PB (breeding pig enterprise), PF (finishing pig enterprise) and HB (hobby farms).
2 Relative to the date of infection.
3 Relative to the onset of clinical signs.
4 Relative to the date of detection of the index case.
5 Relative to the date of application of vaccination.

6.9. References

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7. Economic optimisation of a vaccination-based control strategy for a foot-and-mouth disease epidemic in New Zealand

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7.1. Abstract

Optimal decision making for control of a foot-and-mouth disease (FMD) epidemic in previously FMD-free countries is challenging under great uncertainty about complex interplay of epidemiologic, logistic, economic and political factors. The purpose of this study was to determine an economically optimal strategy of FMD, for a simulated FMD epidemic seeded in the Auckland Region, with local spread potential similar to that of the Cumbria outbreak in 2001, and lasted for longer than 21 days with stamping-out alone (SO). The data were generated by extensive simulation of FMD epidemics randomly seeded, and controlled by SO, vaccinate-to-die (VTD), vaccinate-to-live (VTL) or VTL with a hypothetical shortened waiting period (VTL*), using the pre-developed epidemiological-economic disease modelling system. Generalised additive models (GAMs) were fitted to the data to explain the relationships between vaccination radius (*radius*) and the net present values (NPVs) of vaccination, while accounting for the uncertainty in four other variables. The prediction of GAMs showed that VTL* resulted in the highest NPVs, followed by VTD with a modest ring radius (1 km). The positive predicted net present vales (NPVs) for VTD were robust to the uncertainty in *resource* (100 – 500 premises/day), *effectiveness* (75 – 100%), cumulative number of infected premises on day 14 (1 – 71 IPs) and estimated dissemination rate on day 21 (0.1 – 8.5), but sensitive to *radius*. The predicted NPVs of VTL* was always positive, while it was always negative for VTL. The implications of this analysis are useful for contingency planning and decision making for FMD control in New Zealand, while the methodology presented here can be applicable for other optimisation problems based on agent-based stochastic disease simulation models.

7.2. Introduction

Foot-and-mouth disease (FMD) is a highly contagious viral disease of cloven-hoofed animals. If FMD were introduced into a formerly disease-free country, primary control strategies typically include depopulation of infected premises (IPs), quarantine, active surveillance and movement controls. Due to resource constraints for depopulation activities, such early control efforts could fail to contain the disease to the initial infection zone at the early stage of an outbreak. Once disease outbreaks spread to multiple infection foci, as in the epidemic in the UK in 2001, the epidemic would become less controllable and prolonged, with a higher risk of developing an endemic state. To prevent further spread of infection with given logistical limitations, emergency vaccination can be used in addition to stamping-out. Emergency vaccination will protect targeted populations at high-risk of infection by creating an immune belt between infected and susceptible populations (Geering and Lubroth, 2002). In the historical epidemics in previously FMD-free countries, emergency vaccination was implemented within a 2 km radius around IPs in The Netherlands in 2001, a 10 km radius in the Republic of Korea in 2000 and Japan in 2010, and the whole country ('blanket vaccination') in Taiwan (1997), Uruguay (2001), and the Republic of Korea (2010), mostly within a month of the first detection (Muroga et al., 2012, Pluimers et al., 2002, Yang et al., 1999, Park et al., 2004, Park et al., 2013, Anonymous, 2001b). Except for the Netherlands (2001) and Japan (2010), vaccinate-to-live policies were used, where all vaccinated animals were not subsequently culled.

Over the last decade, there has been a shift of international attitudes towards the use of emergency vaccination for the control of FMD in formerly FMD-free countries. This is supported by various modelling studies in different FMD-free countries, showing the epidemiological as well as economic benefits over the costs of emergency vaccination (Hagerman et al., 2012, Kobayashi et al., 2007a, Backer et al., 2012, Wada et al., in preparation, Garner et al., 2014). While these studies estimated the effectiveness of a limited number of predefined vaccination strategies, it has been suggested that epidemiologically optimal vaccination strategies were influenced by various factors, such as ring radius, logistic resources, epidemiological conditions, vaccine effectiveness, characteristics of the virus strain and prioritisation for vaccination (Tildesley et al., 2006). Due to lack of local knowledge about complex interplay of epidemiologic, logistic, economic and political factors in the face of an epidemic, a poorly designed vaccination strategy would not bring its maximum possible benefits and, could even worsen the economic outcomes. Hence, it is valuable to know *a priori* how the epidemiologically or

economic optimal vaccination strategy might be influenced by the variation in the factors that have wide uncertainties for contingency planning and decision making.

As a country that relies heavily on export of livestock products, New Zealand is highly concerned about mitigating the economic impacts of an FMD epidemic if there were an incursion of FMD. As part of the preparedness programme for FMD, New Zealand has been reviewing potential use of emergency vaccination (Anonymous, 2003b, Anonymous, 2013a). In implementing vaccination strategies, decision makers need to consider not only epidemiological but also economic benefits of emergency vaccination, which may not necessarily match each other. This is because use of emergency vaccination could affect time to resume trade of livestock products. For international trades of livestock products, the OIE's official FMD-free status ('FMD-free where vaccination is not practised') is often a necessary requirement for importing countries to resume trade of livestock products from a country that has recently had an FMD outbreak. Acquiring this status indicates that the livestock commodities meets a sufficient level of biosafety, and facilitates access to lucrative international markets. Although in reality, factors other than the OIE's status are likely to affect the process of risk assessment, recovery of the FMD-free status in the shortest time possible would still be the key to minimise the economic impacts of an FMD epidemic for New Zealand. Under the current OIE ruling, time to recover the FMD-free status ('FMD-free where vaccination is not practiced') is three months after the last case for a 'stamping-out only' policy, three months after the slaughter of all vaccinated animals for a 'vaccinate-to-die' policy (i.e., stamping-out and emergency vaccination followed by subsequent culling), or six months after the last case or last vaccination for a 'vaccinate-to-live' policy (i.e., stamping-out and emergency vaccination without subsequent culling) (Anonymous, 2014g), making use of vaccinate-to-live less attractive than stamping-out alone or vaccinate to die.

This study aimed at identifying an economically optimal strategy for control and eradication of a hypothetical FMD epidemic in New Zealand, using adjusted New Zealand Standard Model (NZSM), a pre-developed stochastic simulation model for FMD (Sanson et al., 2006a). Stamping-out only, vaccinate-to-die, and vaccinate-to-live were compared for an epidemic in the high density region, considering different vaccination radii for the two vaccination strategies. The objective function to be minimised was measured as the long-term net economic impacts, including expenses for control and eradication of FMD and export losses. Robustness of the economically optimal decision

to variations in epidemiological conditions, logistical resources, and vaccine effectiveness was also examined.

7.3. Materials and methods

7.3.1. Stochastic modelling system

A stochastic modelling system was designed to estimate the effects of vaccinate-to-die (VTD), vaccinate-to-live (VTL) or VTL with a hypothetical change in the OIE's waiting period from 6 to 3 months (91 days) (VTL*) policies relative to stamping-out alone (SO), in terms of reduction in the total number of IPs, time to eradication, direct costs and macroeconomic costs, for simulated FMD epidemics in New Zealand. The modelling system was comprised of four sub-models, or sets of an FMD epidemic simulation model (section 7.3.2), direct cost module (section 7.3.3), and macroeconomic cost module (section 7.3.4), specific to SO, VTD, VTL and VTL*. For each run of the modelling system, each sub-model simulated an FMD epidemic for a single iteration and estimated its direct and macroeconomic cost, using the same seed premises randomly selected from the region of interest, with the same pseudorandom seed number for Monte Carlo sampling of stochastic parameters, with the only difference being the control policy (SO/VTD/VTL/VTL*).

The modelling system was repeatedly run to examine the effects of variations in the following three variables (one decision variable and two uncertain variables) on the outcome variable (NPV). The variables (and their presumed potential ranges) were: (i) *radius*, or vaccination radius (1 – 20 km), (ii) *resource*, or vaccination resource (100 – 500 premises per day), and (iii) *effectiveness*, or the proportion of premises protected by immunity among all vaccinated premises (75 – 100%). Using the Monte Carlo method, three values were randomly sampled from the three predefined distributions, i.e., uniform distributions with the presumed maximum and minimum values, for each run of the modelling system. In addition, two indicators which were shown to modify the effects of vaccination policies (Chapter 6) were recorded. The indicators were the cumulative number of detected IPs on day 14 (*CIP*) and the estimated dissemination rate on day 21, on the basis of a 7-day window (*EDR*).

The modelling system was repeatedly run for <48 hours, using 48 CPUs in parallel. A total of 18,000 rows of data (i.e., NPV, *radius*, *resource*, *effectiveness*, *CIP*, and *EDR*) were generated, which was sufficient for the analyses described in sections 7.3.5 and 7.3.6.

7.3.2. FMD epidemic simulation

FMD epidemic simulation was carried out by InterSpread Plus (Stevenson et al., 2012) ver. 4.02.17, using New Zealand Standard Model for FMD (NZSM) (Sanson et al., 2006a) as a template, with some modification as described below and shown in Appendix 7-1. The same assumptions used in the NZSM were used for disease spread; transmission of FMD occurred either by explicit contacts or local spread. For the former, the patterns of movements were estimated from the field survey in New Zealand (Sanson, 2005). For the latter, the local spread patterns specific to the outbreak in Cumbria, UK, in 2001 were extrapolated from the previous analysis (Sanson et al., 2006b).

The New Zealand national livestock database, AgriBase (Sanson and Pearson, 1997) was obtained from AsureQuality in April 2011. The data had a list of 81,759 premises with beef, dairy, deer, sheep, pigs and goats, recording their explicit locations, counts of animals and enterprise types. The Auckland Region was selected for incursion because of its characteristics for having a relatively high density of small-scale livestock premises (a total of 7,278 livestock holdings with 667,795 FMD-susceptible animals, 4,940 km^2).

The sub-model for SO simulated an FMD epidemic with the response parameters which were in line with the current New Zealand contingency plan (Anonymous, 2011c); active surveillance was conducted on premises within the 3-km high risk zone or those that were traced for high and medium risk movements; movement restrictions with a relatively high or low compliance were applied within the 10-km surveillance zone, or 50-km radius control area; detected IPs were depopulated at the enterprise-specific rate, considering resource limitations.

The sub-model for VTD, VTL or VTL* simulated an FMD epidemic with the same response parameters as those of SO, except for addition of emergency vaccination. Vaccination was applied on day 21 after detection of the index case, which was considered to be a realistic delay for arranging vaccines from overseas vaccine bank (Owen, personal communication). Vaccination was applied to premises locating in the ring buffers around all detected IPs, until no new infection was detected outside the current vaccination zone. A value for the radius of a ring was randomly chosen from a range between 1 and 20 km. Vaccination activities were constrained by the resource capacity, of which a value was randomly chosen from a range between 100 and 500 premises per day. A priority was given to premises locating in the outer radius. The effectiveness of vaccination was assumed to be 0%, 50%, and 75%, on day <3, 4, and 5 after application of vaccination,

respectively. A value for the effectiveness of vaccination after day 6 onwards was randomly chosen from a range between 75% and 100%.

7.3.3. Estimation of the direct cost of FMD

The direct cost of FMD was the aggregated short-term cost associated with eradication of the epidemic, i.e., active surveillance, movement restriction, depopulation and vaccination. For each simulated epidemic, its direct cost was estimated, using the direct cost module described in Chapter 5 (SO) and 6 (VTD/VTL/VTL*) with some modifications. For VTL or VTL*, the parameter for the percentage value loss of vaccinated animals was made stochastic, to account for its uncertainty. A uniform distribution with minimum and maximum of 0 and 100% was assigned.

7.3.4. Estimation of the macroeconomic cost of FMD

The macroeconomic cost of FMD was the cumulative net reduction in the GDP over 8 years in the present value, associated with the various shocks caused by an FMD epidemic, including export bans and tourism losses. A discount rate of 8% was used, which was the current rate commonly used for economic analyses in the public sectors in New Zealand (Makhlouf, 2015). The macroeconomic costs of simulated epidemics were estimated, using the macroeconomic module described in Chapter 5 (SO) and 6 (VTD/VTL/VTL*) with some modifications. For VTD, two parameters for determining the timing of recovery of OIE's FMD-free status were made stochastic, to account for their uncertainties. Specifically, the date of completion of culling all vaccinated animals was calculated by dividing the simulated number of vaccinated animals by a stochastic daily rate of subsequent culling of vaccinated animals, plus a stochastic delay for deciding when to start culling and arranging logistics (slaughterhouses and transport). For the rate of culling, a triangular distribution with minimum, mode and maximum of 2,800 (2010 – 2014 regional average rate), 4,100 (2010 – 2014 high season regional average rate), and 4,500 (2010 – 2014 regional maximum rate) (animals/day) was used (Statistics New Zealand, 2015). For the unknown delay, a uniform discrete distribution with a minimum and maximum of 0 and 14 (days) was used. Two weeks was considered to be the maximum possible delay, considering the Netherlands' strategy used in 2001 (Pluimers et al., 2002).

7.3.5. Nonparametric sensitivity analyses (PRCC)

The relative statistical importance of the uncertainty in explanatory variables on the outcome variables was evaluated by partial rank correlation coefficients (PRCCs), following the approaches described by Blower and Dowlatabadi (1994) and Owen *et al.* (2011). A PRCC is a measure of monotonicity between an input variable and an outcome variable, after removing the linear effects of all the other input variables (Marino et al., 2008). It is one of the most robust, efficient, and reliable techniques used in combination with the Monte Carlo sampling method, to identify the most influential parameters to the model response of an interest (Marino et al., 2008, Saltelli and Marivoet, 1990). Note the use of PRCCs is appropriate for outcome variables that are nonlinearly but monotonically related to the input parameters, but not if the relationship is non-monotonic. The methods of calculation of PRCCs and significance testing can be referred to the review by Marino *et al.* (Marino et al., 2008). A PRCC varies between -1 and +1. The sign of a PRCC indicates a negative or positive linear relationship between each input variable and each output variable, while its absolute value indicates the importance of the variation in the values of the input variable in contributing to the imprecision in the outcome variable.

Initially, the assumption on a monotonic relationship between the outcome variables and each explanatory variable was assessed by a visual evaluation of a scatter plot. PRCCs with their 95% CI were then calculated for each of the four outcome variables (i.e., reduction in the total number of IPs, reduction time to eradication, reduction in direct costs and reduction in macroeconomic costs) for the explanatory variables: *radius*, *resource*, *effectiveness*, *CIP* and *EDR* for each vaccination policy (VTD/VTL/VTL*), using an R package 'sensitivity' version 1.12.2 (Pujol et al., 2016).

7.3.6. Semiparametric response surface model (GAM)

Response surface models were built to determine the optimum *radius* while accounting for variation in the other uncertain explanatory variables (i.e., *resource*, *effectiveness*, *CIP* and *EDR*). A response surface model is an approximation model that best represents, or mimic the relationship between the decision variable and the objective function of the response system. As an objective function, a net present value (NPV), i.e., reduction in the sum of the direct costs and the macroeconomic costs (total costs) of an epidemic, was used as this variable took into account all epidemiological and economic consequences of an FMD epidemic.

Generalised additive models (GAMs) were used to fit models that represented the response of the system while controlling for variability. A GAM is an extension of a generalised linear model (GLM), with difference being that a GAM uses some smooth functions of covariates. The structure of GAMs in general is as follows (Wood, 2006):

$$g\{\mathbb{E}(y_i)\} = \beta_0 + \beta X_i^* + \sum_{j=1} L_{ij} f_j(x_{ij}) \quad (1)$$

where g is a link function, y_i is a response variable of ith observation, β_0 is an intercept, X_i^* is a row of the model matrix for the parametric model components, β is the corresponding parameter vector, f_j is a smooth function of the covariate x_{ij}, and L_{ij} is a linear function. Smooth functions can be estimated using a method within the spline family. For example, if cubic regression splines were used, piecewise cubic polynomials are fitted within each segment of the covariate and then polynomial lines are connected smoothly at each knot. The optimal smoothness, i.e., effective degrees of freedom (the number of knots), was estimated from the data within a specified maximum degree of freedom, k. All the GAM parameters were estimated using package 'mgcv' (Wood, 2015) in R version 3.2.2 (R Development Core Team, 2015).

For each policy and for each uncertain variable, a multivariable GAM was fitted using the following predetermined formula:

$$y = \beta_0 + f(radius, x) \quad (2)$$

where y is the NPV, x is an explanatory variable (*resource*, *effectiveness*, *CIP* and *EDR*), and f is the smooth function for a product of *radius* and x. Based on the fitted GAMs, the vaccination radii that minimised the predicted NPVs were determined for the quantiles of the sampled values for *resource* and *effectiveness*, or simulated values for *CIP* and *EDR*.

7.4. Results

7.4.1. Descriptive statistics of the simulated epidemics

Of 18,000 simulated epidemics randomly seeded in Auckland Region, 26% (n = 4,766) were contained within 21 days after detection of the index case by SO. Throughout the following analyses, only the results of the simulated epidemics in which at least one new case was detected on day 21 or later (n = 13,234) were used. The summary statistics of the simulated FMD epidemics and their economic outcomes, for SO, VTD, VTL and VTL* are shown in Table 7-1. Emergency vaccination reduced the simulated total number of

IPs from 108 to 63, and time till eradication from 77 to 46 days. The estimated median direct costs of simulated epidemics ranged from USD 79 million to 221 million, and the order from lowest to highest was SO, VTL/VTL* and VTD. The estimated median macroeconomic costs ranged from USD 7.1 billion to 11.3 billion, and the order from lowest to highest was VTL*, SO/VTD and VTL.

Figure 7-1 shows the cumulative density functions of the two epidemiological outcomes and two economic outcomes. All the distributions of the four outcome variables were right-skewed, indicating occurrence of extreme outcomes with a small probability. The long-tails for the total number of IPs (>520 IPs, <1%) and time to eradication (>230 days, <1%) for SO were not observed with emergency vaccination (Figure 7-1A and B). For the distributions of the direct costs, VTD had a relatively longer tail (>USD 1,850 million, <1%), whereas for the macroeconomic costs, a longer tail (>USD 16 billion, <1%) was observed for both SO and VTD.

Table 7-1 The median and the 5th and 95th percentiles (in parenthesis) of simulated foot-and-mouth disease (FMD) epidemics lasting for ≥21 days in the Auckland Region, controlled by stamping-out only (SO), vaccinate-to-die (VTD), vaccinate-to-live (VTL), and VTL with a hypothetical 3-month waiting period for recognition of FMD-free status (VTL*) (13,459 iterations).

	SO	VTD	VTL	VTL*
Silent spread phase [1] (days)	14 (7 and 25)	"	"	"
EDR [2]	1.4 (0.3 and 8.0)	"	"	"
CIP [3]	17 (2 and 70)	"	"	"
Total number of vaccinated premises	0 (0 and 0)	2,733 (273 and 7,676)	"	"
Total number of vaccinated animals ($\times 10^3$)	0 (0 and 0)	159 (13 and 818)	"	"
Total number of IPs	108 (12 and 397)	63 (11 and 222)	"	"
Time till eradication [4] (days)	77 (28 and 176)	46 (28 and 75)	"	"
Time to recover the OIE's FMD-free status	167 (118 and 266)	167 (132 and 248)	226 (209 and 257)	136 (119 and 167)
Direct cost (USD million)	79 (33 and 216)	221 (58 and 958)	177 (57 and 660)	177 (57 and 660)
Macroeconomic cost (USD billion)	8.5 (6.2 and 13.2)	8.5 (6.9 and 12.3)	11.3 (10.5 and 12.7)	7.1 (6.3 and 8.5)
Total cost (USD billion)	8.6 (6.2 and 13.3)	8.7 (6.9 and 13.2)	11.5 (10.6 and 13.2)	7.3 (6.4 and 9.0)

1 The interval between infection in the primary case and detection of the index case
2 Estimated dissemination rate on the 7-day basis on day 21
3 Cumulative number of detected infected premises (IPs) on day 14
4 The number of days taken from detection of the index case until depopulation of the last case
" Same as values on the left.

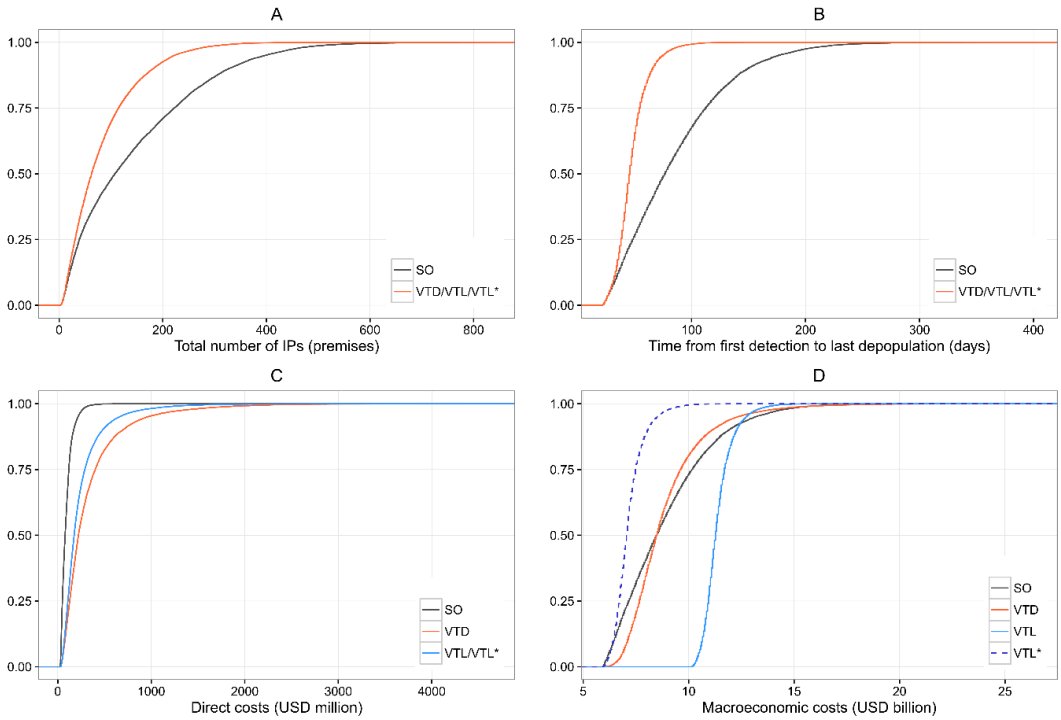

Figure 7-1 Cumulative distribution functions of the [A] total number of infected premises (IPs), [B] time till eradication, [C] direct costs and [D] macroeconomic costs for simulated foot-and-mouth disease (FMD) epidemics lasting for ≥21 days in the Auckland Region, controlled by stamping-out (SO), vaccinate-to-die (VTD), vaccinate-to-live (VTL), and vaccinate-to-live with a 3-month waiting period (VTL*) (n = 13,459).

7.4.2. PRCC

PRCCs between the explanatory variables and reduction in the total number of IPs, time to eradication, direct costs and macroeconomic costs of the simulated epidemics for each policy are shown in Figure 7-2. For the total number of IPs, PRCC values for *CIP*, *EDR* and *resource* (in the order of higher PRCC) were significantly positive, indicating an increase in these variables enhanced the effects of vaccination in reducing the total number of IPs. The magnitude of PRCCs for *CIP* and *EDR* were relatively high (0.3 – 0.4), indicating greater influence on reduction in the total number of IPs. For time to eradication, all explanatory variables resulted in significantly positive PRCC values, indicating an increase in any of the explanatory variables were associated with an increase in the effects of vaccination in shortening time to eradication. The magnitude of PRCCs were relatively higher for *CIP* and *EDR* (0.2 – 0.3) than *resource*, *radius* and *effectiveness* (<0.1), indicating the relative importance of these two variables. For direct costs, significantly negative PRCC values for *radius*, *CIP* and *EDR* (in the order of lower PRCC), indicated an increase in these variables were associated with an increase in direct costs. The degree of association was higher in the order of *radius*, *CIP* and *EDR*, and the association were generally stronger than that of VTL/VTL*. *Resource* and *effectiveness* were significantly greater than zero, although the magnitudes were small (<0.1). For macroeconomic costs, all the explanatory variables, except for *radius,* had significantly positive PRCC, indicating an increase in these variables were associated with a decrease in macroeconomic costs. The degree of association was higher in the order of *CIP*, *EDR*, *resource* and *effectiveness*, and the association of *CIP* and *EDR* were generally stronger for VTL/VTL* than that of VTD. *Radius* for VTD was significantly negative, indicating an increase in macroeconomic costs by an increase in *radius*.

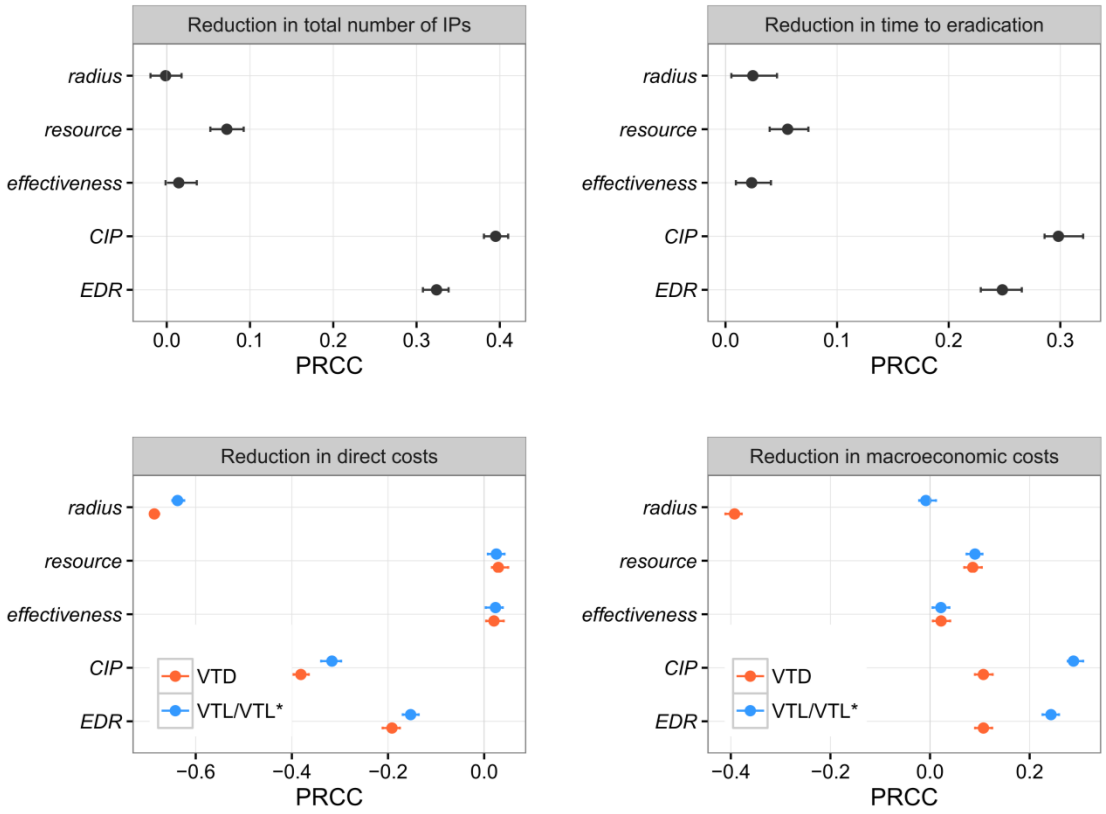

Figure 7-2 Partial rank correlation coefficients (PRCC) for varied explanatory variables: vaccination radius (*radius*, 1 – 20 km), resource capacity (*resource*, 100 – 500 premises/day), effectiveness of vaccination (*effectiveness*, 75% - 100%), cumulative number of IPs (*CIP*) and estimated dissemination rate (*EDR*) for four outcome variables for 21st-day start vaccinate-to-die (VTD), vaccinate-to-live (VTL), and vaccinate-to-live with a 3-month waiting period (VTL*) for control of a simulated foot-and-mouth (FMD) disease epidemic in Auckland Region (n = 13,459).

7.4.3. GAM

The predicted relationships between the NPVs and *radius* while adjusting for each of the four uncertain variables are shown in Figure 7-3. The explained deviance (R^2) was 14.1 – 14.8%, 0.3 – 2.5% and 0.3 – 2.4 % for VTD, VTL and VTL*, respectively. The predicted NPVs were generally higher in the order of VTL*, VTD and VTL, with the maximised predicted NPVs ranging from USD 0.9 to1.7 billion, from USD -2.9 to -1.9 billion, and from USD 1.3 to 2.3 billion for VTD, VTL and VTL*, respectively. While the predicted NPVs of VTL or VTL* was robust to the change in *radius* in terms of the consistent sign, that of VTD decreased, breaking even (i.e., NPV = 0) with vaccination radii of 8.1 – 10.8 km.

The optimum *radius* for each policy (dots in Figure 7-3) is plotted against each of the uncertain variables in Figure 7-4. For VTD, the optimum *radius* was constantly 1.0 km, except when *EDR* was <1.7 (*radius* <2.9 km). For both VTL and VTL*, the optimal *radius* ranged from 1.0 to 20.0 km (median: 5.6 km, 5^{th} and 95^{th} percentiles: 4.3 and 6.2 km). The optimal *radius* for VTL or VTL* was relatively robust to the change in *effectiveness* and *CIP*, whereas fluctuations were observed when *resource* <200, or *resource* >400, or *EDR*>10.

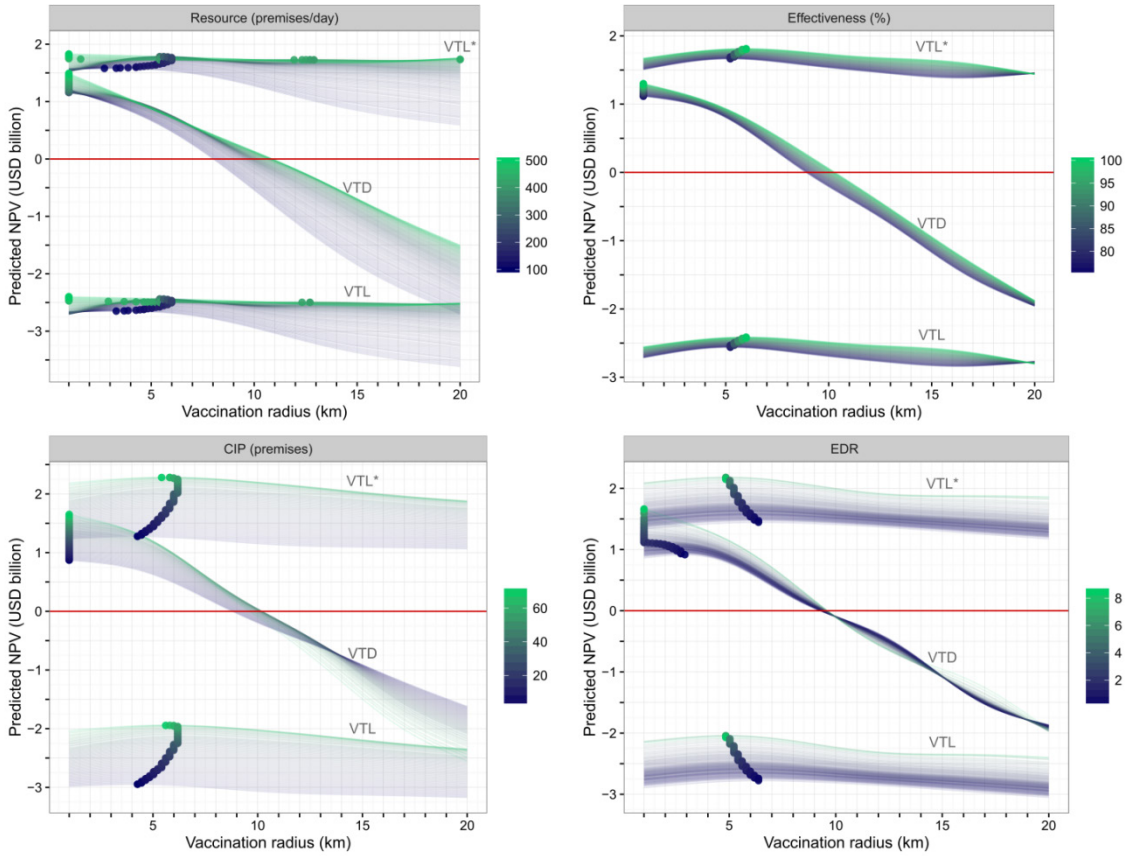

Figure 7-3 Predicted net present values (NPVs) of simulated foot-and-mouth disease (FMD) epidemics in the Auckland Region controlled by vaccinate-to-die (VTD), vaccinate-to-live (VTL), and VTL of a shortened waiting period (VTL*) relative to stamping-out alone, with varying vaccination radii, adjusted for resource capacity, effectiveness of vaccination, cumulative number of IPs (CIP) and estimated dissemination rate (EDR).

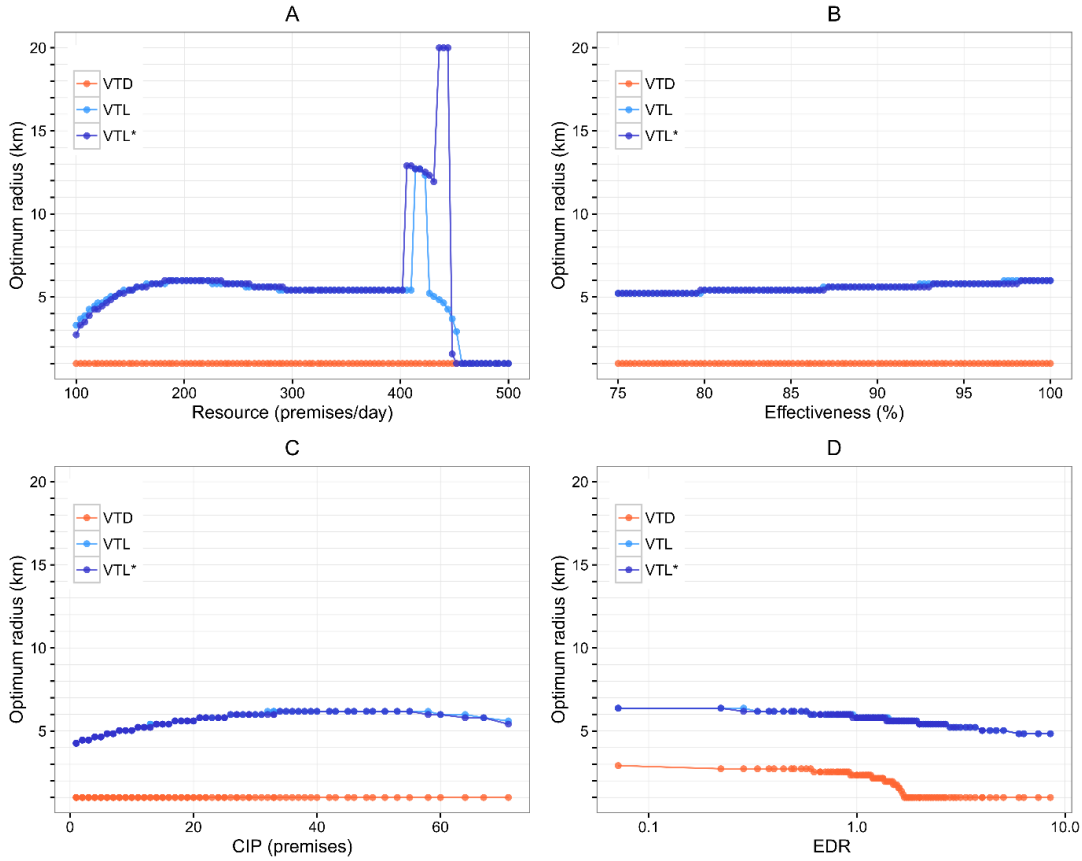

Figure 7-4 Optimal vaccination radius that minimised the predicted NPVs of vaccinate-to-die (VTD), vaccinate-to-live (VTL), and VTL of a shortened waiting period (VTL*) relative to stamping-out alone, while resource capacity [A], effectiveness of vaccination [B], cumulative number of IPs (*CIP*) [C] and estimated dissemination rate (*EDR*) [D] were varied to the quantiles of the designed or simulated values, for a simulated foot-and-mouth disease (FMD) epidemics in the Auckland Region.

7.5. Discussion

This study demonstrated a quantitative approach to determine an economically optimal vaccination radius for vaccination-based control strategies for a particular FMD incursion scenario. It was based on an extensive use of the recently developed FMD simulation modelling system, which subjoined the currently available epidemiologic and economic knowledge for New Zealand. It should be recognised that the resulting optimal vaccination radius was specific to the particular predefined scenario, and further sensitivity analyses would be required to test how it might be influenced by uncertainty in other unexamined epidemiological, logistic and economic parameters (e.g., local spread, resource for depopulation, discount rate, etc.). Nevertheless, studies of this kind would provide useful information for policy makers or disease modellers to understand how a particular aspect of a control measures would influence the epidemiological or economic outcomes of an epidemic, and draw implications on how its efficiency might be improved for similar situations. In addition, sensitivity analyses help prioritise the areas, where refining the current imprecise knowledge through further analyses, or further communications among researchers, policy makers and stakeholders, would influence determination of optimal control strategies.

The findings in general were intuitive, and made biological and economic sense. It was indicated that VTD was economically more advantageous than SO or VTL in terms of reduction in the overall costs of FMD (i.e., the sum of direct costs and macroeconomic costs). The net benefits of VTL were highly sensitive to the selection of vaccination radius, and in general, maximised with the examined minimum vaccination radius of 1.0 km. Under the current OIE's code, VTL was consistently a suboptimal option in terms of the increased overall costs of FMD due to the macroeconomic shock of lost export by a 3-month delay in recovering OIE's FMD-free status. If, ever, the waiting periods were aligned for all strategies, the use of VTL should be reconsidered, as this strategy would then become highly attractive in terms of reduction in the overall costs, as well as minimising the chance of extreme outcomes. With the assumed uncertain range, the optimal strategy was somewhat robust to the variations in the four uncertain explanatory variables: resource capacity (100 – 500 premises per day), vaccine effectiveness (75 – 100%), *CIP* (1 – 71 IPs) and *EDR* (0.1 – 8.5). In particular, robustness of the optimal strategy to the variation in vaccine effectiveness $\geq$75% implied a potential benefit of targeted VTD, such as cattle-only vaccination, which would minimise the costs of resources and compensation while maximising the benefits of emergency vaccination. The

sensitivity analyses by PRCC complementary added understandings of the optimal strategy; *radius* for VTD was the key factor that contributed an increase in both the direct and macroeconomic costs of an epidemic, while it was less important for the two epidemiological outcomes. This suggested that the additional costs of resource, compensation, prolonged time to complete culling, and resulting delay in recovery of FMD-free status by an increase in *radius* was relative more important than the greater savings achieved by more reduction in the total number of IPs and time to eradication.

In epidemiological terms (without considering the economic aspects), vaccination radius should be designed to encompass the range of local spread and a safety margin to include unidentified IPs, although there would be limited knowledge during the actual outbreak. The results of this study showed that the economically optimal vaccination radius for VTD (1 km) was smaller than the maximum assumed range of local spread (<3 km), and the risk of local spread existed at a relatively low level beyond the vaccination zone (<4 cases per 1,000 susceptible premises at risk per day). The optimal radius would be greater, if the risk of local spread for >1 km was greater (as estimated for the first 3 weeks of Cumbria outbreak in 2001, see Chapter 3). Variations in the pattern of local spread by various epidemiological factors were reported in the previous analyses of the field data (Wilesmith et al., 2003)(Chapters 3 and 4). It is desirable to consider the variability in the pattern of local spread, rather than treating them as constant. Although not examined in this study, prioritisation of vaccination within the vaccination zones is likely to be important for determining the optimal vaccination radius, as suggested by Tildesley *et al.* (2006), for a wider vaccination radius, smaller resource capacity, or a higher extent of local spread. This study considered outer-to-in vaccination, by which an immune belt was created from the outer to inner perimeter. If a vaccination radius was designed too large and the resource was insufficient to achieve an immediate vaccination in all premises within the vaccination zone, outer-to-in vaccination would not provide prompt protection in premises immediately at risk of infection, locating in the proximity of the current IPs. In such circumstances, alternative prioritisation (e.g., inside-out, larger herds/flocks, cattle, or random) may be more effective than outside-in in reducing the spread of disease. It is recommended that further simulation studies be carried out to examine the interaction among prioritisation of vaccination, vaccination radius (including <1 km), the local density of premises in the infected area, and patterns of local spread.

The analyses in this study were based on nonparametric, or semiparametric methods, because assumptions of linearity and additivity were considered inappropriate, and complex interactions were expected in the simulated data, which would be typical problems in data simulated by agent-based disease simulation models. PRCC was used for global sensitivity analyses of five uncertain explanatory variables including a decision variable, exploring the entire plausible parameter domain. This method allowed effectively determining the relative importance of each variable in the precision of the outcome variables, while simultaneously adjusting for uncertainty in other variables. A GAM-based response surface method was used to optimise the decision variable (*radius*), while adjusting for an unknown, potential two-way interaction of *radius* and each of the four uncertain explanatory variables. While PRCC indicated the degree of global monotonicity, GAM allowed examining the changes in the relationships between the explanatory variable and the outcome variable at different points in the input space, due to interactions with other variables (Owen et al., 2011). It is proposed that these methods be used complementary for other optimisation problems with absence of good prior knowledge about the response of the system, such as agent-based disease simulation models, which commonly have complex features, such as non-linear, non-smooth and noisy.

7.6. Conclusion

Addition of VTD with a modest ring radius (1.0 km) reduced the predicted overall costs of an FMD epidemic comprised of the direct and macroeconomic costs, compared with SO or VTL, for a simulated FMD epidemic seeded in the Auckland Region, with local spread potential similar to that of the Cumbria outbreak in 2001, and lasted for longer than 21 days with SO. The positive predicted NPVs for VTD were robust to the uncertainty in *resource* (100 – 500 premises/day), *effectiveness* (75 – 100%), and an early scale of an epidemic (*CIP* and *EDR*), but sensitive to *radius*. VTL was always economically suboptimal under the current OIE code, but would be advantageous if the OIE's waiting period was shortened by 3 months.

7.7. Acknowledgements

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7.8. Supplementary data

Appendix 7-1 Parameters for New Zealand Standard Model (NZSM) for simulation of a foot-and-mouth disease (FMD) epidemic

Parameters	Values
Disease transmission	
(1) Movements	
(i) Distance probability	
High risk, between-herd	0 to 20 km: 71%, 20 to 40 km: 18%, 40 to 60 km: 3%, 60 to 80 km: 4%, 80 to 100 km: 1%, 100 to 200 km: 2%, and 200 to 1000 km: <1%
Medium risk, between-herd	0 to 20 km: 81%, 20 to 40 km: 12%, 40 to 60 km: 2%, 60 to 80 km: 2%, 80 to 100 km: <1%, 100 to 200 km: 1%, and 200 to 1000 km: 1%
Low risk, between-herd	0 to 20 km: 91%, 20 to 40 km: 5%, 40 to 60 km: 2%, 60 to 80 km: 1%, 80 to 100 km: 0%, 100 to 200 km: <1%, and 200 to 1000 km: <1%
Pastoral livestock, via saleyards	0 to 80 km: 95%, 80 to 120 km: 3%, and 120 to 900 km: 2%
Breeding pigs, via saleyards	0 to 50 km: 69%, 50 to 100 km: 14%, 100 to 150 km: 7%, 150 to 200 km: 6%, 200 to 250 km: 1%, and 250 to 400 km: 2%
(ii) Frequency [1]	
High risk, between-herd	Poisson distribution, λ = 0.03 (PL), 0.04 (DR), 0.11 (GD and PB), and <0.01 (HB)
Medium risk, between-herd	Poisson distribution, λ = 0.47 (PL), 0.88 (DR), 0.91 (GD), 0.33 (PB), 0.29 (PF), and 0.14 (HB)
Low risk, between-herd	Poisson distribution, λ = 0.26
Pastoral livestock, via saleyards	Poisson distribution, λ = 0.01 (PL and DR), <0.01 (GD and HB)
Breeding pigs, via saleyards	Poisson distribution, λ = 0.01 (PB), and <0.01 (HB)
(iii) Transmission probability [2]	
High risk, between-herd	Day 1: 53% (PL and HB), 62% (DR), 67% (GD) and 46% (PB), day 2 to 11: 80%, and day 12 to 16: 100%
Medium risk, between-herd	Day 1: 10%, day 2 to 6: 20%, day 7 to 11: 40%, and day 12 to 16: 50%
Low risk, between-herd	Day 1: 2%, day 2 to 6: 4%, day 7 to 11: 9%, and day 12 to 16: 10%
Pastoral livestock/breeding pigs, via saleyards	Day 1: 46%, day 2 to 11: 78%, and day 12 to 16: 100%
(iv) Number of contacts	
High/medium/low risk, between-herd	Constant, 1.0
Pastoral livestock/breeding pigs, via saleyards	Poisson distribution, λ = 1.9 (PL) and 2.6 (PB)
(2) Local spread	
(i) Transmission probability [3]	
Day -1	0 to 1 km: 0, 1 to 2 km: 0, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 0	0 to 1 km: 7, 1 to 2 km: 2, 2 to 3 km: 0, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 1	0 to 1 km: 12, 1 to 2 km: 3, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 2	0 to 1 km: 12, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
Day 3	0 to 1 km: 9, 1 to 2 km: 4, 2 to 3 km: 1, and 3 to 4 km: 0 (per 10^3 premises at risk per day)
(ii) Adjustment	
Relative susceptibility by species	1.0 (cattle), 0.9 (sheep, goats and deer) and 0.8 (pigs)
Detection status	1.0 (undetected) and 0.5 (detected)

Disease characteristics	
(1) The onset of clinical signs [2]	Day 1: 0%, day 2: 4%, day 3: 16%, day 4: 33%, day 5: 77%, day 6: 79%, day 7: 83%, day 8: 88%, day 9: 91%, day 11: 95%, day 12: 97% and day 16 onwards: 98%
(2) The onset of infectivity	Day 1 to 16: 100%, day 17: 94%, day 18: 88%, day 19: 82%, day 20: 76%, day 21: 71%, day 22: 65%, day 23: 59%, day 24: 53%, day 25: 47%, day 26: 41%, day 27: 35%, day 28: 29%, day 29: 23%, day 30: 17%, day 31: 12%, day 32: 6% and day 33 onwards: 0%
Control measures	
(1) Depopulation	
(i) Start date [4]	Day 0
(ii) Resource [4]	
Day 0 to 4	Day 1: 1, day 2: 2, day 3: 10, and day 4: 20 (premises/day)
Day 5 onwards	Triangular distribution, {minimum, mode, maximum} = {0, 1, 5} (PL), {1, 1, 3} (DR), {0, 1, 4} (GD), {0, 1, 3} (PB/PF), and {0, 0, 1} (HB) (days/premises)
(2) Vaccination	
(i) Start date [4]	Day 21
(ii) Radius	Varied from 1 to 20 (km)
(iii) Resource	Varied from 100 to 500 (premises/day)
(iv) Suppression in infectivity [5]	Day 4 onwards: 50%
(v) Effectiveness [5]	Day 1 to 3: 0%, day 4: 50%, day 5: 75%, and day 6: varied from 75 to 100%
(3) Surveillance	
(i) Detection probability	
Background surveillance (DR, PB and PF)	Day 1: 6%, day 2: 16%, day 3: 21%, day 4: 17%, day 5: 13%, day 6: 9%, day 7: 6%, day 8: 4%, day 9: 3%, day 10: 2%, day 11 to 13: 1%, day 14 onwards: <1%
Background surveillance (PL, GD and HB)	Day 1: 2%, day 2: 6%, day 3 to 5: 9%, day 6: 7%, day 7 to 8: 6%, day 9 to 11: 5%, day 12 to 14: 4%, day 15 to 17: 3%, day 18 to 20: 2%, day 21 to 26: 1%, and day 27 onwards: <1%
Passive surveillance (DR, PB and PF)	Day 1: 7%, day 2: 20%, day 3: 24%, day 4: 17%, day 5: 11%, day 6: 7%, day 7: 5%, day 8: 3%, day 9: 2%, day 10 to 12: 1%, and day 13 onwards: <1%
Passive surveillance (PL, GD and HB)	Day 1: 3%, day 2: 7%, day 3: 10%, day 4: 9%, day 5: 8%, day 6: 7%, day 7: 6%, day 8 to 10: 5%, day 11 to 14: 4%, day 15 to 16: 3%, day 17 to 20: 2%, day 21 to 24: 1%, day 25 onwards: <1%
Patrol visit	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (high risk)	Constantly 100%
Tracing (medium risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
Tracing (low risk)	Constantly 100% (cattle, pigs and deer) and Day 1: 52%, day 2: 66%, day 3: 80%, day 4: 89%, day 5: 94%, day 6: 97%, day 7: 98%, day 8 onwards: 99% (sheep and goats)
(ii) Buffer for patrol visit (km)	3
(4) Movement restriction	
(i) Restriction probability	
First 14 days (initial standstill)	High risk: 91%, medium risk: 60%, and low risk: 24%
Day 15 onwards: outside10 km surveillance zone and inside 50 km infected zone	High risk: 94%, medium risk: 80%, and low risk: 39%
Day 15 onwards: inside 10 km surveillance zone	High risk: 95%, medium risk: 85%, and low risk: 52%
Day 15 onwards: outside 50 km control area	High risk: 100%, medium risk: 90%, and low risk: 80%

1 Classification of New Zealand livestock premises: PL (pastoral livestock enterprise), DR (dairy enterprise), GD (dry grazing enterprise), PB (breeding pig enterprise), PF (finishing pig enterprise) and HB (hobby farms).
2 Relative to the date of infection.
3 Relative to the onset of clinical signs.
4 Relative to the date of detection of the index case.
5 Relative to the date of application of vaccination.

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8. General Discussion

8.1. Overview

This thesis focused on enhancing the currently available epidemiological simulation modelling systems for FMD, with a special focus on New Zealand. The thesis began with a critical review of the previous work for development and use of simulation models for an FMD epidemic, and approaches to quantify the economic aspects of FMD. The thesis then addressed two major problems in the current FMD simulation model for New Zealand, the need to improve the precision of current estimates of model parameters for local spread, and absence of economic components that were necessary for evaluation of alternative control strategies for FMD. The first part of the thesis (Chapters 3 and 4) proposed a new approach to investigate local spread in a particular FMD outbreak, which was a modification of the previous approach (Sanson and Morris, 1994, Sanson et al., 2006b). The data obtained from three recent adequately recorded FMD epidemics (UK 2001, Japan 2010 and Republic of Korea, 2010) were analysed to produce estimates of local spread parameters and investigate the uncertainty and variability in the estimates for local spread patterns, taking risk factors into account (Chapter 3). The subsequent study demonstrated application of the estimated local spread parameters to the simulation model framework, InterSpread Plus, as well as evaluating how alternative control strategies could be assessed by using the typically available epidemic data (Chapter 4). A high level of agreement was obtained between simulated and observed epidemics, supporting the validity of the proposed approach. The case study for the 2010 Japan FMD epidemic emphasised the importance of management of the local spread hazard by enhanced community awareness, and showed the epidemiological advantage of addition of emergency vaccination to the control policy, over stamping-out only. The conclusion about use of vaccination was in agreement with the previous modelling study by Hayama *et al.* (2013).

The second part of the thesis (Chapters 5, 6, and 7) focused on developing economic components of the model for New Zealand and its application for decision making. In Chapter 5, the parameter values for the immediate costs of eradication for a hypothetical FMD epidemic in New Zealand were estimated, and the disease simulation model was linked with a macroeconomic model to quantify the long-term impacts on the wider economy. Using the estimates of the economic outcomes of an epidemic, Chapter 6 demonstrated evaluation of two alternative eradication strategies for FMD (i.e., additional emergency vaccination within 3 km ring radius with and without subsequent culling of vaccinated animals). The results indicated that vaccinate-to-die would be more economically favourable than stamping-out alone, for an epidemic which had a high potential of becoming large, indicated by a higher cumulative number of IPs (CIP) and a higher estimated dissemination rate (EDR) in the area with a higher density of livestock premises. The findings were in line with other overseas studies using simulation models (Kobayashi et al., 2007a, Hagerman et al., 2012, Boklund et al., 2013). The findings also implied that the expected economic benefits of emergency vaccination were sensitive to the requirements specified in the OIE's Animal Health Code regarding recovery of FMD-free status, and various epidemiological and logistic factors. This implication was further elaborated through the analyses of the data generated by an extensive set of simulations of epidemics within a high density region in New Zealand, considering the uncertainty in vaccination radius, resource capacity, effectiveness, CIP and EDR (Chapter 7). The vaccination radii for both vaccinate-to-die and vaccinate-to-live were optimised, adjusting for a range of epidemiological and logistical uncertainties. The overall trends were shown to be in accordance with a previous study for the UK by Tildesley *et al.* (2006).

8.2. Local spread of FMD

Historically, what is termed local spread (some epidemiologically uncertain mechanisms of localised disease transmission) often played an important role in development of an FMD epidemic in formerly FMD-free countries (Gibbens et al., 2001, Sanson, 1993). Unlike disease transmission by explicit between-herd movements for which the source for each infection can be identified with reasonable confidence, there is no accurate information to quantify local spread in the absence of molecular epidemiological data. This is because the fundamental nature of local spread is that the source of infection is uncertain and the mechanism of disease transfer is unknown. It may not even be truly local, as normally defined, and missing or withheld information (e.g., unreported animal movements) may

result in spread being broadly attributed to local spread. It is particularly problematic to identify sources when infected herds cluster spatially and temporally, which is often the case for an FMD epidemic. Hence, it proved challenging to estimate local spread parameters for use in simulation models.

Previous studies of local spread (Sanson and Morris, 1994, Sanson et al., 2006b) suffered from a number of limitations, such as potential bias in attribution of sources, lack of consideration for risk factors, imprecise measurements due to broadly categorising distance, and so on. Chapters 3 and 4 addressed these issues and described a new epidemiological approach to attribute local spread pathways, taking all biologically plausible sources into account. The method is generically applicable to the information typically available from the field epidemic data. Based on the analyses of the data from Cumbria (UK, 2001), Miyazaki (Japan, 2010), and Andong (Republic of Korea, 2010), species and herd/flock size were identified as important risk factors for FMD local spread (Chapter 3). Cattle were the most susceptible species, while pigs were the most infectious species when cattle, pigs and small ruminants (sheep and goats) were compared; the larger herd/flock size was associated with increased risk of receiving local spread. These findings coincided with a number of experimental studies reporting variation of FMD virus behaviour between the principal host animals (Sellers and Parker, 1969, Donaldson and Alexandersen, 2001, Donaldson et al., 2001) and previous analyses of the same epidemics (Nishiura and Omori, 2010, Ferguson et al., 2001). The case study for the 2010 Japan epidemic (Chapter 4) showed large variations in the pattern of local spread by the stage of an epidemic, suggesting contribution of dynamic inter-farm contact activities in addition to static environmental factors. The variation by the stage of an epidemic was in line with the findings of the analyses of the UK 2001 epidemic by Wilesmith *et al.* (2003). Therefore, it is emphasised that the greatest attention be paid to stringent movement restrictions and enhanced biosecurity measures by the owners of large scale herds, cattle herds, and pig herds, as well as any herds surrounding those high risk herds, for better management of local spread during an FMD epidemic. The findings may also be useful for targeting (e.g., cattle only) or prioritising (e.g., starting from the largest herds) emergency vaccination, to give immediate protection to the herds most susceptible to local spread infection.

After adjusting for the risk factors, substantial variation in the pattern of local spread was identified among the three epidemics (Chapter 3). The hazard of local spread for the

Cumbria (UK, 2001) outbreak was the highest, i.e., 7 and 5 times that of Miyazaki (Japan, 2010) and Andong (Republic of Korea, 2010) outbreaks, respectively. The new estimates for the hazard of local spread for the Cumbria outbreak was in general lower in the proximity of IPs, but the hazard extended to a longer distance, compared with the previous estimates. In the absence of accurate information on sources of local spread, we cannot possibly determine which estimates are more correct. It may, however, serve the purpose, to use the estimated highest hazard of local spread, to prepare for the worst case scenario (that ever occurred). In this context, use of the local spread parameters for the Cumbria (UK, 2001) outbreak may be justified, as they were the highest of the three outbreaks analysed (i.e., Cumbria, Miyazaki and Andong). It is recommended, however, that additional disease simulation should be carried out with a range of potential local spread parameters (e.g., Cumbria, Miyazaki and Andong) to provide information on what might possibly happen, and efforts should be continuously made to improve the knowledge on the pattern of local spread. For contingency planning and decision making for New Zealand, additional simulation studies should take place to consider different local spread parameters, and the current interpretation from the simulated results solely based on the Cumbria local spread patterns should be reassessed.

8.3. Economic impacts of FMD in New Zealand

In Chapter 5, the FMD economic modules for New Zealand were developed, and integrated with the existing FMD simulation model to generate simulation outcomes in an economic term. While this kind of study was actively carried out in some other countries (Mourits et al., 2010, Tomassen et al., 2002, Hagerman et al., 2012), it was the first study of this kind for New Zealand. The direct cost module was based on the MPI's experts' estimation on the amounts and costs of resources, while the macroeconomic module interpolated the results of the computable general equilibrium model (CGEM) (Schilling et al., 2014). While the economic impacts of FMD in New Zealand were estimated previously (Forbes and van Halderen, 2014, Belton, 2004), they were for predefined sets of epidemic scenarios. The system developed in this study allowed examining the direct and macroeconomic costs for any simulated FMD epidemics. The use of the system was demonstrated in Chapter 6 and 7.

As a case study, the costs of simulated epidemics introduced into Auckland Region, with the local spread patterns similar to that of Cumbria (UK, 2001) outbreak (median total number of IPs: 353, median time to eradication: 132 days) were estimated. The magnitude

of the estimated macroeconomic costs (median: USD 11.1 billion) were much greater than the estimated direct costs (USD 180 million). The higher scale of the macroeconomic costs relative to the direct costs was comparable with the estimates in other FMD-free countries, e.g., US, UK, and Australia (Paarlberg et al., 2002, Thompson et al., 2002, Buetre et al., 2013). The estimated macroeconomic costs of an FMD epidemic was equivalent to 3.5 – 7.0% of the New Zealand's GDP (MacPherson, 2015), which was much greater than what was estimated (<1%) for the UK, Australia and the US (Paarlberg et al., 2002, Thompson et al., 2002, Buetre et al., 2013). As anticipated for New Zealand, the majority (> 96%) of the expected economic impacts of an FMD epidemic were, in long term, attributable to the macroeconomic impacts, associated with the shock of export bans, disruption in the livestock industries, a decrease in the interest rate and exchange rate, a decrease in domestic consumption and overall weaker domestic economic activity. Further work is required to refine the estimation in the macroeconomic costs by making stronger linkage between the FMD simulation model and the CGEM.

The findings highlighted the vulnerability of the New Zealand economy to the reactions of trading partners, irrespective of the intensity of eradication efforts themselves, should there be an incursion of FMD into the country. It emphasised the importance of solid planning by stakeholders to mitigate such adverse effects, by, for instance, establishing pre agreement with the current trading partners about recognition of the risk of various livestock products. For example, it is of particular interest for New Zealand livestock industries and the related private sectors to know whether (or when) processed milk powder or heat-treated meat would be accepted as 'safe' for trade if there were an FMD epidemic in the country. Historically, fears for FMD by trading partners have led to export bans against racehorses, used agricultural machinery, and an array of processed food products containing milk powder (e.g., chocolate) (Matthews, 2011). Presence of a stipulated prior agreement with the trading partners would reduce the uncertainty and identify areas, which needs improvement, prioritising, or communication among related industries to enhance preparedness. In addition, it would help subduing confusion about perception of the risk of FMD, and minimize irrational refusal of trade without scientific justification.

8.4. Evaluations of vaccination-based FMD control strategies

For New Zealand, maintenance of the OIE's recognition, 'FMD-free where vaccination is not practiced,' is crucial because the revenues from the agricultural industries are important for the country's economy. Thus, the main objective of the adopted control strategy should focus on recovery of its FMD-free status in the shortest time possible to minimise the economic impacts. Chapters 6 and 7 demonstrated that an additional use of emergency vaccination provided a prompt form of protection for the susceptible population from local spread of FMD, reducing the overall epidemiological outcomes and the chance of a large-scale epidemic. The implications were similar to the recent modelling studies for other currently FMD-free countries (Boklund et al., 2013, Hagerman et al., 2012, Buetre et al., 2013). The relative benefits of emergency vaccination (vaccinate-to-die or vaccinate-to-live) in comparison with stamping-out alone were shown to be modified by various epidemiological and logistic factors. The key finding was that vaccinate-to-die was generally beneficial for an FMD epidemic in the region with a high density of livestock premises (Auckland Region) (Chapters 6 and 7), while stamping-out alone was preferred for an outbreak in the low density region (Otago Region) (Chapters 6), under the current OIE's standard. The benefits of vaccinate-to-die was sensitive to the choice of a vaccination radius; vaccinate-to-die with a larger vaccination radius (>8 km) was shown to be suboptimal to stamping-out alone, because of an increase in the direct costs and a delay in the recovery of FMD-free status due to a longer time required to complete culling vaccinated animals (Chapter 7). It highlighted the risk of an undesirable economic consequences with vaccinate-to-die, by applying vaccinate-to-die in a larger vaccination radius, without a good prior knowledge on the extent of local spread. In contrast, vaccinate-to-live had an advantage in that the consequence of an epidemic was robust to the choice of vaccination radius. Vaccinate-to-live would be an attractive option if the waiting period for this policy was aligned with others for recognition of OIE's FMD-free status.

Under an emergency situation such as an FMD outbreak, decision makers may opt for intuitive decisions which may be made in haste, but decision making could be more transparent, rational, reliable, rigorous and likely to be correct, if it were based on the structured framework, supported by statistical and quantitative analyses of past data (Perry et al., 2001). Simulation-based studies such as Chapter 6 and 7 can provide quantitative outputs, which can serve as the basis of a communication with decision makers and

stakeholders, and encourage informed discussion around disease control measures. The implications drawn from these studies are useful for New Zealand decision makers and industries, while implications are still limited to the epidemiological scenarios investigated and to the New Zealand context. The problems addressed in the thesis are, however, of great interest to the whole FMD-free community worldwide where regaining its FMD-free status after an incursion is the major concern. The studies demonstrated how disease simulation models can be used to inform contingency planning and decision making for FMD, without requiring an actual experience. The methodology described in the thesis can also be applicable for different countries, provided population data and movement data are available, or control of different contagious disease with similar characteristics to FMD. Once farm-based simulation models have been developed and maintained, not only *a priori* evaluation but also real time assessment of alternative control strategies for an on-going FMD epidemic can be done smoothly in response to an immediate need.

8.5. Future perspectives

The thesis identified a number of areas for future work.

The proposed quantitative approach for FMD local spread is generically applicable, both for retrospective analyses of past FMD epidemics and real time analyses of an ongoing FMD epidemic (or even other contagious disease of similar kind). It is recommended to analyse or reanalyse the historical FMD epidemic data worldwide to quantify the scale of local spread patterns more precisely and investigate detailed risk factors for each epidemic. The results will be a valuable addition to the knowledge base for FMD, which can be shared and used to improve the predictive ability of the current simulation models for each country, and will add flexibility to respond to a range of possible epidemiological scenarios. Because only three outbreak data were investigated in this study, the importance of country specific factors (e.g., breed, farming community, geography, or climate) for the variation in the local spread patterns could not be determined. The findings of the studies emphasised a precaution in using the current simulation models for FMD, which commonly use the local spread parameters extrapolated from other overseas epidemics without any adjustment for local conditions.

This study emphasised the importance of collection of detailed epidemic data. Obtaining epidemic data for analyses may be challenging, due to the highly political nature of FMD; they may not be disclosed to the third parties because the livestock owners and disease

control authorities are usually very sensitive to their experience with FMD. This thesis demonstrated the value of analysing such data, while describing the required information and the methods of analyses. It is recommended that more collaborative work should be carried out to improve the current knowledge about FMD epidemiology for better management in the affected countries, or global communities (both FMD-endemic and FMD-free) for better control of FMD.

This study also emphasised the importance of collection and maintenance of livestock population data, recording explicit farm locations, species, farm types and counts of animals for improving country's biosecurity level in general. Absence of such data, or use of out-dated or inaccurate data may result in misleading information regarding FMD control. In addition, absence of an accurate population data will make outbreak response activities inefficient, if there is an actual outbreak of FMD. For New Zealand, two databases, AgriBase and FarmsOnLine exist, and they are maintained by AsureQuality and MPI. They are shown to be inconsistent by the recent study. Further studies should be carried out to examine the influence of use of inaccurate population data on the FMD model implications.

Estimation of the macroeconomic costs of an FMD epidemic should be refined, by strengthening the linkage between the disease simulation model and the macroeconomic model (CGEM). It is desirable to directly link the two models, although it would become computationally expensive to run the whole system, and it would require intensive collaborative work between disease modellers and macroeconomic modellers to understand each model and develop a sub-model to link them. If such work is not feasible, an alternative approach would be to run the CGEM with additional sets of assumptions to improve the current simple linear assumption between the two variables (time to recover FMD-free status and the macroeconomic costs), by account for unexplained factors such as region, policy, production and larger epidemics. Considering the high importance of livestock exports, such studies would be highly valuable for improving the FMD simulation modelling system and potentially protecting the country's economy, if an FMD outbreak occurred.

As the knowledge base for FMD develops, vaccine technologies improve, and the international standard regarding FMD control changes, simulation models should be updated and the current best alternative policy should be thoroughly explored. Previous analyses for the UK by Tildesley (2006) indicated alternative prioritisation methods for

vaccination, such as inside out, larger herds, and closer to infected premises were epidemiologically more advantageous than the outer-in methods. Drawn from the results of the studies, species-specific vaccination for vaccinate-to-die may be potentially beneficial for New Zealand, providing sufficient population immunity, while saving the number of animals to vaccinate and cull, and hence shortening time to regain FMD-free status. More studies should be carried out, using the existing simulation models with the refined parameters.

8.6. Conclusion

This thesis addressed one of the major problems for New Zealand's society, the rational control of FMD, based on the currently available knowledge about the disease characteristics. Applying epidemiological and economic techniques, the knowledge about the key transmission mechanism of FMD was reinforced, while enhancing a currently available simulation model for FMD. Its use as a decision support tool was also demonstrated.

The findings of the thesis will contribute to informing decision makers and stakeholders about optimal alternative policies, and areas of weakness that should be improved for better preparedness. It is recommended that the enhanced decision support systems for FMD in New Zealand continuously be used to examine a better alternative policy that meets the current economic, political, and societal preference for various epidemiological scenarios. The simulated results should then form the basis of communication with decision makers and stakeholders to encourage informed discussion around disease control measures. Although the focus was on FMD for New Zealand, the techniques used in the analyses are applicable for other infectious diseases for other countries.

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