

DISSERTATION

USES OF QUANTITATIVE SPATIAL ANALYSIS AND EPIDEMIOLOGICAL
SIMULATION MODELING FOR ASSESSING CONTROL STRATEGIES
FOR FOOT-AND-MOUTH DISEASE

Submitted by

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ABSTRACT

USES OF QUANTITATIVE SPATIAL ANALYSIS AND EPIDEMIOLOGICAL SIMULATION MODELING FOR ASSESSING CONTROL STRATEGIES FOR FOOT-AND-MOUTH DISEASE

This study addressed issues related to a hypothetical outbreak of foot-and-mouth disease (FMD) comparing a limited control measure to additional control strategies where there were limited control strategies within FMD virus free area. The central United States was selected as the study area, and the spatial pattern of FMD and its determinants were observed after FMD was introduced into the center of the area. The research reported the magnitude of the outbreaks in different scenarios having different control strategies. The first four chapters in this dissertation cover the sequence of research methods, and the final chapter includes the results and discussion.

Chapter 1 reviews aspects of epidemiology of FMD, epidemiological simulation modeling, and spatial analysis with the focus on FMD in terms of disease control. The review stimulated some ideas to generate parameters for the FMD simulation modeling that was done in Chapter 2.

Chapter 2 explains the process for generating parameters for a hypothetical outbreak of FMD in the central United States. The process included gathering location study premises in the study area from many sources and a simulator. The disease stage and transmission parameters of FMD were estimated from reviews and statistical analyses of data distribution, adjusted for study premises size. The sensitivity analysis of important parameters was analyzed by comparing disease spread for various values of the input parameters.

Chapter 3 examines the practical plans in place for FMD control and eradication. The baseline scenario was set up from the base parameters from Chapter 2 and included some limited control strategies. The additional five strategies included additional intensive disease control measures such as restricted animal movement, additional animal destruction, or ring vaccination. The baseline and extra five scenarios were simulated in a simulator and their magnitude was observed, including epidemic duration and estimated number of destroyed and/or vaccinated animals.

Chapter 4 identifies the simulated outbreak region and its spatial determinants in the baseline scenario. The density estimation of affected areas was determined and illustrated by maps. Additional quantitative spatial methods such as spatial continuity, autocorrelation, and autoregressive model were analyzed to explain spatial trends and factors related to the affected areas.

Chapter 5 concludes the important findings of this research. The overall conclusion summarizes the results from the previous chapters. A hypothetical outbreak of FMD in a large study area such as the one in this research should identify the premises of livestock as the unit of interest. The spread of FMD in the area may be primarily caused

by indirect contact rather than direct contact and airborne transmission. The change of parameters in the indirect contact rates was sensitive to the outcome of the simulation. All additional disease control strategies were better than the baseline scenario in terms of reducing the magnitude of the outbreak, but not in shortening the epidemic duration. For example, restricted animal movement was the best strategy to reduce magnitude of the outbreak, but it lengthened the epidemic duration. The kernel density estimation method demonstrated that the outbreak would spread throughout most of the study area. More affected premises in each county arose when higher numbers of livestock premises were in it and neighboring zones.

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**CHAPTER 1: EPIDEMIOLOGICAL SIMULATION
MODELING AND SPATIAL ANALYSIS FOR FOOT-AND-
MOUTH DISEASE CONTROL STRATEGIES: A
COMPREHENSIVE REVIEW**

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Summary

Foot-and-mouth disease (FMD) is one of the most serious transboundary, contagious viral diseases of cloven-hoofed livestock, because it can spread rapidly with high morbidity rates when introduced into disease-free herds or areas. Epidemiological simulation modeling can be developed to study the hypothetical spread of FMD and to evaluate potential disease control strategies that can be implemented to decrease the impact of an outbreak or to eradicate the virus from an area. Spatial analysis, a study of the distributions of events in space, can be applied to an area to investigate the spread of animal disease. Hypothetical FMD outbreaks can be spatially analyzed to evaluate the effect of the event under different control strategies. The main objective of this paper is to review FMD-related articles on FMD epidemiology, epidemiological simulation modeling and spatial analysis with the focus on disease control. This review will contribute to the development of models used to simulate FMD outbreaks under various control strategies, and to the application of spatial analysis to assess the outcome of FMD spread and its control.

Key words: foot-and-mouth disease, simulation, modeling, spatial analysis

Introduction

Livestock animal diseases are a major constraint on economic growth, poverty reduction, and food security. Among the most important diseases that can damage the national economy and trade is foot-and-mouth disease (FMD) (Forman *et al.*, 2009). FMD is a highly contagious viral disease in cloven-hoofed animals that may rapidly and unexpectedly spread in a country or across national boundaries. When FMD virus is introduced into disease-free herds, areas, or countries it is likely to spread rapidly and be associated with high morbidity rates (Geering *et al.*, 2002). Because the United States has not experienced an FMD outbreak since 1929 (Graves, 1979), relevant real data related to the disease and animal contact parameters referred from real disease spread are not available for the country. However, simulation models may be used to mimic situations if the disease occurs in the country. Furthermore, while using some specific assumptions related to spatial distribution of livestock populations and their dynamics, spatial analysis can be applied to comprehend the distribution of disease events. Hence, these simulation modeling techniques can also be implemented to understand the geographical aspects of a hypothetical outbreak of FMD.

Epidemiological simulation modeling has been developed to understand the epidemiology and evaluate control programs of infectious diseases, and several studies have focused on FMD. Some of these models have helped develop information about FMD transmission in different situations, places, and times. Many of these have aided in the evaluation of different control programs by predicting the consequences of a hypothetical outbreak and spread of FMD. All of the information gleaned from a real

outbreak or from simulation model could be useful to some countries that want to initiate or modify a contingency plan for FMD control.

Spatial analysis is a methodology used to describe the geographical patterns of disease; these patterns are foundational for understanding the epidemiology and potential risks. Spatial analysis using FMD data could help identify the high risk areas for virus introduction or transmission. Spatial analysis could be used to inform epidemiological simulation modeling. Furthermore, control measures would be more accurately applied in some areas or zones that could be identified by spatial analysis.

The main objective of this review is to examine different aspects of the epidemiology of FMD, epidemiological simulation modeling, and spatial analysis with the focus on FMD especially in terms of disease control. This review can serve as a basis for a study on FMD simulation modeling and spatial analysis.

Foot-and-mouth disease

Foot-and-mouth disease and its epidemiology

Foot-and-mouth disease is a highly contagious animal viral disease in cloven-hoofed animals. FMD is generally considered to be the most contagious of all diseases of farm animals, and it can spread rapidly and unexpectedly on a national and international scale. Therefore, it is also regarded as one of the most serious transboundary animal diseases (Geering *et al.*, 2002).

This transmissible disease was described in 1897 by Loeffler and Frosch, who theorized that it could be caused by a distinct agent. With the advancement in microbiological techniques, the causative agent was found to be a virus called FMD virus

(FMDV) which is a member of the Aphthovirus genus of the Picornaviridae family. There are seven serotypes of FMD virus and all cause a disease that is clinically similar but has immunologically distinct properties. The three distinct serotypes O, A, and C were recovered by scientists in France and Germany in the 1920s. The other four serotypes SAT 1-3 and Asia 1 were lately recognized by the UK Pirbright team in the 1940s and 1950s (Sobrino and Domingo, 2004).

All domestic and wild cloven-hoofed animals are susceptible to FMD virus infection, but the severity of the resulting disease varies with the level of immunity, the infectious dose, the virus strain and the host species (Sobrino and Domingo, 2004). Domestic livestock species that are susceptible to FMD are cattle, buffaloes, pigs, sheep, goats and deer, but the disease is generally most severe in cattle and pigs. Wild cloven-hoofed species also are susceptible, however the clinical disease is rarely observed in those species. There have been some reports of infection in humans but these were rare and the clinical signs and symptoms were mild (Geering *et al.*, 2002).

FMDV infection is characterized by vesicular lesions on the mucous membranes of the mouth, muzzle, snout, udder, and feet. The first clinical sign is salivation then the mucosa of the oral cavity becomes reddened. Shortly after, erosions develop in the interdigital spaces of the feet and on the udder. Infected animals then become lame and show unwillingness to stand (Geering *et al.*, 2002; Sobrino and Domingo, 2004).

Susceptible animals generally acquire the infection via the respiratory route. Very small doses of FMDV can initiate infection. Pigs are usually infected via the respiratory route, but this omnivore is more susceptible to infection by the oral route than are ruminants. The virus can also enter through abrasions in the skin or mucosa. After

infection, the virus is excreted in large quantities in expired air, secretions, excretions, and ruptured vesicles. Excretion of FMDV can begin up to four days before clinical signs appear. FMDV can retain infectivity for very long periods in frozen or chilled lymph nodes, bone marrow, and residual blood clots. Additionally, the FMDV can remain infective for considerable periods in an environment where it is protected from desiccation, heat, and adverse pH conditions (Geering *et al.*, 2002).

FMD can be transmitted by direct contact and by indirect transmission. Direct contact between infected and susceptible animals may lead to a faster spread in intensive farm situations than in low stock density areas. In indirect transmission, FMDV can spread mechanically by a variety of fomites including animal foodstuffs, artificial insemination equipment, vehicles, livestock holding areas, and livestock equipment that could be contaminated with infected secretions and excretions (Geering *et al.*, 2002). Other research has shown that certain farm situations encourage the faster spread of FMD. Bates *et al.* (2001) found that larger livestock facilities had a higher frequency of direct and indirect contacts. Veterinarians and other people who have close contact with livestock can be at risk of carrying the virus from farm to farm. In temperate climates, infection can be spread over considerable distances by the airborne route. In past outbreaks, airborne spread has generally been from pigs at source to cattle downwind. Windborne transmission requires a slow and steady wind speed and direction, high relative humidity, weak sunlight, and an absence of heavy rain (Geering *et al.*, 2002).

The introduction of new virus to naïve susceptible herds, areas, or countries is likely to result in rapid spreading with high morbidity rates. FMD can be rapidly spread by direct contact, but the ability of the virus to survive in the environment means that

indirect transmission through fomites may be as important as direct contact. Livestock trading and the movement of infected animals often cause disease transmission between different locations (Geering *et al.*, 2002). After an absence of 33 years, FMD was confirmed in pigs in the UK in 2001. This was an example of a serious outbreak of FMD in a country formerly free of the disease. The UK spent 11 months to regain its FMD-free status. Nearly 4 million animals were slaughtered; the cost of the outbreak was estimated as 3.1 billion pounds sterling from losses to agriculture and food (Sobrino and Domingo, 2004).

This important transboundary disease is endemic in many countries in Africa, Asia, the Middle East, and parts of South America; however, the countries in Europe, North and Central America, the Pacific, and the Caribbean are mostly free from disease (Geering *et al.*, 2002). Paton *et al.* (2009) adapted geographical information from the FMD World Reference Laboratory to create a map of the global FMD status in 2008. FMD was listed in many parts of the world. Endemic areas were located in many parts of Asia, the Middle-East, Africa, and some northern parts of South America. Sporadic areas of FMDV infection occur in the northern part of Asia and in the northern and some southern parts of Africa. Many countries in South America were observed as free with vaccination or free with multiple zones. North America, the majority of European countries and Australia were listed as free from FMD. Serotypes O and A could be found in almost all FMD areas except in the southern part of Africa. Serotype Asia 1 was located in southeast, south, and west Asia and the three serotypes of SAT were found in the African continent (Paton *et al.*, 2009).

Foot-and-mouth disease in the United States

According to Graves (1979), the United States had nine FMD outbreaks from 1914-1929. With the exception of two outbreaks in 1914 and 1924, the disease was eradicated within a few months. The 1914 and 1924 outbreaks involved a considerably longer duration and much national-level effort to finally eradicate the disease. The author did not state the reasons for the difference in the outbreaks of 1914 and 1924 as compared to the other years. With an extensive cooperative eradication program between the United States and Mexico, the disease in that bordering country was eliminated in 1952. The last occurrence of FMD in North America was in 1952 in Saskatchewan, Canada, and eradication was complete in 1953 (Graves, 1979).

According to the United State Department of Agriculture (2001 and 2007), cloven-hoofed animals in the United States are highly susceptible to FMD because they have not been exposed to allow for development of immunity to the virus nor have they been vaccinated since 1929. If an outbreak occurred in the United States, the disease could spread rapidly and widely in the country through routine livestock movements, unless the outbreak was detected early and eradicated immediately. Because the disease occurs in many parts of the world, there is always a chance of accidental introduction of the virus into the United States. Therefore, animals and animal byproducts from areas known to be affected are prohibited entry into the United States (U.S. Dept. of Agriculture, 2001, 2007). A major challenge of FMD prevention in the US is to design an appropriate prevention and control plan which effectively partners capable officials with livestock stakeholders.

Foot-and-mouth disease control and prevention strategies and their justifications

Disease prevention encompasses all measures designed to exclude disease from an unaffected population of animals. Prevention measures include the exclusion of the causative agent from a given area and protection of uninfected populations from disease that already occurs in the area. Disease control measures are used to reduce the frequency of illness already present in a population by eliminating causes of illness or reducing them to levels of little or no consequence (Schwabe *et al.*, 1977). The fundamental concepts of prevention and control of FMD or other infectious animal diseases are 1) control access of the virus to a susceptible host, 2) control contact between infected and susceptible animals, 3) reduce the number of infected animals, and 4) reduce the number of susceptible animals. To apply these concepts in the field as practical strategies for control of infectious animal diseases such as FMD, they become 1) animal movement control by quarantine or zoning, 2) planned destruction of infected animals or herds, and 3) vaccination of susceptible animals. Options and requirements for control of FMD in FMD-free countries are different from those in endemic countries. In FMD-free countries or zones, such as the United States, early reaction and rapid containment of disease to the zone of infection and eradication within the shortest time frame are critical to stop the progression to an endemic status (Geering *et al.*, 2002; Paton *et al.*, 2009).

Animal movement is a high risk factor for the spread of FMD infection; therefore, it is important to ban the movement of susceptible animal species and animal products within and out of the infected zone. The size and shape of the infected zones are dependent upon control activity plans. It is recommended that the zone be at a minimum

10 kilometers radius around the disease foci and perhaps as much as 50 kilometers in an area of intense livestock raising (Geering *et al.*, 2002). A ban of animal movement in some areas could affect many aspects of livestock production and trade. Therefore it is difficult for the disease control authorities to effectively prohibit at all times 100 percent of animal movement in the infected area or specified zone during an outbreak.

The slaughtering of a minority of diseased animals to protect the healthy majority has been a control measure option in veterinary medicine for a long time (Schwabe *et al.*, 1977). The slaughtering of infected animals as well as those in close contact with infected animals, also called stamping-out, is generally operated to control FMD outbreaks in areas previously free from FMD. However, an FMD stamping-out campaign should not be considered unless there are adequate provisions for compensation (Geering *et al.*, 2002). An FMD slaughter policy with strict movement controls was first applied in the UK in the late twentieth century. The measure was successful in stamping out the disease, but the scale of slaughter at times overwhelmed the financial or organizational capacity (Paton *et al.*, 2009). Stamping-out sometimes can be used along with other control measures such as vaccination and restricted animal movement.

Another notable FMD prevention and control strategic program is vaccination. In South America, vaccination for FMD has been a major component of the national FMD control and eradication program since the 1960s. During an outbreak in Uruguay in 2001, the use of vaccines in an endemic situation and as an anti-epidemic tool showed its effectiveness in creating FMD-free areas in South America. In 2004, over 200 million cattle were vaccinated twice yearly throughout the continent (Schudel and Lombard, 2004). In order to be effective, disease control by vaccination must be used in

conjunction with zoosanitary measures. Globally, two billion animals are vaccinated annually, but the use of vaccination in endemic countries is not uniform. Many African and south and south-east Asian countries use vaccination to a very limited extent. The majority of FMD vaccine is used in large-scale programs in China, South American countries, and parts of India and the Middle East (Paton *et al.*, 2009).

According to Paton *et al.* (2009), effective options for control of FMD must consider knowledge, capability, and policy. The essential knowledge of FMD control could be gathered from publications. However, a good FMD control policy should not only apply knowledge, but must also take capability into consideration. Estimation of capability outside an actual outbreak is difficult. However, epidemiological simulation modeling and spatial analysis can help define the hypothetical FMD spread; this approach can allow the capability for disease control to be estimated.

Epidemiological simulation modeling

According to Schwabe *et al.* (1977), the purpose of epidemiological modeling, whether analytic or simulation, is 1) to make predictions of disease incidence or prevalence, 2) to better understand underlying biomedical mechanisms, or 3) to test hypotheses about disease mechanisms. The predictive capacity of the model depends on the determinants that influence the disease to behave in the same way in the future. According to the authors, updated observational information is very important for epidemiological modeling. The requirements of an effective model are that 1) it should behave in a biologically and mathematically reasonable way, 2) it must be sensitive to important factors and insensitive to unimportant factors, 3) its mechanisms should be intuitively

acceptable, and 4) it should mimic real-life situations (Schwabe *et al.*, 1977). The ultimate aim of any epidemiological model is to compare various strategies for controlling infectious animal disease. Many disease control methodologies have been implemented to reduce the effect and spread of disease. Epidemiological simulation modeling can improve the effectiveness of control methods by examining various control strategies within a hypothetical disease outbreak. Several such studies have been conducted on FMD (Bates *et al.*, 2001, 2003b; Schoenbaum and Disney, 2003; Le Menach *et al.*, 2005; Wongsathapornchai *et al.*, 2008; Martinez-Lopez *et al.*, 2010).

According to Keusch *et al.* (2009), dynamic models of zoonosis transmission developed in the epidemiological process have four main aims: 1) A greater understanding of concepts relating to disease transmission; 2) The generation of new hypotheses by the simulation process; 3) Prediction of future epidemics and the impact of preventive measures; and 4) Identification of the types of data needed to understand disease epidemiology and make better predictions. Models are sometimes applied retrospectively to interpret historical data and are sometimes used prospectively to generate predictions. Predictive modeling is used to evaluate future scenarios and to explore the possible benefits and risks of alternative realities. Although foot-and-mouth disease is not a zoonotic disease, Keusch *et al.* (2009) have proposed ideas regarding the simulation of FMD spread under various control strategies in FMD-virus-free areas. The FMD emergence model will be used to evaluate future scenarios, but it is a difficult and complex challenge. Some biological and ecological characteristics data are needed, but are unknown. Therefore, to improve the science behind the modeling effort, hypotheses need to be generated and data gathered to strengthen and support or refute and abandon

the premise being studied. For example, one hypothesis is that different FMD control strategies result in different outbreak magnitudes. Data on livestock population and disease and contact parameters of the study area are needed. The specific data and parameters will improve the ability of the model to mimic hypothetical outbreaks under different control strategies.

Many models, including epidemiological simulation models, are based on mathematical expressions that describe the system. Mathematical models can help describe the biological dynamics of the determinants of disease processes. In addition, advances in computer technology allow simulation modeling to be integrated with mathematical models; this has the potential to accurately forecast disease incidence (Thrusfield, 2005). According to Clayton and Hills (1993), the two main groups of mathematical models used in scientific study are deterministic and stochastic. The authors give the laws of classical physics as the most familiar examples of deterministic models, such as *Ohm's law* which applies to the relationship between electrical potential (or voltage) applied across a conductor and the flowing current. The law holds that there is a strict proportionality between the two; if the potential is doubled then the current will double. The phenomena studied by scientists are rarely as predictable as is seen in deterministic relationships. Since many occurrences cannot be described purely deterministically, stochastic, also called probability, models are necessary. These models can predict a range of more probable future observations and indicate the uncertainty in the estimation (Clayton and Hills, 1993).

According to Wongsathapornchai (2006), the development of human infectious disease modeling in the early 20th century provided a key contribution to the fundamental

understanding of epidemiology and assisted in designing control programs for major infectious diseases. Examples of the application of mathematical modeling in human diseases include the study of human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS), and tuberculosis. Mathematical modeling was recently applied to animal diseases such as bovine spongiform encephalitis (BSE), classical swine fever, scrapie, pseudorabies, bovine viral diarrhea, various wildlife diseases, and also foot-and-mouth disease. These studies have demonstrated the usefulness of mathematical and epidemiological models to evaluate control programs for infectious diseases (Wongsathapornchai, 2006).

Epidemiological modeling for foot-and-mouth disease and other infectious animal diseases

The aim of modeling infectious animal diseases such as FMD is to predict or to understand the behavior of an epidemic (Gerbier *et al.*, 2002) and to assess potential effectiveness of various control and eradication strategies (Bates *et al.*, 2003b). Many models have been applied to study the transmission of FMD or other infectious diseases and to predict the impact of control measures. These models are limited, however, by the gap between the data requirements and data availability. This inadequacy could be improved by collection of more data. For example, livestock premises census data were needed to model the FMD spread in the US, but were not available. As a way to reduce the limitation of the model, spatial simulation for livestock farm locations could be applied to estimate the census of livestock premises.

There have been several studies using epidemiological modeling techniques for FMD in order to advance the development of FMD modeling. For example, a study conducted in California enhanced the current understanding of transmission of FMD by estimating contact rates of FMD in livestock (Bates *et al.*, 2001). The authors worked within a 3-county region of California, and estimated the direct and indirect contact rates in livestock facilities and the distance traveled between herd contacts. These researchers found that direct and indirect contacts occurred in livestock facilities over a wide geographic area, with larger facilities having a higher frequency of contacts (Bates *et al.*, 2001). One of the conclusions was that the results of their study may be useful for developing biosecurity programs at herd, state, and national levels and for modeling transmission potential for FMD virus. Later, these researchers used the rates and other information from this study as parameters to study epidemic simulation modeling to evaluate control strategies during an outbreak of foot-and-mouth disease (Bates *et al.*, 2003a, b).

After the FMD epidemic in the United Kingdom in 2001, French researchers Le Menach *et al.* (2005), developed a farm-based stochastic model to evaluate the consequences of virus introduction into France. This study identified and mapped the high-risk zones for the spread of FMD if the virus was imported. With the standard control policy simulated in the same 50 initially infected farms, the hypothetical outbreak would infect 16,350 of approximately 280,000 susceptible farms in France. The high-risk zones were the regions having high densities of cows and sheep. When farms were tightly clustered, the disease was transmitted quickly within the cluster. This study demonstrated

that the epidemic process for FMD depends upon the location, size, and species type of the initially infected farms (Le Menach *et al.*, 2005).

Carpenter *et al.* (2004) used simulation modeling to predict the spread and control of FMDV if it were introduced into a disease-free country. Simulation models have also been used to evaluate strategies and aid decision makers in identifying the optimal disease eradication plan. Carpenter *et al.* constructed a model using a commercial spreadsheet and a simulation add-in for Monte Carlo sampling. The Monte Carlo simulation technique involves the random sampling of each probability distribution within the model to produce hundreds or even thousands of scenarios (also called iterations or trials) (Vose, 2000). Each probability distribution is sampled under a distribution shape, and then the distribution of the values is calculated for the model outcome. The level of mathematics required to perform a Monte Carlo simulation is quite basic, but complex mathematics (e.g. power functions, logs, if statements) can also be included.

The North American Animal Disease Spread Model or NAADSM is a stochastic, state-transition simulation model for the spread of highly contagious diseases of animals. NAADSM users can establish parameters to define model behavior in terms of disease progression; direct contact, indirect contact, airborne dissemination; and implementation of control measures such as destruction and vaccination while the direct costs associated with these measures are considered. This model is being used to evaluate outbreak scenarios and potential control strategies for foot-and-mouth disease and exotic animal diseases in the United States, Canada, and elsewhere. NAADSM can define model behavior in terms of disease progression while taking into consideration the

implementation of control measures such as destruction and vaccination. Therefore, this model can be used effectively to evaluate outbreak scenarios and potential control strategies for foot-and-mouth disease. NAADSM is freely available via the internet at <http://www.naadsm.org> (Harvey *et al.*, 2007). Many models mentioned assumed that individuals within the population have equal opportunity to come into contact with any other individual. The NAADSM redefined individuals as the fixed locations of premises or flocks or herds. Contact rates for premises were unequally dependent on the defined production types and the distance of premises from other premise locations. This may be more acceptable for the simulation of FMD spread within a large study area having a large number of premises.

Foot-and-mouth disease simulation modeling with the aim to assess control measures

Several studies have used simulation models to assess FMD control measures. In 2003, Bates *et al.* (2003b) published the results from epidemic simulation modeling to evaluate control strategies of FMD in Fresno, Kings, and Tulare counties of California; in this study they used the estimated contact rates that had been calculated in 2001 (Bates *et al.*, 2001). The authors used a spatial stochastic model to evaluate a hypothetical outbreak of FMD under control scenarios that included baseline control strategies, vaccination strategies, and preemptive herd slaughter strategies. The authors concluded that preemptive slaughter of the highest-risk herds and vaccination of all animals within a specified distance of an infected herd consistently decreased the size and duration of an epidemic, compared with the baseline eradication strategy (Bates *et al.*, 2003b).

Schoenbaum and Disney (2003) modeled alternative mitigation strategies for a hypothetical outbreak of foot-and-mouth disease in the United States. Using 72 different scenarios, the authors compared epidemiologic and economic consequences among simulated FMD outbreaks in a generated population of susceptible herds. They suggested that the choice of an appropriate disease control strategy depends on herd demographics and the rate of contact among the herds. They concluded that preemptive slaughter and early ring vaccination could decrease the duration of an outbreak. Even though these mitigation strategies would initially be costly, they would decrease the duration and overall cost of an outbreak (Schoenbaum and Disney, 2003).

Le Menach *et al.* (2005) also assessed control policies in their FMD outbreak simulation model. The authors developed a stochastic farm-based model adapted to the French farm structure from models of the 2001 epidemic in the United Kingdom. The livestock data were only available at the town scale, so the farm location and number of animals in each farm were simulated over the boundary area of each French town. They found that preemptive culling and ring vaccination had the greatest impact on reducing the number of FMD cases and the length of the epidemic. The results of this model provide useful information for decision makers planning the response to an epidemic of FMD re-emerging in France.

Results from simulation models suggest that in some situations control measures under current legislation would not be sufficient to control FMD in a particular area. According to Martinez-Lopez *et al.* (2010), results from their simulation model in the Castile and Leon region of Spain suggested that the control measures specified in the Spanish and EU legislations were not the most effective strategies to control FMD

spread. The authors modified a stochastic spatial disease state-transition model to simulate the hypothetical spread of FMD in the study area. They concluded that preventive depopulation or vaccination at <1 km and < 3 km radii, respectively, around infected premises, was more effective in controlling the spread of FMD epidemics in the Castile and Leon region. The current strategy is limited by Spanish legislation to < 3 km and < 5 km radii for depopulation and vaccination, respectively. When evaluated within the simulation model, the conventional strategy did not result in any significant reduction of the magnitude of the epidemic in the region and was not cost-effective (Martinez-Lopez *et al.*, 2010).

Epidemiological modeling is not only studied in FMD-free countries but it has been applied in FMD-endemic countries as well. Wongsathapornchai *et al.* (2008) used epidemiologic risk modeling to evaluate various FMD control programs in southern Thailand, where FMD is endemic. The authors used a quantitative risk assessment to ascertain the probability of FMD introduction and used an intrinsic model to evaluate impact. Five scenarios were created to assess the estimated cumulative incidence of FMD and the impacts of nonstructural protein (NSP) testing, mass vaccination, and culling. The results of the study suggested that vaccination has a greater impact than the use of NSP testing (Wongsathapornchai *et al.*, 2008).

Spatial analysis

Drawing maps and studying spatial patterns have been done for thousands of years. The human eye and brain are not capable of completely analyzing complex spatial patterns;

therefore, techniques for examining these patterns have been developed. One of the most popular cartographic tools for geographers is the dot map. If the size of the study objects is small compared with the distances between them, their position may be adequately represented as a dot on a map (Reich and Davis, 2003). In spatial analysis of infectious animal disease, the dot or point usually represents the location of a livestock farm, as was done in the study of a point pattern model of foot-and-mouth disease by Gerbier *et al.* (2002). Sometimes the objects of interest are too numerous to completely map. Methods of sampling, such as quadrant sampling and distance sampling, are then applied in order to detect the type of pattern or spatial association between two or more groups.

A method for analyzing the properties of a point event distribution, such as infected point of livestock farms, is density estimation. Density estimation is the construction of an estimate of the density function from the observed geographical or spatial data (Silverman, 1986). Kernel density estimation is a non-parametric way to estimate the probability density function of a random variable. The smoothness and modeling ability of functional approximation are controlled by the kernel bandwidth, also called window width or smoothing parameter (Bors and Nasios, 2009). Kernel density estimation could be used to extrapolate the data to the entire population, so that this estimation can help visualizing spatial aspect such as many epidemiological data.

In epidemiological study, spatial analysis techniques have been used to study space distribution of diseases, including FMD, and their determinants. Examples of spatial determinants of FMD are density of the livestock population and the distance between susceptible and infected premises. Spatial analysis has also been applied as a tool for disease control arrangement.

Spatial analysis in epidemiological study

The distributions of disease events in space are important because most epidemiological studies attempt to define the geographic limits of disease events or concerns and also the patterns of spatial distribution within those limits. A disease may be limited geographically for many reasons that relate to forces that can act upon the susceptible host populations or upon the disease agents. Spatial patterns of disease distribution are widely divided into random, contagious, and regular patterns. There is special interest in the clustering of disease events because it may help in identifying a common environmental factor or source of exposure (Schwabe *et al.*, 1977).

Spatial epidemiology concerns the analysis of the geographical distribution of the incidence of disease. The simplest unit that can be analyzed is a map of the locations of disease cases using symbols of sizes that are small compared with the distances between them. Therefore, in epidemiological study, the locations of disease cases are sufficiently represented as dots on a map. The associated issues related to map production and the statistical analysis of mapped data must be applied. Since mapped data are spatial in nature, the application of spatial statistical or geostatistical methods is a core part of the analysis. One of the important stages of map construction that can be associated with spatial information is the choice of scale. A suitable scale for the map must be chosen and the choice leads to a process of averaging spatial information from higher levels of resolution. The small scale, for example, could be executed for disease clustering and applied to explore putative sources of hazard. The large scale would be applied for illustrating disease mapping, ecological analysis, infectious disease modeling, and epidemiological surveillance (Lawson, 2006).

In geographical data, the relative risk function over a geographical region can be estimated effectively using kernel density estimation to examine the spatial distribution of disease cases and a sample of controls (Bithell, 1990). Examples of this in the literature include studies by Bithell (1990) and Mukherjee *et al.* (2002). Bithell made use of a two-dimensional Poisson process to estimate the density of cases of childhood leukemia in the vicinity of the Sellafield nuclear reprocessing plant in Cumbria, UK. The author defined the relative function as a ratio of the density of cases of childhood leukemia and controls. Other researchers used the spatial technique of density estimation to explain how the risk of developing goiter varied at different villages within the study area from the Indo-Nepal border to the Sitamarhi district headquarters in Muzaffarpur in the Sub-Himalayan belt area of India (Mukherjee *et al.*, 2002). The results were presented as a three-dimensional perspective plot with the x and y axes representing distances and the z axis representing the probability density function of the goiter-affected population. These studies applied the kernel density estimation technique to determine spatial distribution of disease, including levels of risk factors. Results from the studies were displayed as plots or maps which help in better visualization for understanding disease patterns.

Geostatistical and spatial statistics methods were utilized for studying highly pathogenic avian influenza (HPAI) subtype H5N1 (Ward *et al.*, 2008). The authors stated that the purpose of their study was to evaluate the usefulness of statistical and geostatistical methods to determine how HPAI might spread through a national population of village poultry in Romania. Methods in the study included directional statistics, Moran's correlation statistic, variography, and krigging. Risk mapping was

used to visualize the evolution of the epidemic which could be characterized into two parts: disease introduction, local spread, and sporadic outbreaks; and long-distance disease spread with rapid epidemic propagation. The researchers found that the environmental characteristics and the landscape in the Danube River Delta area played a critical role in the introduction and initial spread of HPAI. In later seasons the movement of poultry might have introduced the infection into central Romania. The authors noted that the outbreaks of HPAI H5N1 in Romania between 2005 and 2006 were not randomly distributed in time and space, and they identified differences in the spatial distribution of the outbreaks during time phases. In this study, HPAI H5N1 could have been introduced into domestic poultry populations from wild waterfowl, but the virus spread within domestic poultry populations was likely to be via the movement of live birds or fomites.

Riley (2007) reviewed studies on four diseases—measles, foot-and-mouth disease, pandemic influenza, and small pox—to demonstrate the benefits of different methodologies for spatial models. Patch models, distance transmission models, multi-group models, and network models were represented as the methodologies of large-scale spatial-transmission models for the four diseases, respectively (Riley, 2007). Riley's review helped characterize the large-scale patterns and evaluate the impact of interventions.

Spatial analysis for foot-and-mouth disease

The spread of foot-and-mouth disease in the United Kingdom was analyzed using a point pattern model (Gerbier *et al.*, 2002). The farm-to-farm process of infection

transmission was examined by point-pattern methodology. In the model description, two broad types of risk factors were classified regarding local transmission and long-distance transmission. From this study, the authors stated that the spatial spread of FMD in the 1967-1968 UK epidemic was influenced by heterogeneity of exposure to the virus, animal density, and the networks formed by contacts between farms.

Spatial clustering of disease may help in identifying a common environmental factor or source of exposure. For example, this technique has been used to quantify the associations between hypothesized epidemiological factors and the spatial distribution of FMD in Nepal (Chhetri *et al.*, 2010). Methods in this study included cluster analysis implemented using SatScan software, and Bayesian mixed-effects Poisson regression to model the association between FMD cases and factors hypothesized to be associated with the risk of having an FMD-positive farm in a district. Spatial scan statistics and cluster analysis techniques identified two significant clusters of FMD reports. The clusters were identified risks of FMD reports, such as size of human, buffalo populations, and number of technicians. This finding increased the knowledge on the epidemiological dynamics of FMD and improved the efficiency of resource allocation and control efforts in Nepal.

The issues relating to the epidemiology of the 2001 FMD epidemic in the UK, including analysis of spatially-referenced data, were examined by Lawson and Zhou (2005). They discussed the use of exploratory statistical tools such as density estimation and nonparametric regression, and considered the need for descriptive models for space, time, and space-time epidemic dynamics. They also discussed the advantages of using Bayesian models for disease spread and applied them to the UK outbreak. From several analyses in this study, the authors concluded that spatial statistical and GIS-based

methods have an important place in the analysis of animal diseases because they can lead to insights in exploratory settings, ecological studies and surveillance.

Spatial analysis can be combined with epidemiologic methods such as a retrospective case-control study to investigate the potential geographic risk factors of disease transmission. Such a study was done on the geographic and topographic determinants of FMD transmission in the 2001 UK epidemic (Bessell *et al.*, 2008). Methods in this study were univariate and multivariate generalized linear mixed model analyses of predictor variables and risk factors for FMD transmission. This study investigated features of the landscape and their impact on transmission during the period of the national movement ban during the outbreak. The results indicated that the presence of rivers and railways had an additional protective effect to reduce the probability of transmission between holdings.

Another study using the spatially-resolved farm census data from the 2001 FMD outbreak in the UK was conducted by a research team to formulate a spatially explicit distance-transmission model of FMD, with farms as the individual units of infection (Riley, 2007). The researcher applied the distance-transmission model to consider the vaccination priority in the UK outbreak. They concluded that prioritization of farms for vaccination based only on their proximity to infected premises (IPs) reported in previous 10 days, or to dangerous contact with those IPs, was better than other vaccination plans. This new priority was shown to be the most effective in terms of reducing the number of animals culled to eradicate the disease.

The FMD epidemic control area may be more effectively identified when local and regional georeferenced data are considered. Using data from Uruguay in 2001, Rivas

et al. (2003) explored whether early analysis of spatial data may result in identification of variables associated with epidemic spread of foot-and-mouth disease. The authors created a georeferenced database and performed a retrospective analysis. They compared mean or median results of day 1 to day 3 versus day 4 to day 6 of the epidemic and the results of correlation analysis. They found that as time progressed, disease spread was significantly associated with increases in road density, cattle density, and dairy cattle production, but decreased with smaller farm size and greater distances between the case farm and the nearest road. It was concluded that the direction of an epidemic can be assessed on the basis of road density and spatial variables as early as six days into the epidemic (Rivas *et al.*, 2003).

Conclusion

In conclusion, this literature review explored background data and epidemiology of FMD, epidemiological modeling and spatial analysis techniques and their application in understanding the epidemiology of FMD and its control measures. Since the costs of a FMD outbreak and all the measures required to control the disease are very high, appropriate prevention and control programs could be economically beneficial.

Simulation modeling and spatial analysis can play an important role in assessing different control strategies for FMD, making it easier for authorities to make appropriate decisions. The fundamental concepts from studies and approaches discussed in this review could be used to initiate a study on FMD simulation modeling and spatial analysis in a particular study area, such as the hypothetical spread of FMD in the central United States. Also, we reviewed these papers in order to stimulate some ideas for parameter generation process

for an FMD simulation model. We have learned that identifying premises as the unit of interest and including their geographical locations would help determine the outbreak area in a large-scale study. Therefore the parameters for a large-scale spatial FMD simulation model should be based on the herd and not on the individual animal. This review is an initial step in the process of developing a model to assess FMD control strategies in the central United States. The published papers noted in this review had limitations with respect to generation of parameters to simulate a model and evaluate simulated disease control strategies. Simulation modeling and spatial analysis for the purpose of evaluating FMD control strategies need many specific parameters and data for each specific study. Therefore, while the papers reported here can be helpful for designing future studies, any investigation must utilize parameters, data, and methodology that uniquely represent the study area.

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CHAPTER 2: SIMULATION MODELS OF AN OUTBREAK OF FOOT-AND-MOUTH DISEASE IN THE CENTRAL UNITED STATES: PARAMETER GENERATION PROCESS

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Summary

Foot-and-mouth disease (FMD) is one of the most important viral infectious diseases of animals. Any FMD-virus-free country or area may want to simulate a hypothetical outbreak in order to prepare control strategies for the disease should the virus be introduced. Input parameters are among the most critical components of any simulation model used for epidemiological study. Because they will affect the model result, the values for input parameters such as premises location, disease stage durations, and disease transmission probabilities should be chosen specifically for each study. The objective of this study is to generate reasonable input parameters for FMD simulation models. The methods of generating the parameters are gathering of study premises with their geographical locations, literature review, gathering expert opinions, and statistical analyses. The sensitivity analysis of specific input parameters was analyzed by comparing disease spread of various values of specific input parameters. Once generated, these parameters will be used as the input parameters for a hypothetical outbreak of FMD in the central United States; different disease control strategies will be examined for this major cattle feeding region. The simulator tool for the study is the North American Animal Disease Spread Model.

Keywords: Simulation model; Disease; Foot and mouth ; Parameter; Central United States

1. Introduction

Foot-and-mouth disease (FMD) is a highly contagious viral disease in cloven-hoofed animals that may spread rapidly and unexpectedly on a national and international scale. Introduction of the FMD virus into disease-free herds, areas, or countries is likely to result in very rapid spread with a high morbidity rate (Geering et al., 2002). The United States has been an FMD-free country since 1929 (Graves, 1979). The U.S. has many areas of intense livestock production such as the beef feedlots found in Colorado, Kansas, Nebraska, Oklahoma, and Texas. In this major cattle feeding region, approximately 78% of cattle fed in the U.S. are finished and more than 65% of cattle slaughter and beef processing occurs here (NASS, 2011a; NASS, 2011b). As demonstrated in Pendell et. al. (2007), an introduction and spread of FMD in this region could have devastating animal health and economic consequences.

Epidemiological simulation modeling can allow better understanding of the pattern of disease if FMD virus was introduced into a novel area. Control strategies can be placed into the model and observed for changes of disease pattern; this can help delineate the most practical strategies to control and eradicate the disease from the area. For this investigation, the study area included 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas). This region is selected because of the intensive beef feedlot region and includes FMD-susceptible livestock animals such as cattle, swine and sheep. This area would be extremely vulnerable to the spread of FMD.

To simulate the spread of FMD, information is needed such as the geographical location of livestock operations, duration of disease stages (latent, subclinical, clinical),

the probability of transmission following contact, and the frequency and distance of contacts among livestock operations. These parameters cannot be obtained from U.S. data because the U.S. has not experienced an FMD outbreak for a long time and national information on the frequency and distance of animal movements is not available.

Although there is a lack of U.S. data to generate parameters, parameters can be generated from literature reviews, statistical techniques, and expert opinions, and brought together and placed in the simulation model scenarios in order to describe a hypothetical FMD outbreak in the specific study area.

The primary objective of this study was to collect and generate livestock premises with their geographical locations, disease stage duration and transmission parameters for FMD, and to quantify the distributions of variables related to the parameters in order to simulate hypothetical outbreaks of FMD in the central United States. The simulation will be run by the North American Animal Disease Spread Model (NAADSM). A secondary objective was to analyze the sensitivity of our model to specific input parameters.

2. Materials and methods

2.1 Gathering of study premises

The study area was composed of 413 U.S. counties in the states of Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas. The main FMD-susceptible livestock species are cattle, pigs, and sheep. Based on differences in disease progression and spread as well as intensity of livestock management, these species were classified into five different production types: beef feedlot, cow-calf, dairy cattle, swine, and sheep.

The unit of interest required by the disease spread model is at the herd or premises level. Because of this, the population database was collected and modified as required to meet the requirements of the disease spread model. For each herd, the disease spread model requires a herd size as well as a geographical location in latitude and longitude using the decimal degree system; some original data had to be changed to this system before it could be incorporated into the model.

The number of premises (or herds), including the maximum herd size and location of each premises within the study area, was derived from several sources. Most livestock operations that are larger in size (e.g., confined animal feeding operation or CAFO) are required to receive environmental permits. Through the Open Records Act, data from the CAFOs were obtained. The maximum number of head at each premises, the majority being beef feedlots, was collected from State agencies (see Table 2.1 for data sources). Unfortunately, the location, size, and number of smaller livestock operations were not available. This information for these livestock operations (cow-calf, dairy cattle, and swine) was generated by a spatial modeling method called Farm Location and Animal Population Simulator (FLAPS) in ArcGIS software starting with the county-level National Agriculture Statistics Service (NASS) data. This spatial modeling method was described by Freier et. al. (2007).

There are three methods by which the States report the location of the CAFO premises. Kansas, New Mexico, Oklahoma, and Texas reported the geographical locations as latitude and longitude. Nebraska reported the geographical locations using the Public Land Survey System (PLSS) while Colorado reported premises by postal address. Google Earth was used to locate geographic site for the Colorado premises. The

sheep premises within Colorado were collected as secondary data from Mayo (2006). The PLSS, which describes land in the United States by a rectangular system, was used in data from Nebraska. These data were then converted to an estimated point location by first locating the central point of the rectangle for the first premises. The subsequent premises within the same rectangle were selected at the points between the center and the corners. Finally, all geographical locations of premises were converted to the decimal degree latitude and longitude system. The sources of study premises by state, production type, and the original geographic location system were listed (Table 2.1).

2.2 North American Animal Disease Spread Model

The North American Animal Disease Spread Model (NAADSM) is a stochastic state-transition model for the spread of highly contagious diseases of animals. NAADSM users can establish parameters to define model behavior in terms of disease progression; direct contact, indirect contact, and airborne dissemination; and implementation of control measures such as destruction and vaccination. The direct cost associated with control measures are also taken into consideration. This model is being used to evaluate outbreak scenarios and potential control strategies for exotic animal diseases in the United States, Canada, and elsewhere. NAADSM is freely available via the internet at <http://www.naadsm.org> (Harvey et al., 2007).

Input parameters of the NAADSM are herd-level, disease and spread parameters, disease detection, tracing out, control measures, and priority of actions. All parameters in this study will be generated following the requirements from the NAADSM. NAADSM also allows for cost accounting, but is not modeled in this study because other additional research will estimate the economic impacts of FMD outbreaks. Depending upon the

parameter, the parameter types can include probability density function, rate, probability (0 to 1), yes/no, degrees, scalar value, relational function, fixed integer value, and rank order. Since the simulation model of an FMD outbreak in the central United States will be run by NAADSM, all input parameters have to be generated following the NAADSM guidelines. The generated parameters are presented in the results of this paper.

2.3 Assumptions for the model

The model described in this study of a hypothetical FMD outbreak in the six-state study area is based on a number of assumptions:

- a) That there are only five production types of livestock operations in the study area. Other possible susceptible species and wildlife are excluded.
- b) That the population is closed and the population size is constant. Individual herds do not enter or leave the study area except via destruction as a control measure.
- c) That there is no host immunity at the start of the outbreak. All animals are naïve to FMD.
- d) That all herds in the same production type have the same disease parameters.
- e) That for within-herd direct contact the models take on the assumptions of the classic Reed-Frost model.
- f) That every individual in the initial population is equally susceptible to disease.
- g) That individuals within a herd in the the population are equally likely to come into contact with any other individual.
- h) That there are homogenous contact rates between specific pairs of production types, such as beef-feedlot to swine, beef-feedlot to cow-calf, etc.
- i) That there is no mortality from FMD or other causes during the simulated outbreak.

j) That there are no virus carrier states for recovered animals.

These assumptions will be described for sensitivity analysis of input parameters. They will also be described for assessing control strategies for FMD by simulation models in next series of research.

2.4 Literature review

Mardones et al. (2010) reported the animal-level duration of different stages of infection of FMD virus (FMDV) based on a systematic review of previously published work, and they determined the animal-level values of critical parameters such as the duration of latent, subclinical, incubation, and infectious periods of FMDV serotype O. The methods of their study were literature review, defining parameters and predictors, collection and extraction of data, statistical analysis of data distributions and time-to-event models. A systematic review of 19 publications, including results from experimental trials and a meta-analysis, was executed to extract individual values related to FMDV transmission. The values for the duration of the stages of FMDV infection were extracted from 295 animals in four reference laboratories (Mardones et al., 2010).

The FMD stage durations were fit using equal width intervals for continuous and discrete data and presented as distribution function types. The animal species were identified as cattle, pig, and small ruminant (Mardones et al., 2010). Based on the results of their study, we modified the distribution of durations as the input disease stages in NAADSM.

The review and meta-analysis of disease stages from Mardones et al. (2010) were based on many experimental animals. The duration determined for the latent and

subclinical periods will be used directly as input parameters on a herd basis for NAADSM because if infection in a herd starts with one infected animal, the duration of the latent and subclinical periods at the herd level is the same as at the individual animal level. The infectious clinical period at the herd level starts when the first animal in the herd becomes clinically infectious, and lasts until the last animal in the herd is no longer clinically infectious. Thus, the duration of the clinically infectious period in the herd depends both on the number and distribution of the study population as well as the duration of the clinically infectious period at the individual animal level. To estimate the duration of the infectious clinical period at the herd level, the animal-level infectious clinical periods from Mardones (2010), distribution of herd size for the production type, and duration of other disease stages were put into WithinHerd (WH) 0.9.4, a software package that estimates herd-level disease state duration. In our study, we separately estimated the herd-level disease state duration for beef feedlot, cow-calf, dairy cattle, swine, and sheep using this software. The figures for period of disease stages can be presented as probability density functions (PDF) distribution graphs.

The immune period is required by NAADSM. Mardones et al. (2010) did not research the immune period for animals recovered from FMD. This immune period is important because the disease control programs, such as animal destruction, could not effectively cover large numbers of infected premises over a long outbreak period. During such an outbreak it is possible to have some immune herds become susceptible again. The immune period parameter is described more fully in section 2.7.

For disease transmission, the mean baseline contact rate for individual production type combinations and the distance distribution of recipient units were estimated by

expert opinion (Sanderson, 2006) and derived from Pendell (2006). Because of some differences in production type classification, some combinations were not estimated. For production type combinations where expert opinion was not available, estimates from similar production types were used.

The parameters for sheep were gleaned from Johnson (2008) in his unpublished report. From this we used the disease parameters, with the exception of the infectious clinical period, as well as the spread parameters.

2.5 Gathering of expert opinions

Some input parameters required for NAADSM, such as disease detection, surveillance, zoning, and disease control, are not currently available in the published literature. As a result, expert opinions were sought to aid in determining these parameters.

The detection option and tracing option were parameterized by expert opinion. Each of production types was estimated disease detection models as cumulative probabilities and converted them to be daily probabilities. Direct and indirect contact tracings were estimated their probabilities of trace success in 28 days before detection (Hill, 2009). The relational function of the zone parameter was estimated by group of experts. The group estimated effect on baseline and restricted movement rates in zones when zones were included in the model (Salman et al., 2009). The destruction and vaccination options were estimated by personal contact with experts. These disease control options were estimated their capacity of implemented programs. Capability of man power and distribution of livestock premises size in the study area was based on

expert opinion (Corso et al., 2009). These estimated parameters were given as opinions based on experiences from related research and work in the United States.

2.6 Statistical analyses of data distribution

In order to determine the clinical infectious period on a herd basis, information on the distribution of the study population was needed. The distribution of population for herds within each production type were fitted to common theoretical distribution and extracted to probability density functions (PDF) by @Risk 5.0 (Palisade Inc., Newfield, NY, USA). A simulator tool called WH version 0.9.4, an extension of NAADSM, helped simulate the iterations of the duration of herd infectious clinical period. The inputs for the WH 0.9.4 were the population distributions and disease stage duration from the review by Mardones et al. (2010). The individual iterations for the infectious clinical period that resulted from the simulation run of the the WH 0.9.4 were fit to common theoretical distributions and the best-fitting distribution was identified via chi-square goodness of fit testing using @Risk 5.0.

For each species/management classification, distribution of population size helped determine more precise herd-level periods. In our study we separately defined the distribution of population of beef feedlots, cow-calf, dairy cattle, swine, and sheep using the WH 0.9.4.

2.7 Animal-level and herd-level FMD immunity: Review of a critical disease parameter for FMD simulation modeling

Because the hypothetical FMD outbreak could cover a long period, animals that had been infected and not destroyed could potentially become re-infected when natural immunity wanes. Therefore, the duration of immune periods of cattle and pigs, the primary species of interest, were reviewed and analyzed to form the parameter for duration of natural immunity used in NAADSM.

There are not many appropriate references for the immune period of convalescent cattle and pigs that can be used to model the simulation of an FMD outbreak. Some experimental studies presented results as the immune period of convalescent animals, but these did not follow animals until immunity waned (Sorensen et al., 1998; Robiolo et al., 2006). In most cases the number of post infection days (dpi) was limited, so the challenged animals were not observed long enough. In addition, serological testing (Sorensen et al., 1998) may not completely reflect immunity to FMD, although there is evidence that protective antibody may be present for the effective lifetime of some cattle (Garland, 1974). In one study involving cattle (Cunliffe, 1964), the author followed cattle through 4.5 years before challenging them with the virus. However, the study was limited to only three experimental animals.

2.7.1 Immune period of cattle

Experimental FMD infection of susceptible cattle has shown that they remained strong seropositive for more than 395 days (Sorensen et al., 1998). In this study, a group of experimental steers was challenged by the intradermatolingual and direct contact

routes with FMDV type O. Detection of non-structural proteins (NSP) 3D, 3AB, and 3ABC in serum by ELISA was used to indicate sero-positive status in this experiment. While monitoring 3 ABC, Robiolo et al. (2006) followed the duration of immunity in 11 experimentally infected animals for up to 233 dpi. Some animals remained positive even to 570 dpi, but the authors did not state how many and did not report the levels of 3ABC in these animals.

When animals were re-challenged with homologous virus within 6 months of an FMD infection, their immunity was found to be protective against the development of clinical signs (Doel, 2005). In a previous experiment (Cunliffe, 1964), convalescent cattle were challenged 1 year after exposure to virus and were found to be protected. Cunliffe (1964) also held cattle for 4.5 years after initial infection and challenged them with the virus. One of three animals was protected. To provide evidence to support the suspicion of effective lifetime immunity to FMD, eight steers were challenged 5.5 years after initial infection and found to have some level of protection (Garland, 1974). This group of experimental animals did not show progressive lesions. Research on the duration of immunity to FMD of convalescent cattle was summarized (Figure 2.1).

2.7.2 Immune period of pigs

The results of exposure of convalescent pigs to FMD virus are variable (Gomes, 1977) (Figure 2.2) and the duration of immunity is shorter than that of cattle (Doel, 2005). In one experiment (Cunliffe, 1962), one out of five convalescent pigs developed the disease after they were challenged at 128 dpi by contact with a virus infected pig. Another study (Gomes, 1977) followed the immune response of experimental pigs convalescent one year from FMD infection. Four out of 12 pigs were found to have some

resistance to developing FMD lesions after being inoculated following the 360-day convalescent period.

2.7.3 Immune period generated from the research

The immune period was analyzed by the survival analysis as double censored data. This approach allowed the immune period to be viewed as success or failure of having protective immunity on the day of observation instead of looking at success only. These will be used as one of the important input disease parameters for the NAADSM to simulate the spread of FMD in the central United States.

2.8 Sensitivity analysis of input parameters

Sensitivity analysis was used for assessing the relative importance of model input factors. These techniques verify which input factors are important in determining the uncertainty in the output of interest (Saltelli, 2004).

From parameter generation process, a baseline scenario was constructed based on the current knowledge of epidemiology of FMD and estimation of disease control activities in central United States. This scenario can be used to run simulation in disease spread model and observed a hypothetical outbreak. Some input parameters in the scenario might be allowed to vary to incorporate the uncertainties in parameter estimations. These input disease parameters were latent period, infectious clinical period, immune period and input contact parameters were contact rates of disease spread, distance of recipient premises, and probability of airborne spread. These input parameters were tested to determine uncertainty in disease spread.

To test the change of output, the input parameters as PDF of baseline distribution were set a range for their 1st, 5th, 25th, 50th, 75th, 95th, and 99th percentiles. These parameters were infectious clinical and immune period. If the change of any output were not much different from of the baseline, the wider range values of input parameters were added to observe the output change. The wider range values included their assumed minimum and maximum values of each input parameter. For the latent period, changes were tested using 0, 2, 5, 10, 20, and 30 days of the period which were estimated from distribution of the latent period of the baseline scenario. For input parameters described as probabilities as the direct and indirect contact rates, changes were tested using half and

double of original values. If the changes of output were not much different from the baseline, the wider range of probabilities were added to observe the output change. The distance input parameters of direct and indirect contacts were set as uniform distribution from 0 kilometer to 3, 10, 50, 100, 200, and 500 kilometers. The probability of airborne spread were set as 0.00, 0.01, 0.02 (baseline probability), 0.04, 0.10, 0.20, and 0.50.

To observe the effect of input parameter changes, a part of study premises in the center of study area were selected. Susceptible premises in southwest Kansas were used for sensitivity analysis. These premises included beef feedlot, cow-calf, dairy cattle and swine. The effects of change from input parameters to outcome as disease spread were estimated by cumulative proportion of infected premises (CPIP) by days post infection (DPI). The simulation was run 400 iterations in NAADSM for each value of input parameter being tested. Entirely, there were 53 sets of simulations run for 8 different input parameters. The medians of daily new infected premises were transformed to be CPIP using the following formula.

$$(1) \text{ CPIP} = \frac{C}{S}$$

where C is cumulative infected premises by DPI and S is initial number of susceptible premises at day zero ($n = 1,774$).

The effect of change was observed by the shape and approximate value of cumulative plots as CPIP. A cumulative plot of baseline scenario was constructed to compare CPIP by DPI to different values of input parameters .

3. Results

3.1 Study premises

Cow-calf operations represented the highest number of premises in the study area (91,629 premises, 89.6% of all study premises) (Table 2.2). The highest number of animals was beef feedlot (16,463,644 head representing 43.7% of all animals).

The geographical locations of the 102,283 premises by production types in the study area are illustrated (Figure 2.3). The study area encompasses 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas). This region has a high concentration of beef feedlots and was set as the initial area for FMD virus introduction in the simulation spread model. The simulated outbreak would spread through the surrounding counties that are an extended radius from this region. The stars in Figure 2.3 mark the location of a large-size beef feedlot (feedlot with a one-time feeding capacity of 20,000 to 35,000 head) in south west Kansas, and represents the origin of our hypothetical FMD outbreak.

3.2 Disease stage parameters

The herd-level disease stage durations as gleaned from the review and/or generated by WH 0.9.4 are presented in Table 2.3. These data are presented by disease stages, production type, and PDF distribution.

Latent and infectious subclinical period of all productypes were developed so that the PDF distributions were identical with the original paper of Mardones et al. (2010). Infectious clinical periods that were fitted to study population had different function

curves, but all wider than the distribution from the original reviews. Means of infectious clinical periods in cattle species were about 20-26 days, but were 64 and 10 days in swine and sheep respectively. The right tails of curves of cattle species were up to 32-42 days, but were approximately up to 70 and 80 days in swine and sheep. The distributions of the immune periods for cattle and pigs from the survival analysis are left-skewed distribution. Mode of cattle immune period was much longer than of swine immune period (2,300 days and 340 days respectively and approximately). The graphs of the PDF distribution can be presented as pdf plots. Details are available from senior authors upon request.

3.3 Disease transmission parameters

The disease transmission parameters in Table 2.4 present the density of distance distribution of recipient units for direct and indirect contact among production type combinations. To illustrate these parameters, these parameters can be presented as graphs of the density of distance distribution of recipient units for the combinations. Details are available from senior authors upon request.

3.4 Sensitivity analysis of input parameters

The cumulative proportion of infected premises (CPIP) of FMD by days post infection (DPI) was measured by various input parameters. The CPIP of baseline scenario reaches its plateau at 0.12 on 50 DPI. The effect of change can be observed and compared to baseline scenario in the cumulative plots in Figure 2.4 to Figure 2.11.

When direct contact parameters were adjusted, CPIP was not sensitive to changes in direct contact rates and distance of recipient premises. All CPIP plots were very similar to the baseline scenario plot (Figure 2.7 and 2.9). When indirect contact

parameters were adjusted, CPIP was sensitive to changes in indirect contact rates and the distances. Half-value of the initial indirect contact rate resulted in lower CPIP, and the double value of contact rate resulted in higher CPIP. The half-value of the contact rate also resulted in longer DPI than both the baseline scenario and the double rate, respectively (Figure 2.8). Among distances tested, the maximum distance of recipient premises that resulted in the highest CPIP is 200 kilometers (Figure 2.10).

Changes in latent period also affected CPIP. In the model, the longer latent period resulted in the lowest CPIP but in the longest DPI. The 0, 2, and 5 days of latent period resulted in higher CPIP than the baseline scenario, but the 10, 20, and 30 days of latent period resulted in lower CPIP than the baseline (Figure 2.4).

Changes in infectious clinical period did not affect CPIP as much. The 5th to 95th percentile of the period of baseline scenario changed CPIP from 0.11 to 0.12 (6.14 percent change). Only the assumed minimum, as no infectious clinical period, caused a very low CPIP (Figure 2.5).

Changes in immune period did not change the CPIP. Only the assumed minimum, supposing no immune period, resulted in distinctly higher CPIP (Figure 2.6). Increase in probability of airborne spread in 1 kilometer in 1 day also affected CPIP (Figure 2.11).

4. Discussion

For the purpose of an FMD hypothetical spread in our study area, the estimated population distribution was collected from different sources. One limitation is the only available premises location data for sheep was for Colorado. Although this might not be identical to the actual population of the local area, these geographical data from systematized collection and generation could be used to study the hypothetical spread of FMD and reflect an outbreak situation in the study area.

Premises could have been grouped into more than five production types, such as by incorporating size of premises (e.g. small dairy, mid-size dairy, large dairy). However, we classified into only five because we examined the model mainly on a herd basis. Furthermore, too many parameters in the model can increase the computational requirements for this population beyond our capabilities.

In a study of the effect of a hypothetical outbreak of FMD, the stage of disease and the disease spread parameters are very important variables to simulate the spread of FMD. Some parameters could be gleaned from the literature review or expert opinion, but some data needed to be modified in order to fit the specific study population. For example, in our six-state study area the primary herd type was cow-calf, but the highest proportion of animal was from beef feedlots. The stages of disease as described by Mardones et al. (2010) could be used for some disease parameters in NAADSM; however, it is better to use values for the infectious clinical period that are fitted specifically to each production type of the study population. In this study, cattle that are reclassified to be beef feedlot, cow-calf, and dairy cattle allow for more specific values for the infectious clinical period according to their production type. For this reason, we

generated the infectious clinical period of each production type by developing separate values for species/management specific herd size distributions.

The U.S. has not experienced an FMD outbreak since 1929, although there have been epidemics of this disease elsewhere in the world. Epidemiologic studies from other FMD epidemics could provide disease spread parameters, and these variables might be used properly in some comparable areas. However, the livestock raising system in the U.S. may not be similar to that in areas where FMD outbreaks have occurred, and differences in production systems could result in different disease spread parameters. Specifically, our study area is an intense beef feedlot area in southwest Kansas plus the surrounding FMD susceptible livestock operation area. Although limited, expert opinions would be the best choice for logical disease spread parameters.

Results of the sensitivity analysis indicated that the effect of changes of contact rate and of distance of premises was only sensitive for simulations using indirect contact model. This result might be because indirect spread of FMD played a more important role than direct spread in the study area. Surprisingly, longer latent period resulted in lower CPIP along the observed DPI. This result also might be related to the effect of major indirect spread role. When disease transmission via indirect contact was modeled, animal premises did not transmit the virus in their herd latent period, but did so during their subclinical and clinical infectious period. The shorter latent period affected probability of trace success in direct contact model because with a shorter latent period, contact herds were more likely to be identified via disease detection rather than contact tracing. However, the direct contact played less role of disease spread in the model than of indirect spread. Charleston et. al. (2011) presented a new method to estimate the latent

and infectious period of FMD and indicated that the duration of infectiousness with clinical signs was shorter than previous other estimates. This experimental method investigated only direct contact with individual animal basis. Charleston et al.'s article is a new observation but could not compare to our sensitivity analysis of disease stages, which is on a herd basis and evaluates spread by both direct and indirect contact in the model.

In conclusion, this study was an attempt to generate the reasonable disease stage duration and disease transmission parameters of FMD for a hypothetical outbreak study in the central United States that will be run by the North American Animal Disease Spread Model (NAADSM). This study could be used as an initial tool to investigate characteristics of a hypothetical outbreak and the related interventions aimed at eradication and control of the outbreak.

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5. Tables

Table 2.1

Source of study premises and their original geographical locations used as input to simulate a hypothetical outbreak of foot-and-mouth disease, using population data from 2006-2008.

State	Production types	Source of data	Original geographical locations
Oklahoma	beef feedlot, dairy, swine	Agricultural Environment Management Service	Latitude/Longitude
	cow-calf, dairy, swine	FLAPS ^a	Latitude/Longitude by simulator
Texas	beef feedlot, dairy, swine	Commission on Environmental Quality	Latitude/Longitude
	cow-calf, dairy, swine	FLAPS	Latitude/Longitude by simulator
Kansas	beef feedlot, dairy, swine	Departments of Health and Environment	Latitude/Longitude
	cow-calf, dairy, swine	FLAPS	Latitude/Longitude by simulator
Nebraska	All species	Department of Environmental Quality	PLSS ^b
Colorado	beef feedlot, dairy, swine	Colorado Department of Public Health & Environment	Postal address
	cow-calf, dairy, swine	FLAPS	Latitude/Longitude by simulator
	Sheep	Research on Flock-level Prevalence of Bluetongue in Colorado (Christie Mayo, 2006)	Postal address
New Mexico	beef feedlot	Ground Water Quality Bureau	Latitude/Longitude
	cow-calf, dairy, swine	FLAPS	Latitude/Longitude by simulator

^a Farm Location and Animal Population Simulator.

^b Public Land Survey System.

Table 2.2

Estimated numbers of livestock within the demographic study area^a and used as input to simulate a hypothetical outbreak of foot-and-mouth disease, using population data from 2006-2008.

Population	Production type					Total
	Beef-feedlot	Cow-Calf	Swine	Dairy	Sheep	
Number of premises	2,875	91,629	4,896	2,777	106	102,283
Number of animals	16,463,644	7,702,702	11,481,555	1,984,164	18,587	37,650,652

^a The study area encompasses 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas).

Table 2.3

Herd-level disease stage parameters gathered from previously published animal-level literature and generated using WH 0.9.4^a. These parameters were used as input to simulate a hypothetical outbreak of foot-and-mouth disease in 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data from 2006-2008.

FMD infection stage	Production types	PDF ^b distribution (parameters)
Latent	Beef feedlot, Cow-calf, Dairy	Weibull (1.78, 3.97)
	Swine	Gamma (1.62, 1.91)
	Sheep	Gamma (9.90, 0.60)
Infectious subclinical	Beef feedlot, Cow-calf, Dairy	Gamma (1.22, 1.67)
	Swine	Exponential (2.53)
	Sheep	Gamma (2.40, 0.90)
Infectious clinical	Beef feedlot	Gaussian (25.53, 5.06)
	Cow-calf	Gaussian (19.54, 3.67)
	Swine	Log logistic (-37.25, 63.66, 10.59)
	Dairy	Triangular (0.00, 21.00, 34.36)
	Sheep	Log logistic (10.25, 11.28, 2.15)
Immune	Beef feedlot	Piecewise (see appendix)
	Cow-calf	Piecewise (see appendix)
	Swine	Piecewise (see appendix)
	Dairy	Piecewise (see appendix)
	Sheep	Triangular (100.00, 300.00, 500.00)

^a WithinHerd version 0.9.4, a software package that estimates herd-level disease state duration.

^b Probability density function.

Table 2.4

Disease transmission parameters for production type combinations, estimated and derived from expert opinion and used as input to simulate a hypothetical outbreak of foot-and-mouth disease in 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data from 2006-2008.

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Beef feedlot -> Beef feedlot	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.1
		Distance distribution of recipient units	Triangular (1.00, 100.00, 500.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	12.8
		Probability of infection transfer (if source positive)	0.1
Beef feedlot -> Cow-calf	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0003
		Distance distribution of recipient units	Triangular (1.00, 50.00, 500.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.026
		Probability of infection transfer (if source positive)	0.1
Beef feedlot -> Swine	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Beef feedlot -> Dairy	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0003
		Distance distribution of recipient units	Triangular (1.00, 50.00, 100.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.75
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (0.00, 30.00, 190.00)
Beef feedlot -> Sheep	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0003
		Distance distribution of recipient units	Triangular (1.00, 50.00, 100.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.026
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Cow-calf -> Beef feedlot	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.00005
		Distance distribution of recipient units	Triangular (1.00, 500.00, 1000.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.8
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Cow-calf -> Cow-calf	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0008
		Distance distribution of recipient units	Triangular (1.00, 20.00, 500.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.078
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Cow-calf -> Swine	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0
Cow-calf -> Dairy	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	Triangular (0.00, 30.00, 100.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.1
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (0.00, 30.00, 100.00)
Cow-calf -> Sheep	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0008
		Distance distribution of recipient units	Triangular (1.00, 20.00, 500.00)
	Indirect contact	Mean baseline contact rate(recipient units/unit/day)	0.078
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Swine -> Beef feedlot	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Swine -> Cow-calf	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate(recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0
Swine -> Swine	Direct contact	Mean baseline contact rate(recipient units/unit/day)	0.33
		Distance distribution of recipient units	Triangular (0.00, 20.00, 181.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	5.3
		Probability of infection transfer (if source positive)	0.2
		Distance distribution of recipient units	Triangular (0.00, 30.00, 90.00)
Swine -> Dairy	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0
Swine -> Sheep	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Dairy -> Beef feedlot	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.28
		Distance distribution of recipient units	Triangular (0.00, 30.00, 190.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	2.4
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Dairy -> Cow-calf	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	Triangular (0.00, 30.00, 100.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.026
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Dairy -> Swine	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0
Dairy -> Dairy	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.57
		Distance distribution of recipient units	Triangular (0.00, 30.00, 190.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	24.76
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (0.00, 39.00, 190.00)

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Dairy -> Sheep	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.026
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Sheep -> Beef feedlot	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.00005
		Distance distribution of recipient units	Triangular (1.00, 500.00, 1000.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.8
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Sheep -> Cow-calf	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0008
		Distance distribution of recipient units	Triangular (1.00, 20.00, 500.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.078
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)
Sheep -> Swine	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	0
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0
		Probability of infection transfer (if source positive)	0.15
		Distance distribution of recipient units	0

Production type combinations	Model	Parameters	Value or PDF distribution (parameters)
Sheep -> Dairy	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0
		Distance distribution of recipient units	Triangular (0.00, 30.00, 100.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.1
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (0.00, 30.00, 100.00)
Sheep -> Sheep	Direct contact	Mean baseline contact rate (recipient units/unit/day)	0.0008
		Distance distribution of recipient units	Triangular (1.00, 20.00, 500.00)
	Indirect contact	Mean baseline contact rate (recipient units/unit/day)	0.078
		Probability of infection transfer (if source positive)	0.1
		Distance distribution of recipient units	Triangular (1.00, 25.00, 100.00)

6. Figures

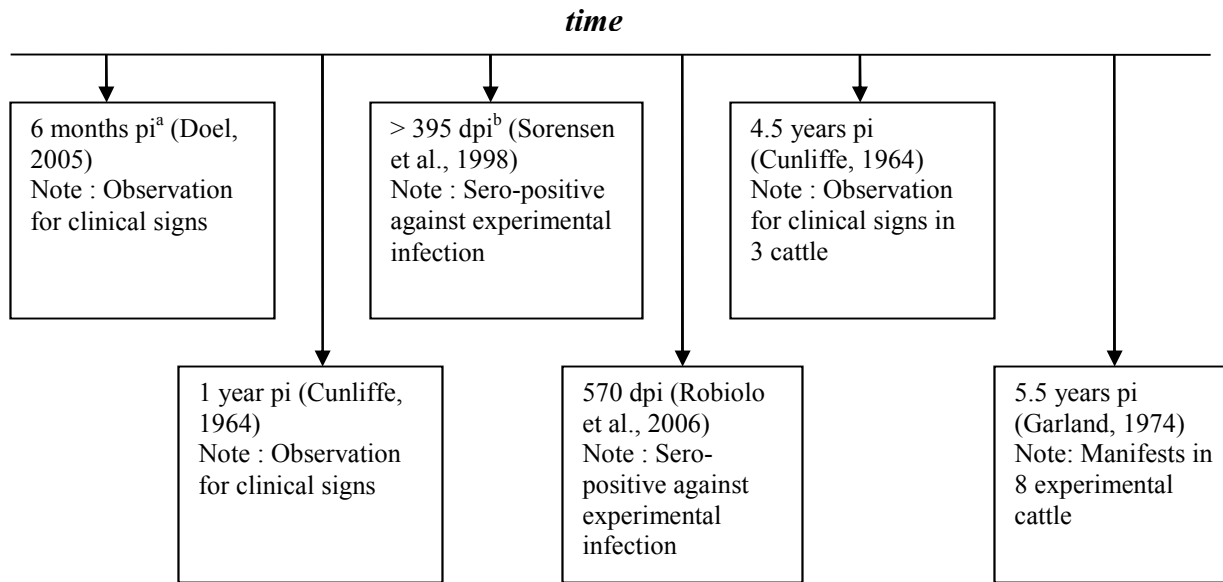


Figure 2.1. Duration of immunity to foot-and-mouth disease in convalescent cattle as shown in experimental studies from 1964-2006.

^a pi = post infection

^b dpi = days post infection

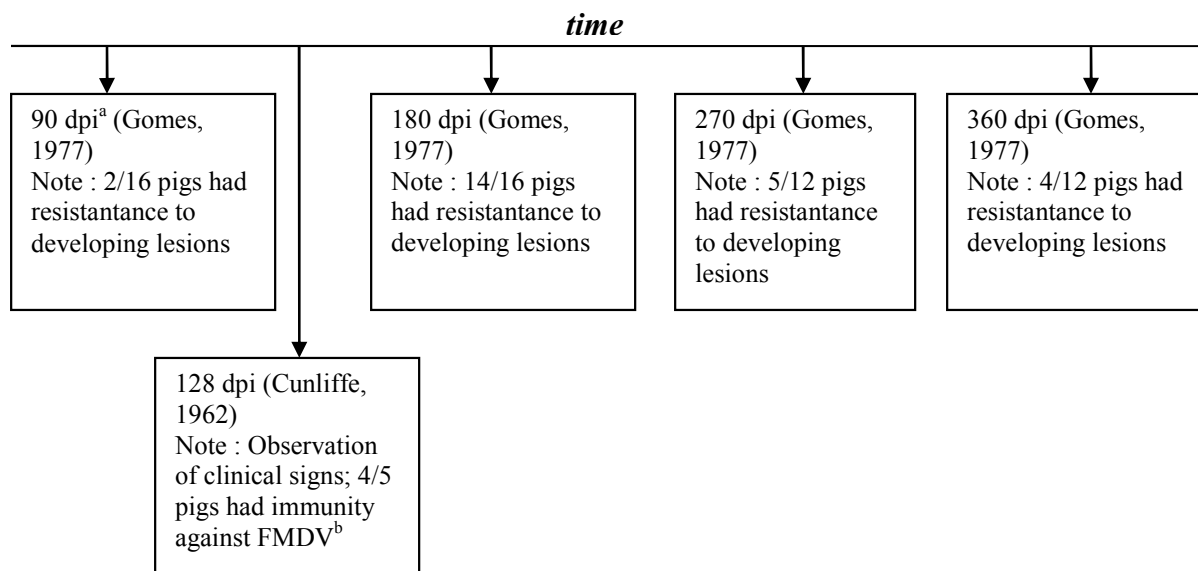


Figure 2.2. Duration of immunity to foot-and-mouth disease in convalescent pigs as shown in experimental studies from 1962-1977.

^a dpi = days post infection

^b Foot-and-Mouth Disease Virus

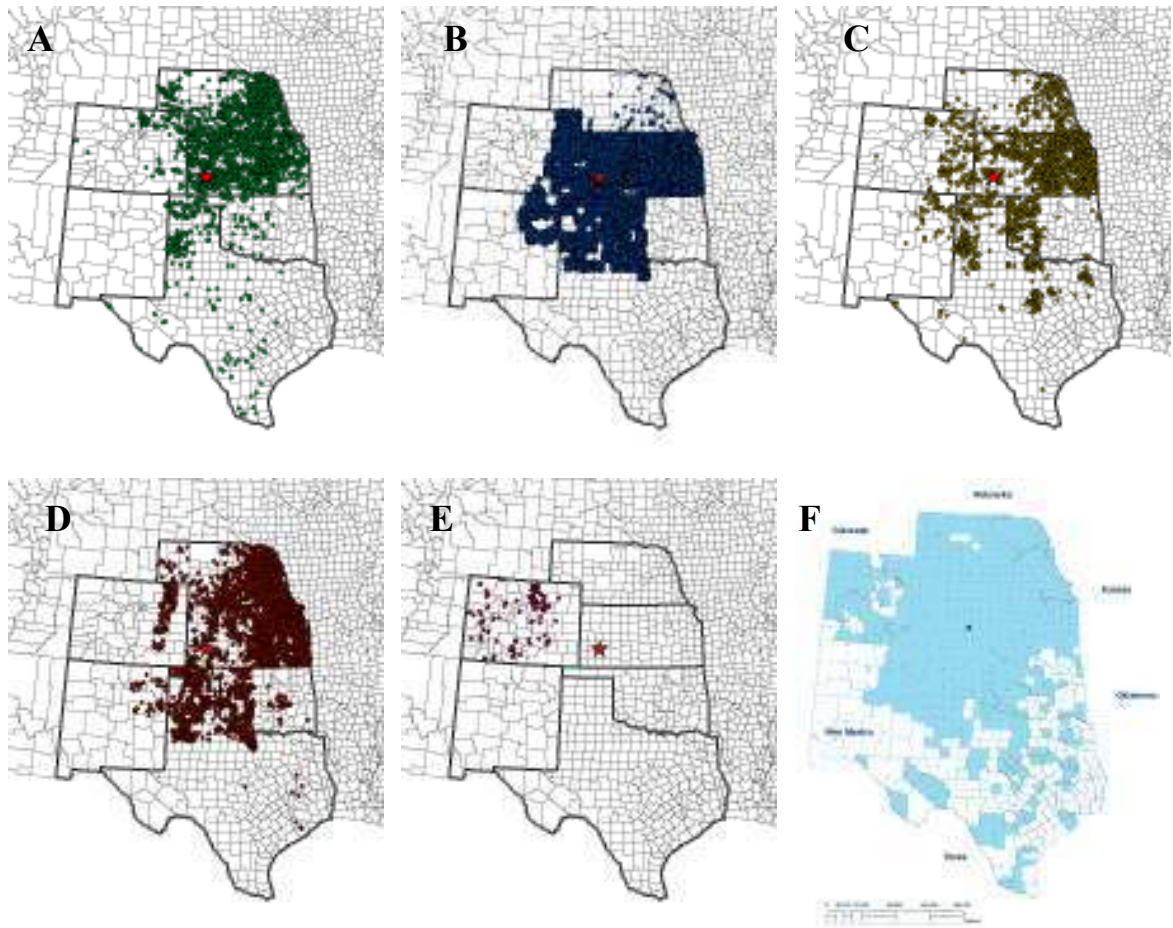


Figure 2.3. A – E represent geographical locations of susceptible livestock premises for a hypothetical outbreak of foot-and-mouth disease in the study area by production types (A=Beef feedlot, B=Cow-calf, C=Dairy cattle, D=Swine, E=Sheep) using population data from 2006-2008. F illustrates the 413 study counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas) that include the susceptible premises. The star represents the approximate point of origin of the hypothetical outbreak.

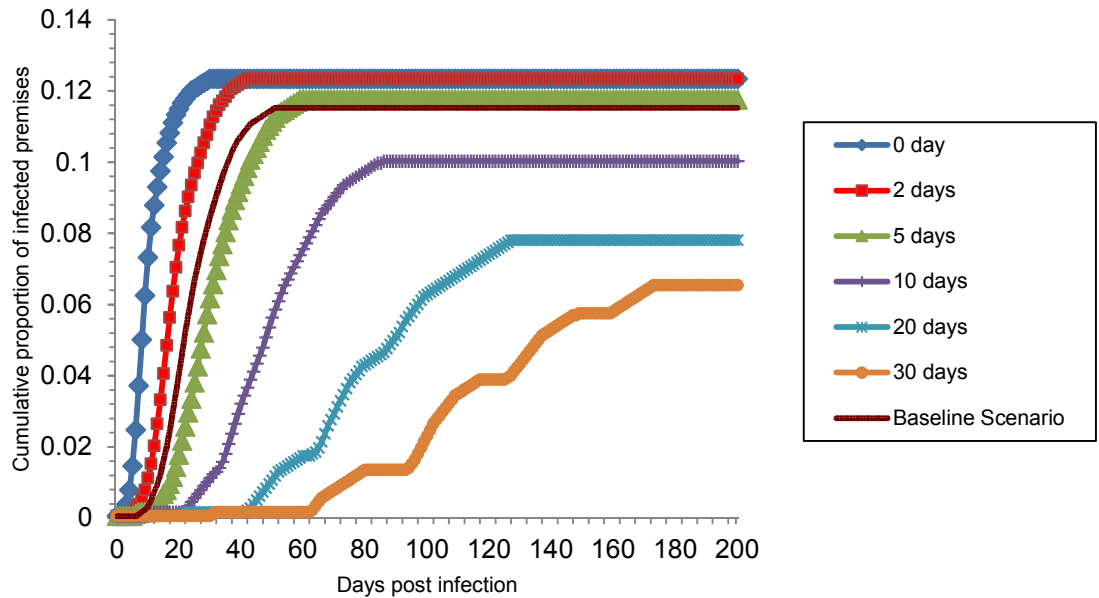


Figure 2.4. Relationship between days post infection and cumulative proportion of infected premises using different latent periods of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. Latent period of the baseline scenario used information from previously published literature. The 0 day, 2 days, 5 days, 10 days, 20 days, and 30 days were estimated values from the distribution of the latent period of the baseline scenario.

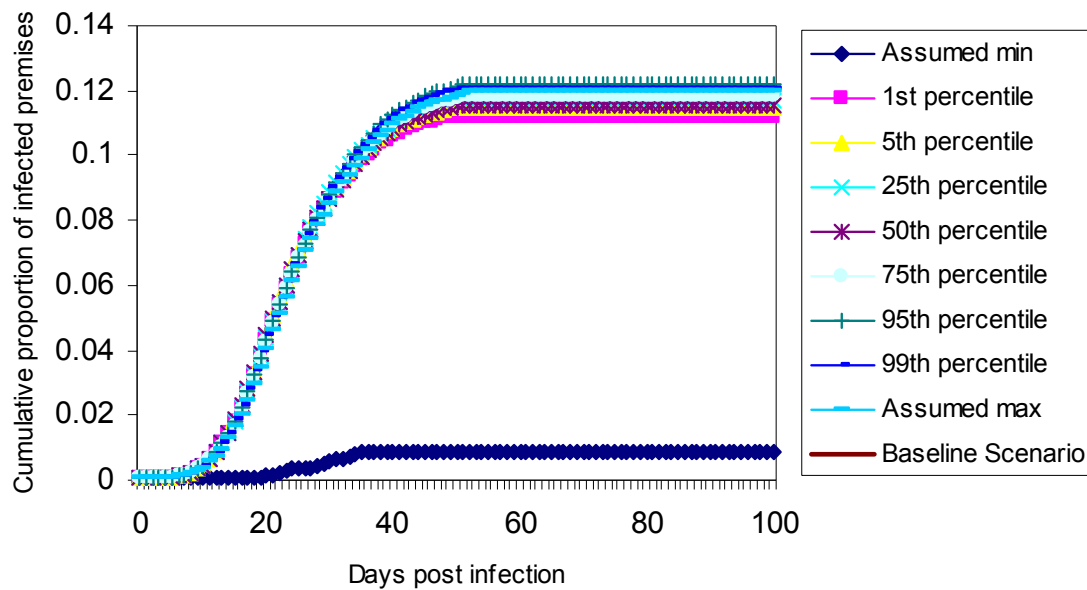


Figure 2.5. Relationship between days post infection and cumulative proportion of infected premises using different infectious clinical periods of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The infectious clinical period of the baseline scenario was drawn from previously published literature and generated using WH 0.9.4^a. The 1st – 99th percentiles were the percentile values from the distribution of the infectious clinical period of the baseline scenario. The assumed minimum and maximum values of infectious clinical periods from the baseline scenario were added to simulate and compare the relationship.

^aWithinHerd version 0.9.4, a software package that estimates herd-level disease state duration.

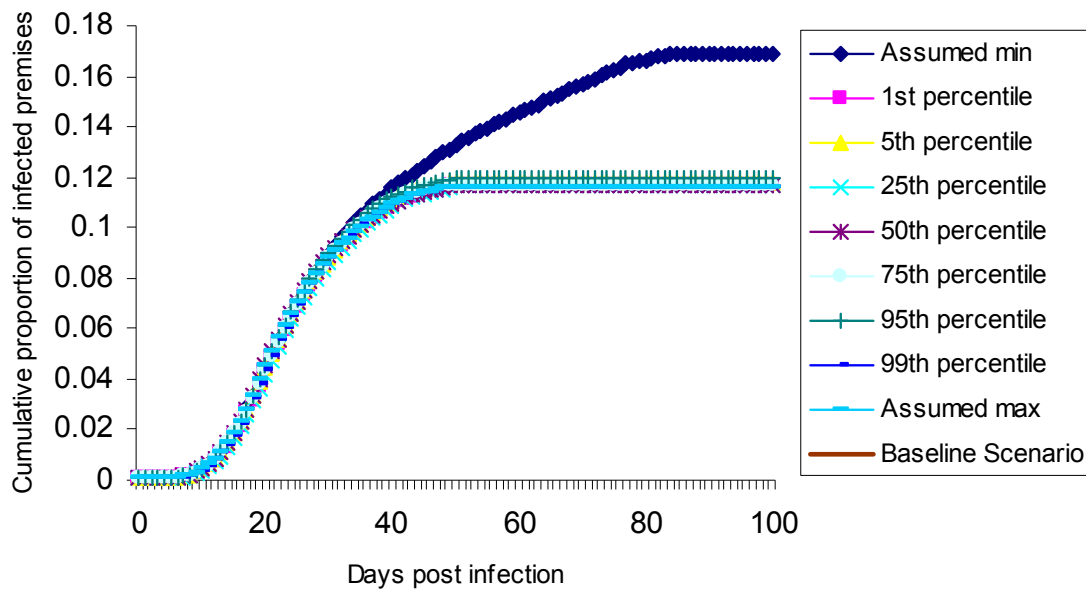


Figure 2.6. Relationship between days post infection and cumulative proportion of infected premises using different immune periods of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The immune period of the baseline scenario used data from previously published literature, survival analysis as double censored data, and was generated using WH 0.9.4^a. The 1st – 99th percentiles were the percentile values from the distribution of the immune period of the baseline scenario. The assumed minimum and maximum values of immune periods from the baseline scenario were added to simulate and compare the relationship.

^aWithinHerd version 0.9.4, a software package that estimates herd-level disease state duration.

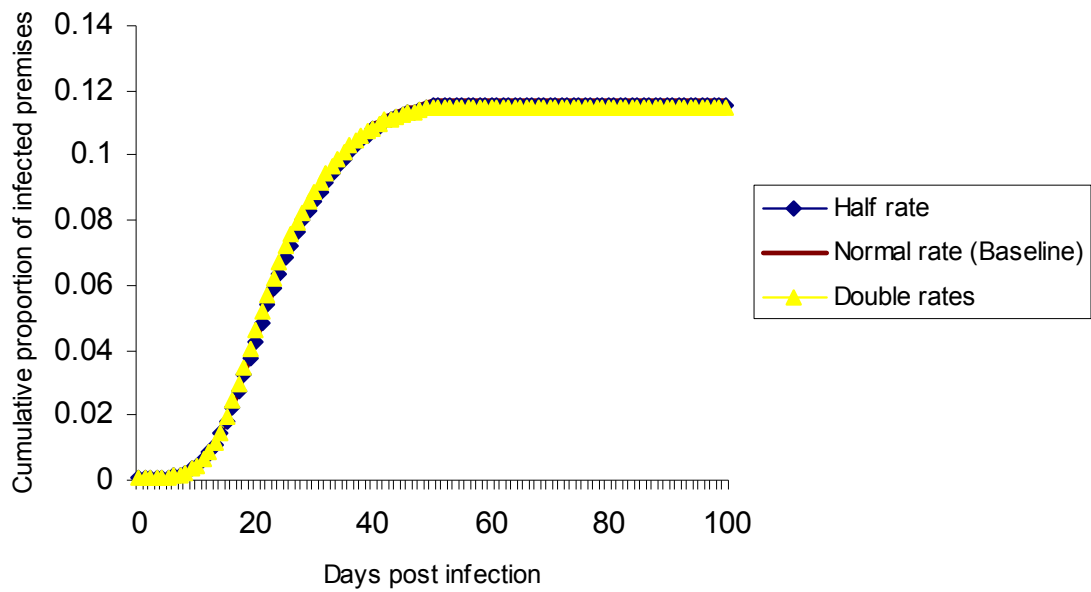


Figure 2.7. Relationship between days post infection and cumulative proportion of infected premises using different contact rates in a direct contact model of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The contact rate of the direct contact model of the baseline scenario was derived from expert opinion. The half and double of the direct contact rates from the baseline scenario were added to simulate and compare the relationship.

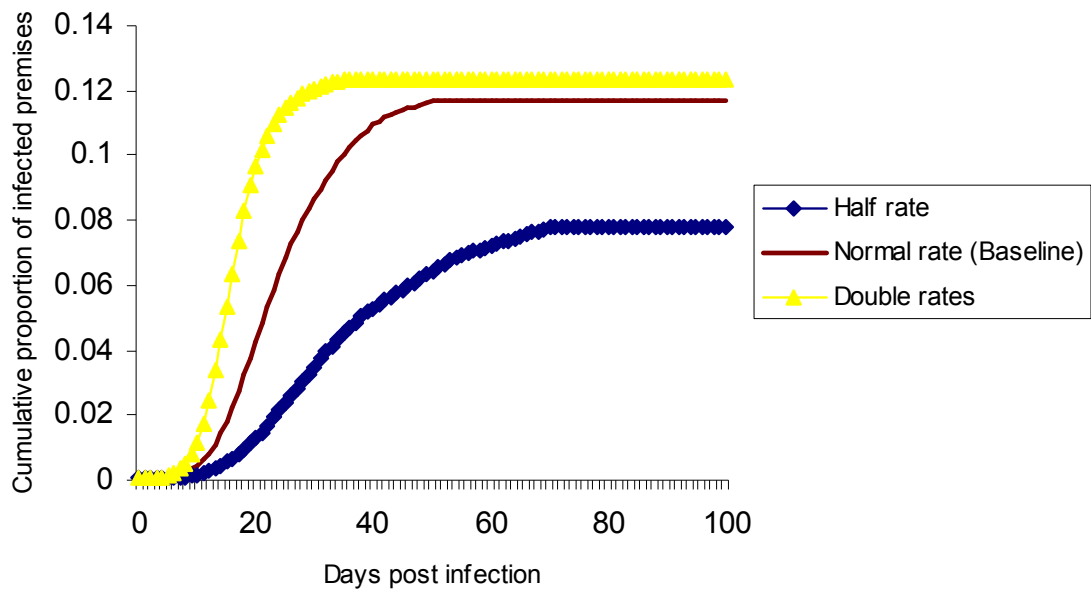


Figure 2.8. Relationship between days post infection and cumulative proportion of infected premises using different contact rates in an indirect contact model of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The contact rate of the indirect contact model of the baseline scenario was derived from expert opinion. The half and double of the indirect contact rates from the baseline scenario were added to simulate and compare the relationship.

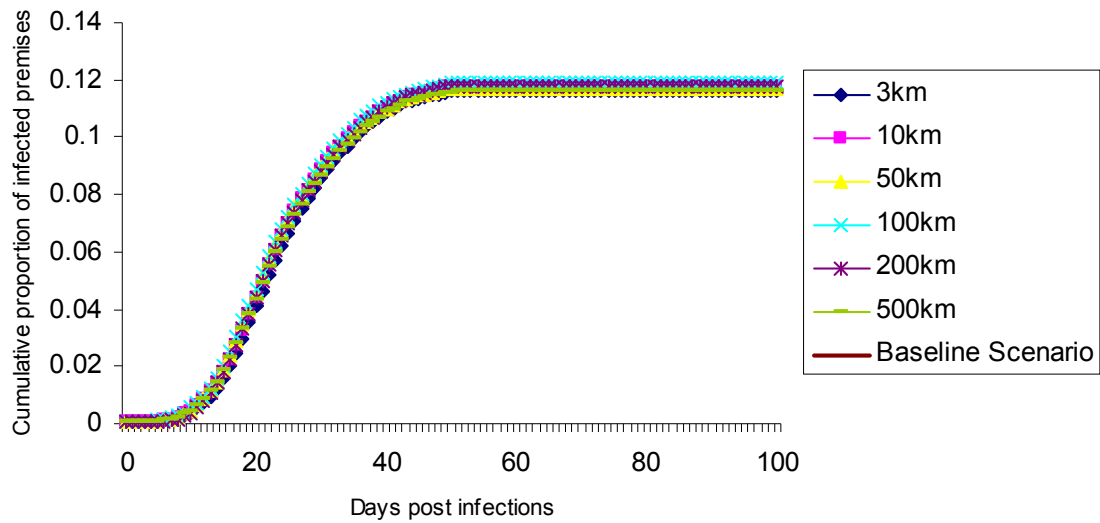


Figure 2.9. Relationship between days post infection and cumulative proportion of infected premises using different distances of recipient premises in a direct contact spread model of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The distance of the recipient premises for the direct contact spread model of baseline scenario was derived from expert opinion. The distances at 3, 10, 50, 100, 200, and 500 kilometers were added to simulate and compare the relationship.

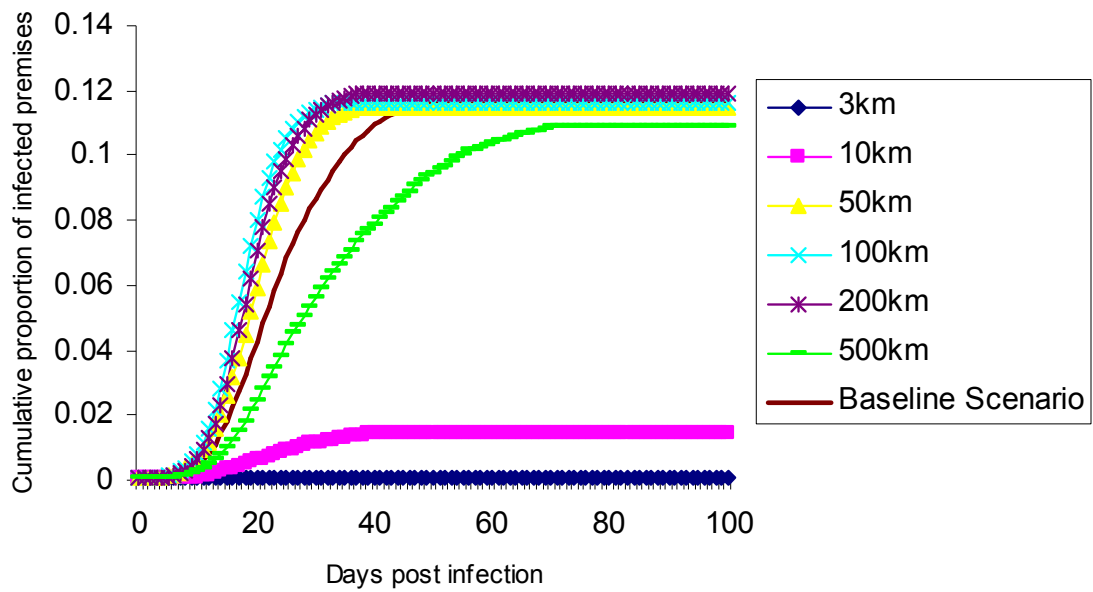


Figure 2.10. Relationship between days post infection and cumulative proportion of infected premises using different distances of recipient premises in an indirect contact spread model of foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. The distance of the recipient premises in the indirect contact spread model of baseline scenario was derived from expert opinion. The distances at 3, 10, 50, 100, 200, and 500 kilometers were added to simulate and compare the relationship.

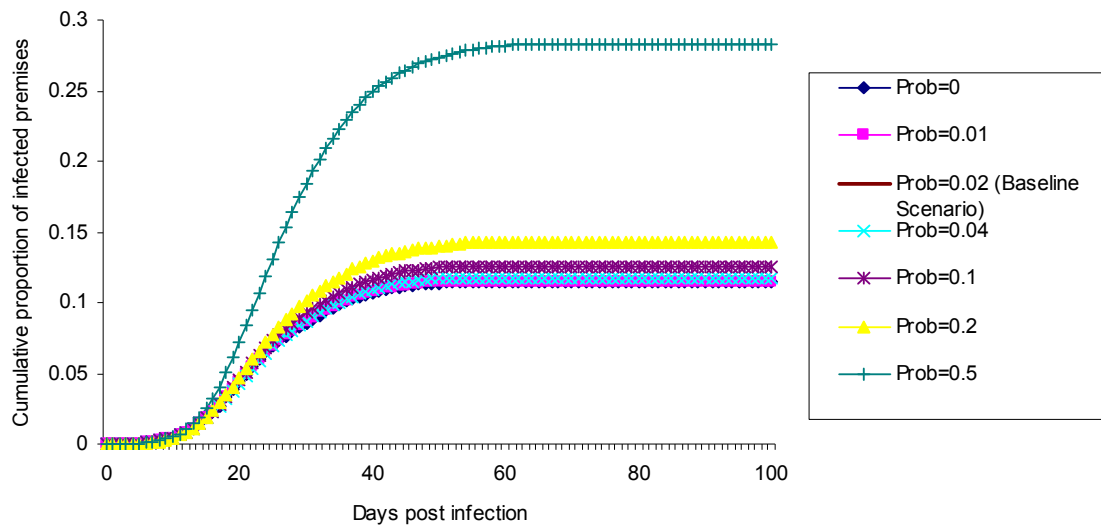


Figure 2.11. Relationship between days post infection and cumulative proportion of infected premises using different probabilities of infected premises from airborne spread over 1 kilometer in 1 day for foot-and-mouth disease (FMD). This was simulated from 1,774 FMD-susceptible premises that included beef feedlot, cow-calf, dairy cattle, and swine in southwest Kansas, using population data from 2006. Probability of FMD infections from airborne spread in the baseline scenario (0.02) was derived from expert opinion. The probabilities at 0, 0.01, 0.04, 0.1, 0.2, and 0.5 were added to simulate and compare the relationship.

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8. Appendices

Appendix I: Disease parameters for foot-and-mouth disease

The figures were created from the North American Animal Disease Spread Model (NAADSM) version 3.1.24. They represent density function types and their parameters and the probability density function (PDF) graphs defining the disease period for FMD.

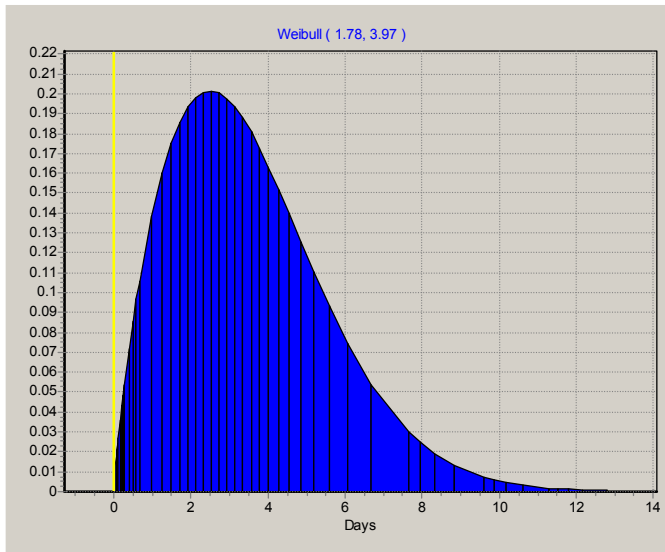


Figure 2.12. PDF defining the duration of the latent period of FMD for beef feedlot, cow-calf, and dairy cattle. (Source: Mardones et al. (2010) for the cattle)

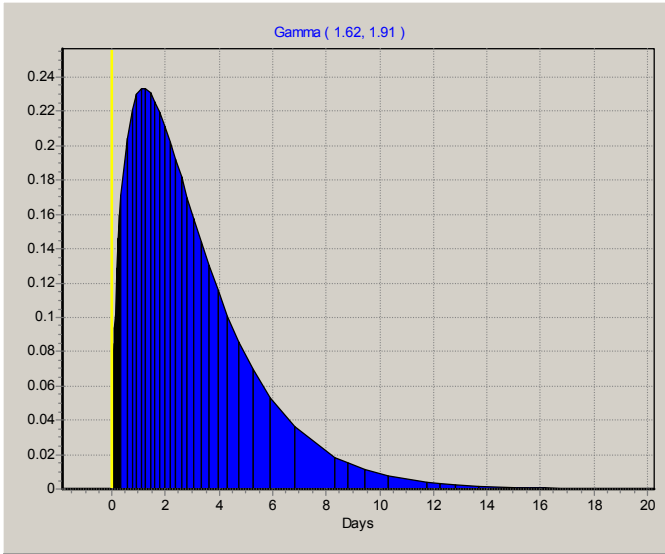


Figure 2.13. PDF defining the duration of the latent period of FMD for swine. (Source: Mardones et al. (2010) for swine)

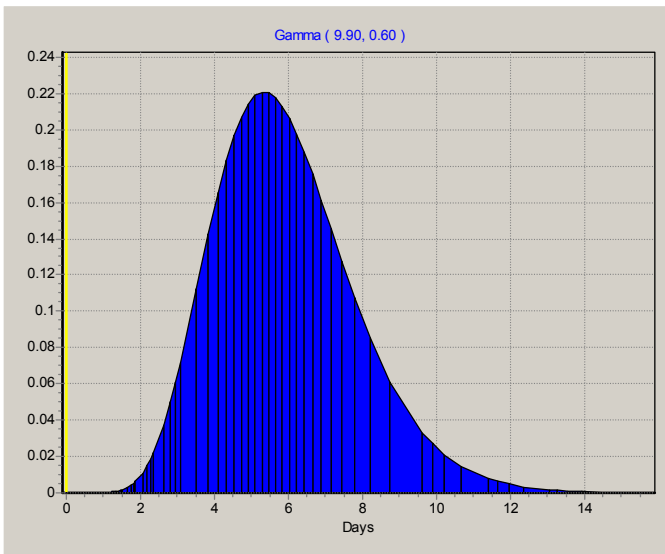


Figure 2.14. PDF defining the duration of the latent period of FMD for sheep. (Source: Mardones et al. (2010) for small ruminants)

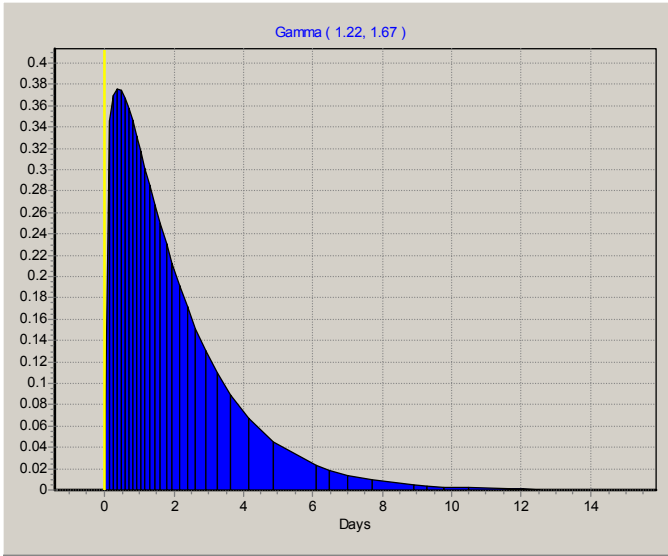


Figure 2.15. PDF defining the duration of the infectious subclinical period of FMD for beef feedlot, cow-calf, and dairy cattle. (Source: Mardones et al. (2010) for cattle)

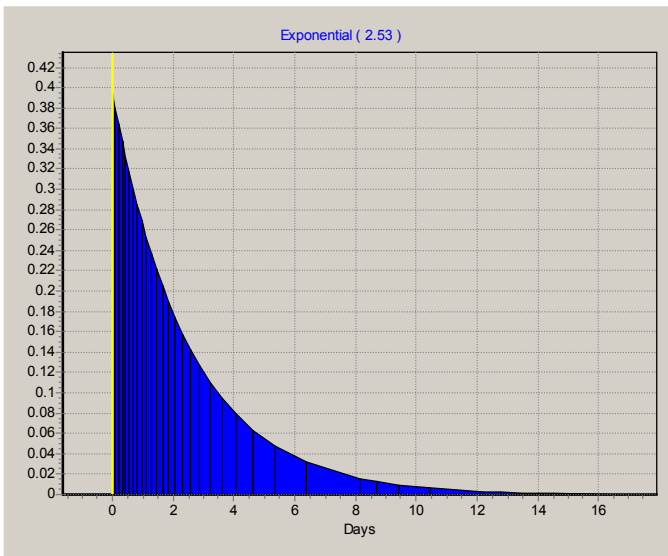


Figure 2.16. PDF defining the duration of the infectious subclinical period of FMD for swine. (Source: Mardones et al. (2010) for swine)

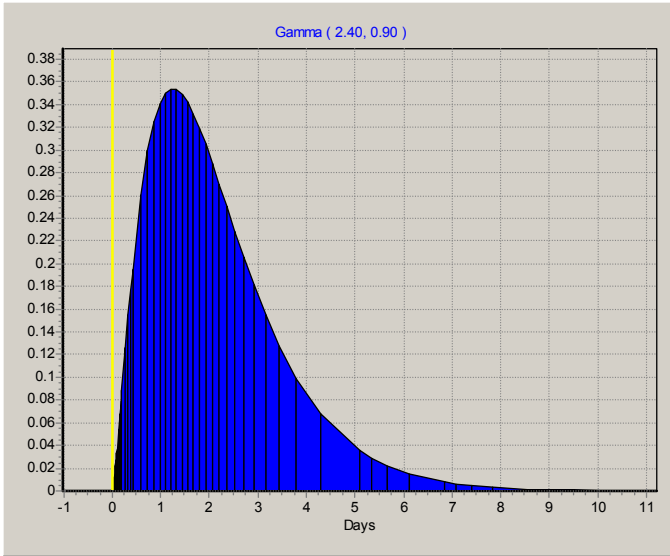


Figure 2.17. PDF defining the duration of the infectious subclinical period of FMD for sheep. (Source: Mardones et al. (2010) for small ruminants)

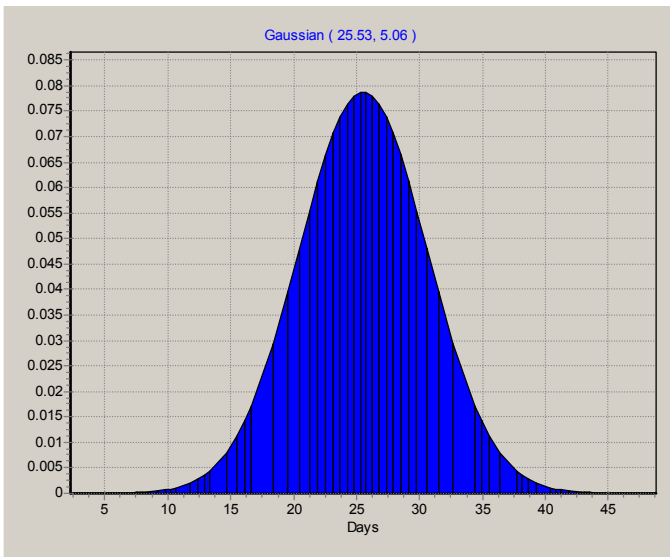


Figure 2.18. PDF defining the duration of the infectious clinical period of FMD for beef feedlot. (Source: Mardones et al. (2010) and run simulation in WH 0.9.4)

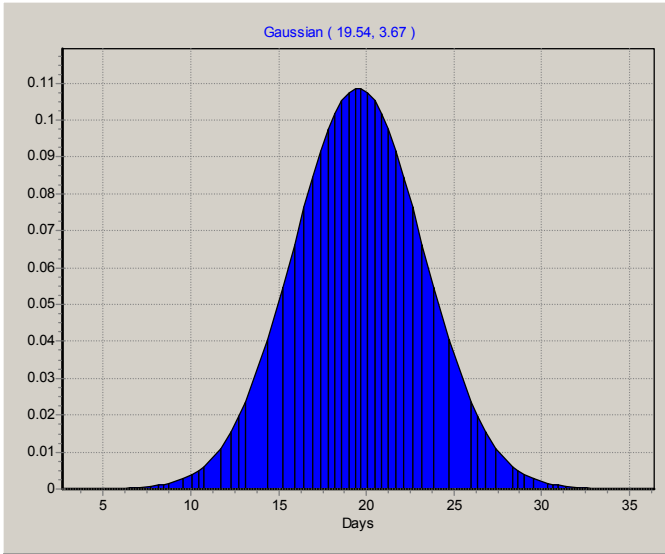


Figure 2.19. PDF defining the duration of the infectious clinical period of FMD for cow-calf. (Source: Mardones et al. (2010) and run simulation in WH 0.9.4)

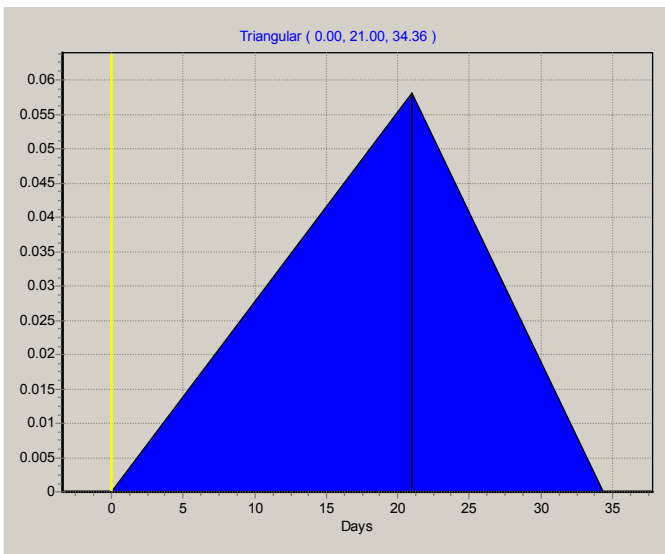


Figure 2.20. PDF defining the duration of the infectious clinical period of FMD for dairy cattle. (Source: Mardones et al. (2010) and run simulation in WH 0.9.4)

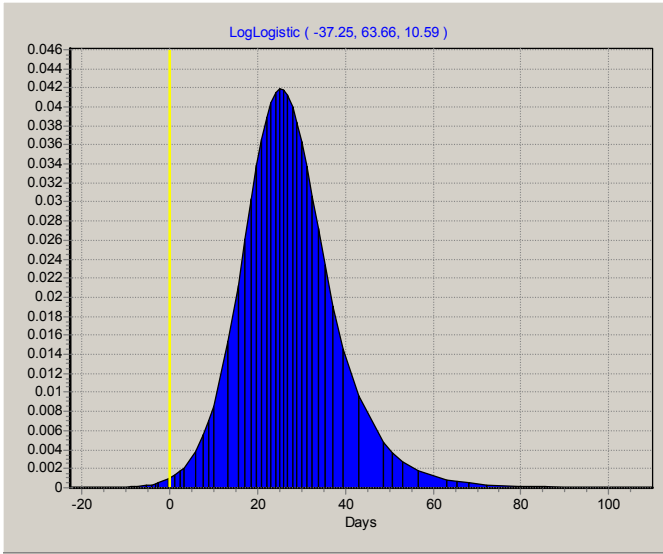


Figure 2.21. PDF defining the duration of the infectious clinical period of FMD for swine. (Source: Mardones et al. (2010) and run simulation in WH 0.9.4)

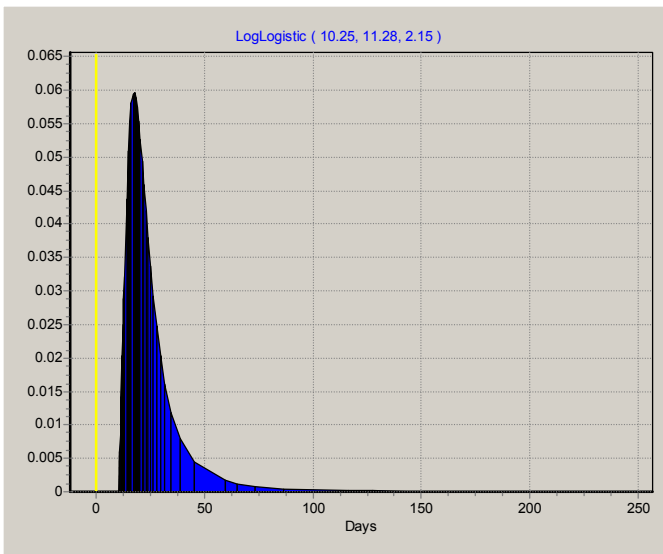


Figure 2.22. PDF defining the duration of the infectious clinical period of FMD for sheep. (Source: Mardones et al. (2010) and run simulation in WH 0.9.4)

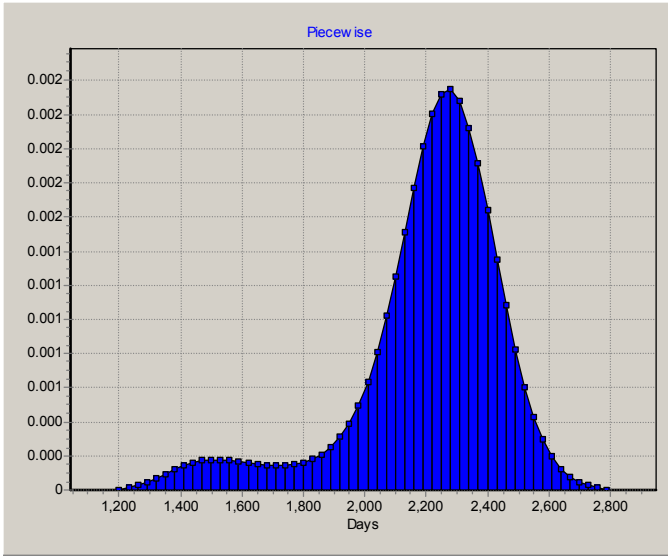


Figure 2.23. PDF defining the duration of the immune period of FMD for beef feedlot, cow-calf, and dairy cattle. (Source: literature reviews and survival analysis)

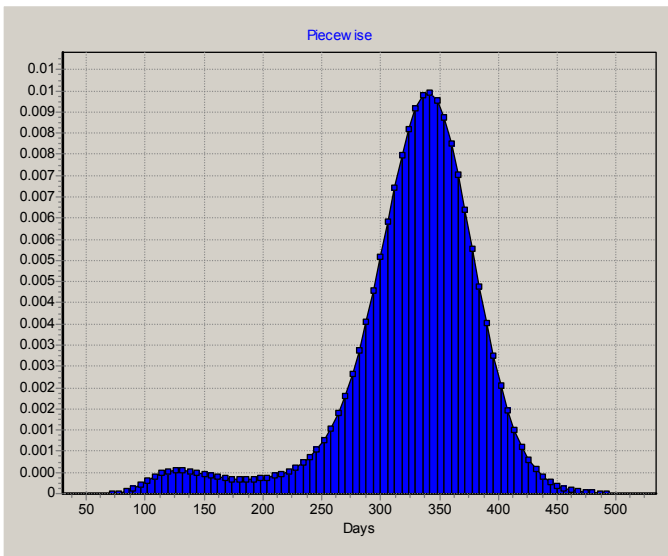


Figure 2.24. PDF defining the duration of the immune period of FMD for swine. (Source: literature reviews and survival analysis)

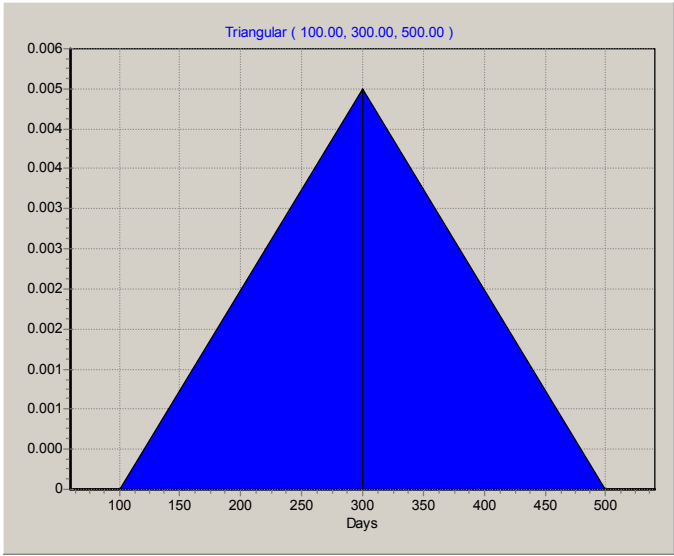


Figure 2.25. PDF defining the duration of the immune period of FMD for sheep. (Source: Johnson, 2008)

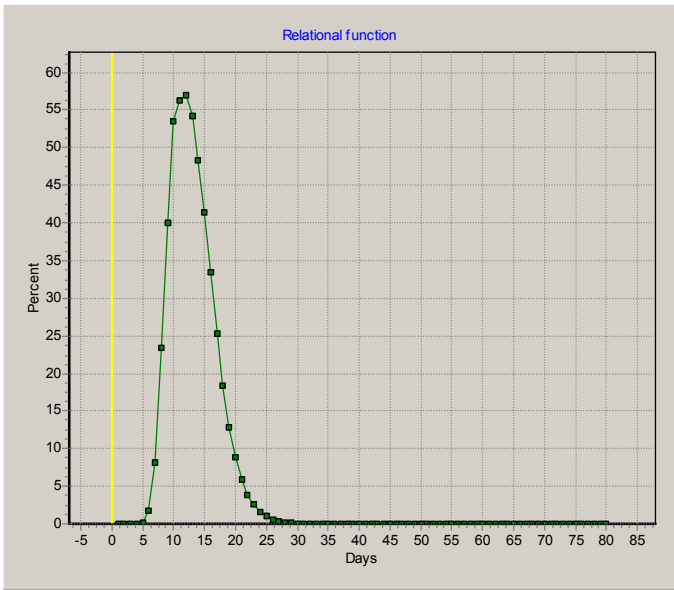


Figure 2.26. Relational function defining the within-unit prevalence of FMD for beef feedlot. (Source: fit the population distribution and run simulation in WH 0.9.4)

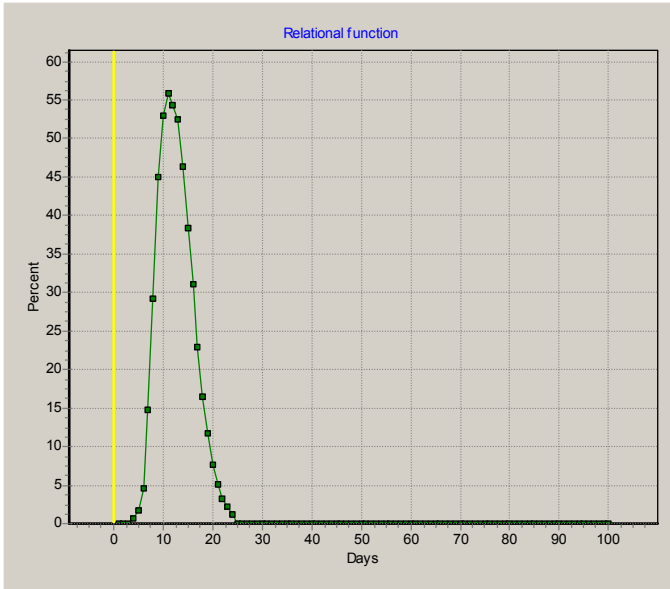


Figure 2.27. Relational function defining the within-unit prevalence of FMD for cow-calf. (Source: fit the population distribution and run simulation in WH 0.9.4)

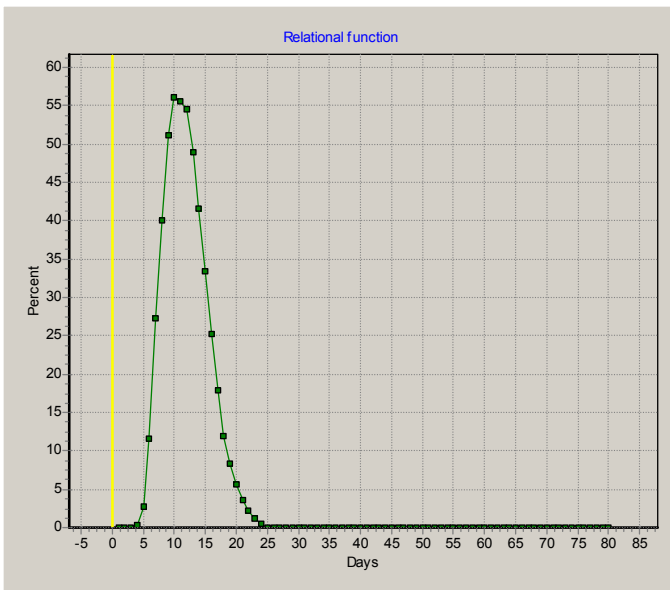


Figure 2.28. Relational function defining the within-unit prevalence for dairy cattle. (Source: fit the population distribution and run simulation in WH 0.9.4)

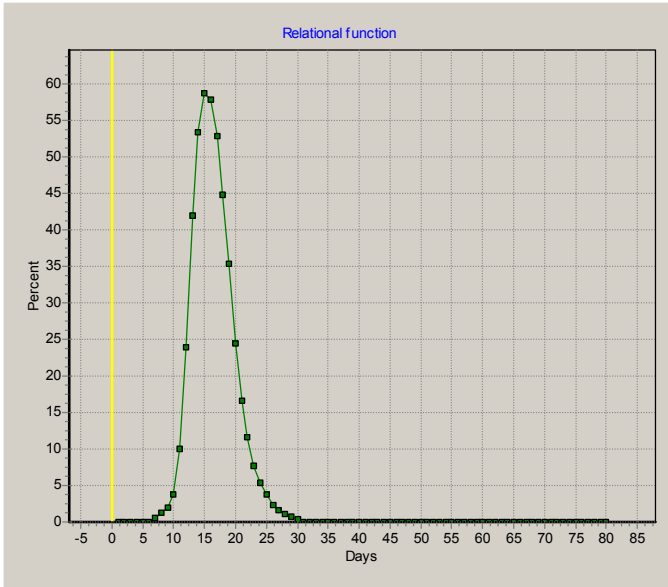


Figure 2.29. Relational function defining the within-unit prevalence of FMD for sheep. (Source: fit the population distribution and run simulation in WH 0.9.4)

Appendix II: Direct contact spread parameters

The figures were created from the North American Animal Disease Spread Model (NAADSM) version 3.1.24. They represent density of distance distribution of recipient units for direct contact among production type combinations.

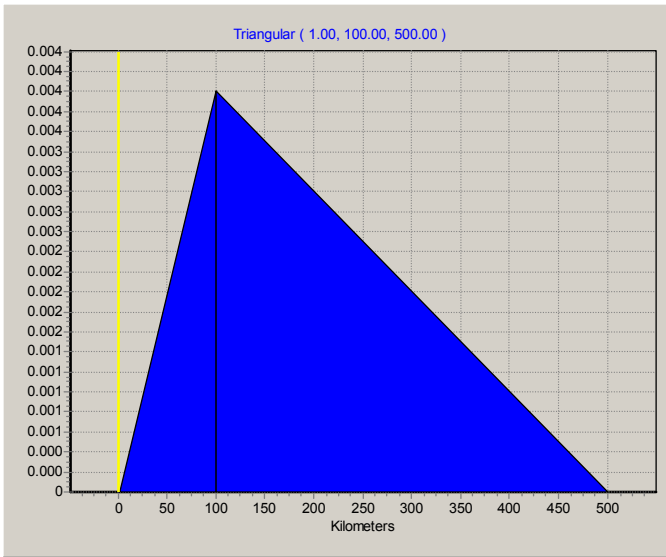


Figure 2.30. Distance distribution of recipient units (beef feedlot to beef feedlot). (Source: Sanderson, 2006)

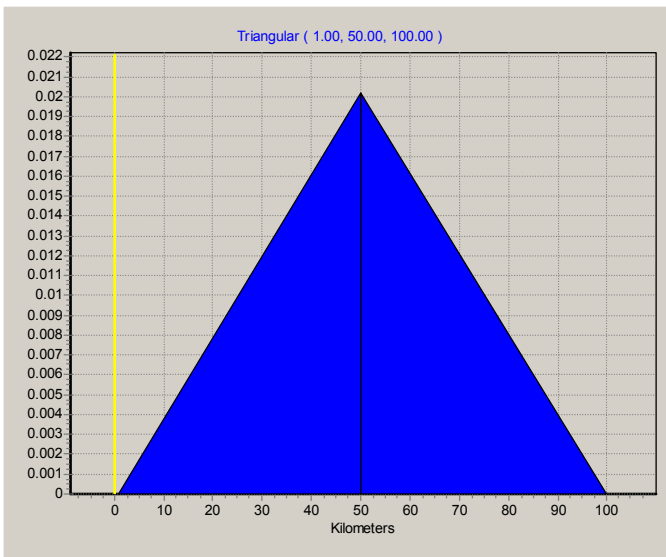


Figure 2.31. Distance distribution of recipient units (beef feedlot to cow-calf, beef feedlot to dairy, and beef feedlot to sheep). (Source: Sanderson, 2006)

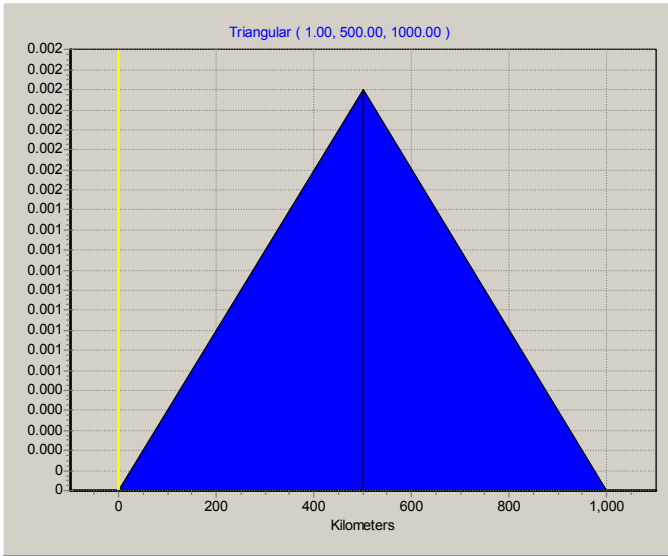


Figure 2.32. Distance distribution of recipient units (cow-calf to beef feedlot). (Source: Sanderson, 2006)

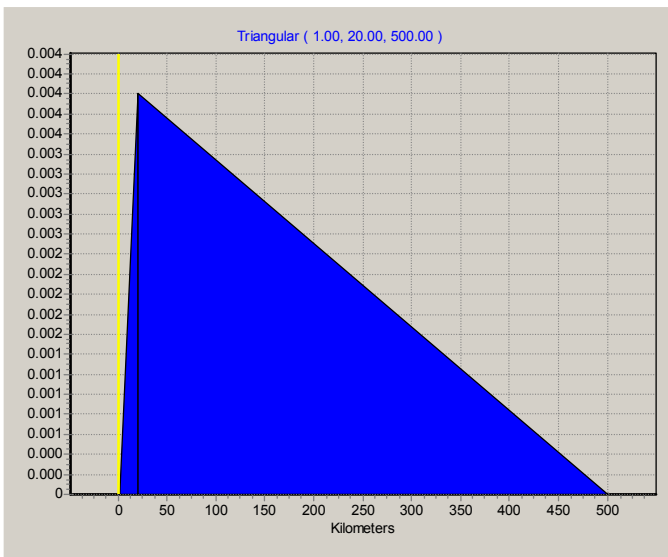


Figure 2.33. Distance distribution of recipient units (cow-calf to cow-calf and cow-calf to sheep). (Source: Sanderson, 2006)

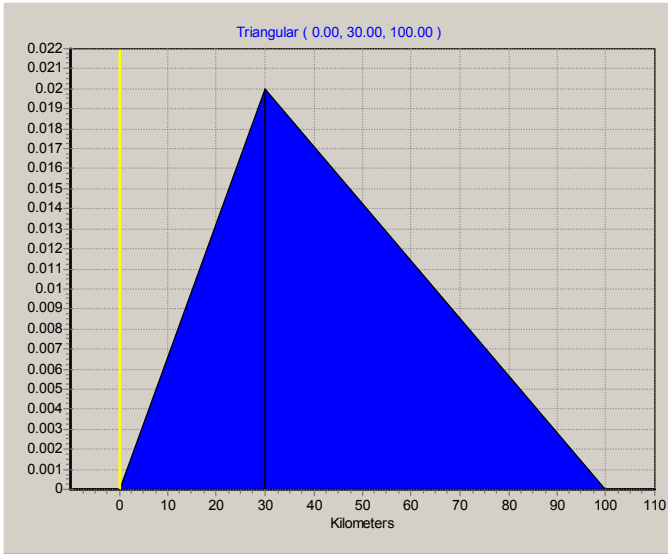


Figure 2.34. Distance distribution of recipient units (cow-calf to dairy).
 (Source: Pendell, 2006)

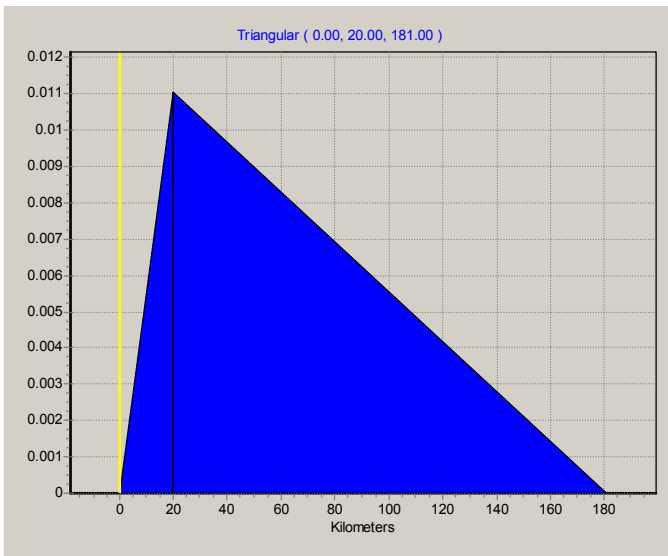


Figure 2.35. Distance distribution of recipient units (swine to swine).
 (Source: Pendell, 2006)

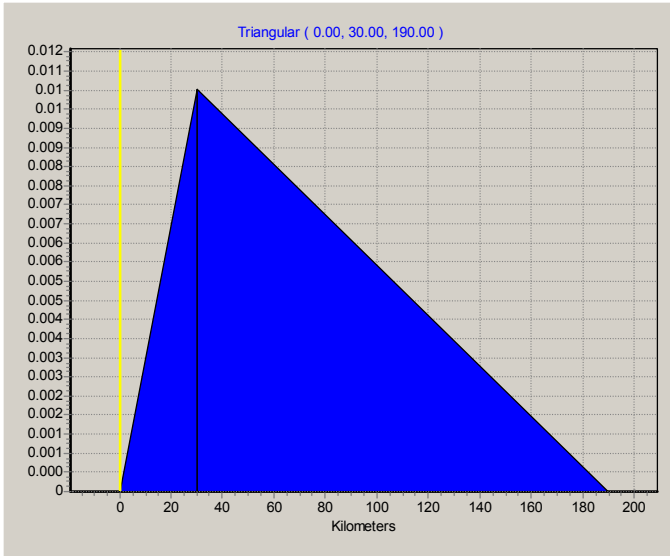


Figure 2.36. Distance distribution of recipient units (dairy cattle to beef feedlot and dairy cattle to dairy cattle). (Source: Pendell, 2006)

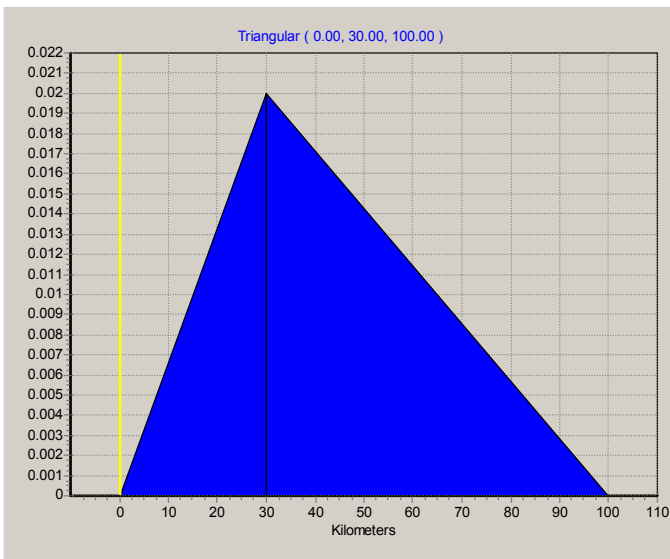


Figure 2.37. Distance distribution of recipient units (dairy cattle to cow-calf). (Source: Pendell, 2006)

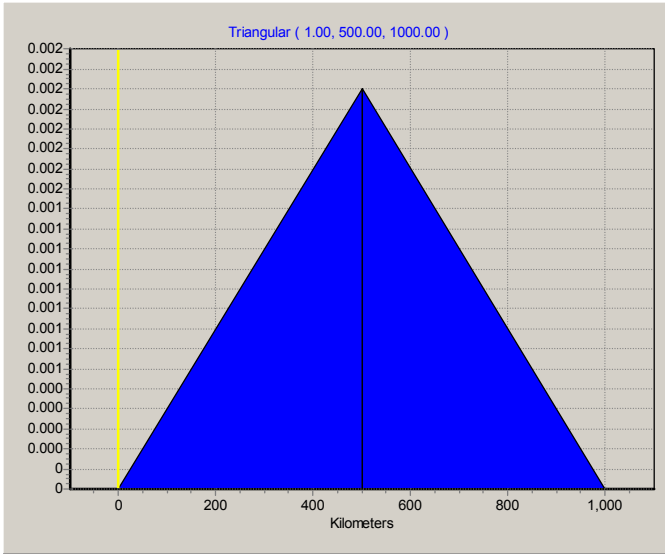


Figure 2.38. Distance distribution of recipient units (sheep to beef feedlot). (Source: Sanderson, 2006)

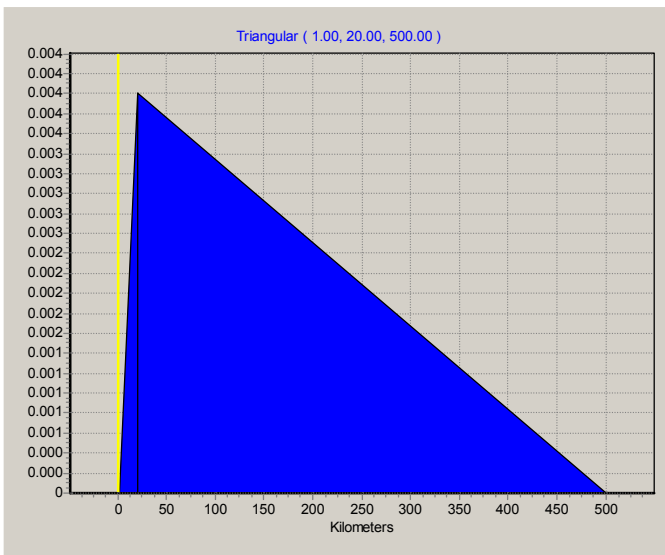


Figure 2.39. Distance distribution of recipient units (sheep to cow-calf and sheep to sheep). (Source: Sanderson, 2006)

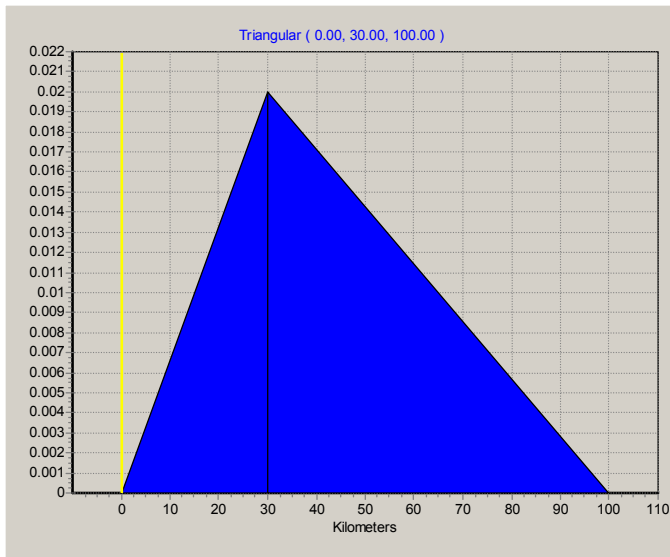


Figure 2.40. Distance distribution of recipient units (sheep to dairy).
(Source: Pendell, 2006)

Appendix III: Indirect contact spread parameters

The figures were created from the North American Animal Disease Spread Model (NAADSM) version 3.1.24. They represent density of distance distribution of recipient units for indirect contact among production type combinations.

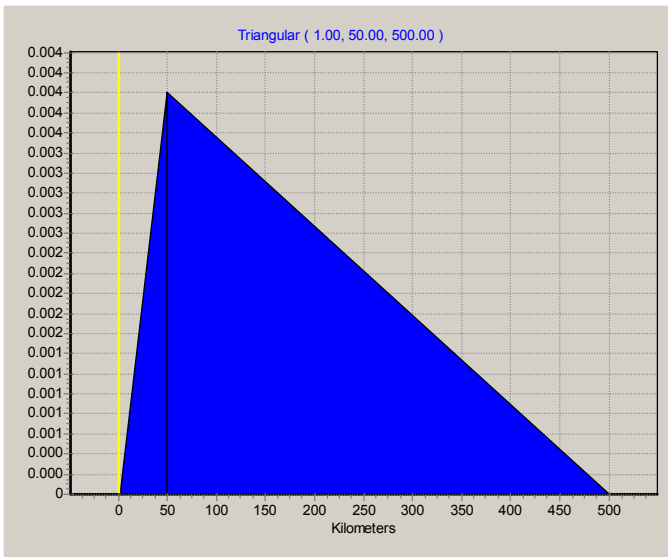


Figure 2.41. Distance distribution of recipient units for indirect contact (beef feedlot to beef feedlot). (Source: Sanderson, 2006)

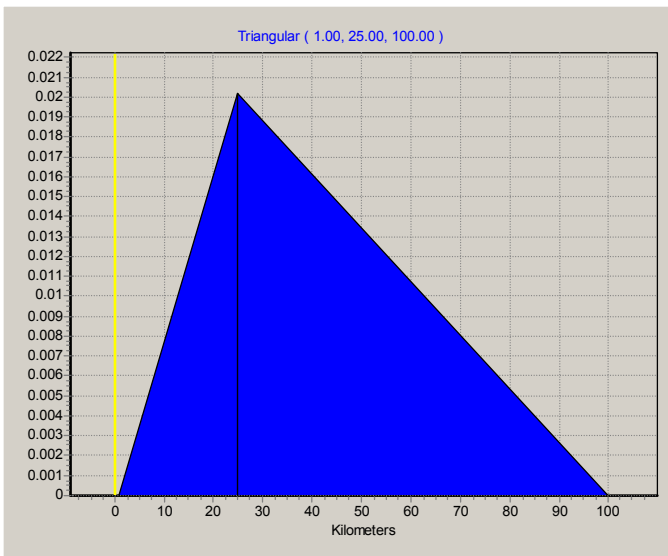


Figure 2.42. Distance distribution of recipient units for indirect contact (beef feedlot to cow-calf and beef feedlot to sheep). (Source: Sanderson, 2006)

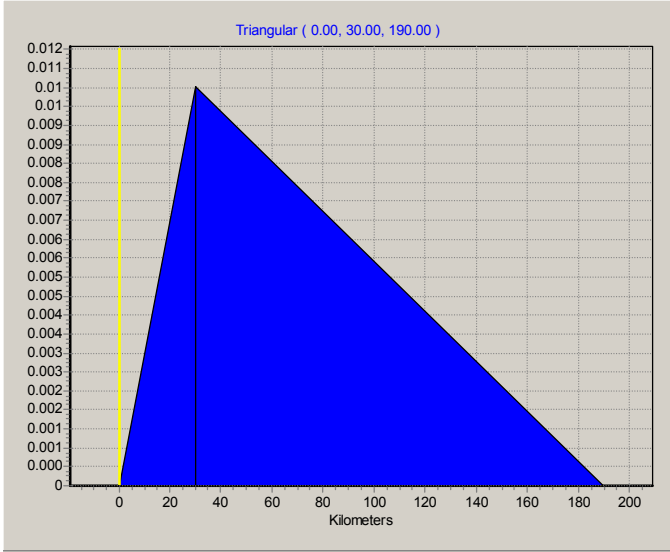


Figure 2.43. Distance distribution of recipient units for indirect contact (beef feedlot to dairy). (Source: Pendell, 2006)

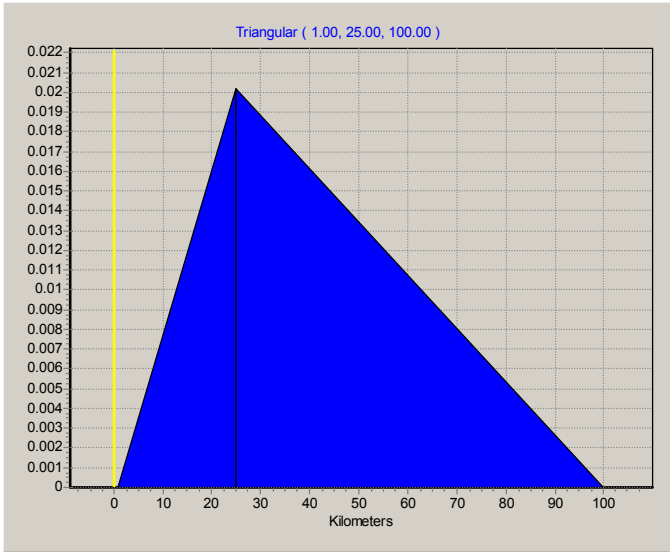


Figure 2.44. Distance distribution of recipient units for indirect contact (cow-calf to beef feedlot, cow-calf to cow-calf, and cow-calf to sheep). (Source: Sanderson, 2006)

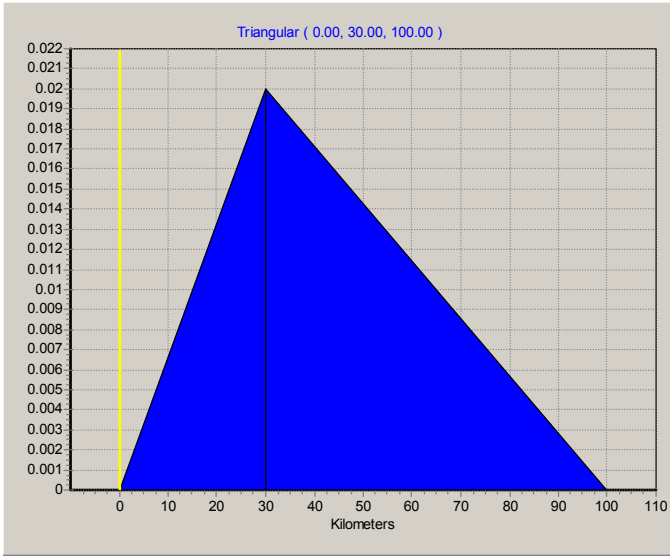


Figure 2.45. Distance distribution of recipient units for indirect contact (cow-calf to dairy). (Source: Pendell, 2006)

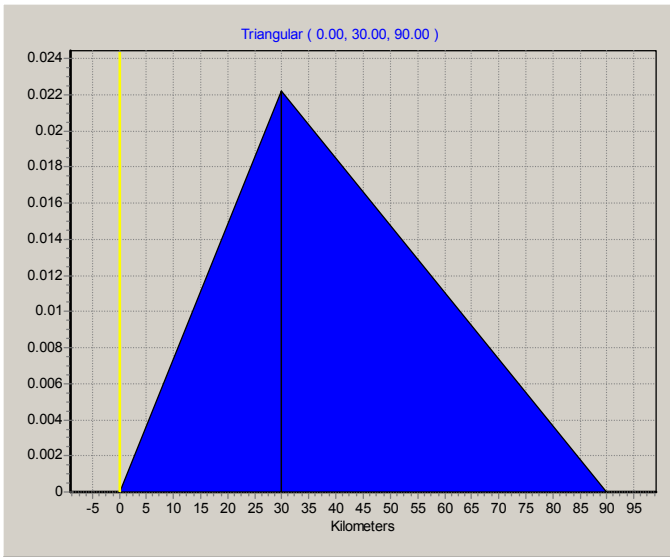


Figure 2.46. Distance distribution of recipient units for indirect contact (swine to swine). (Source: Pendell, 2006)

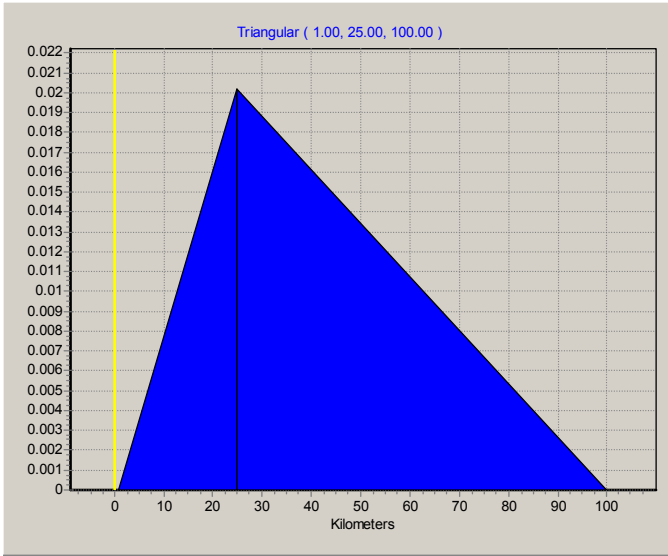


Figure 2.47: Distance distribution of recipient units for indirect contact (dairy cattle to beef feedlot, dairy cattle to cow-calf, and dairy cattle to sheep). (Source: Sanderson, 2006)

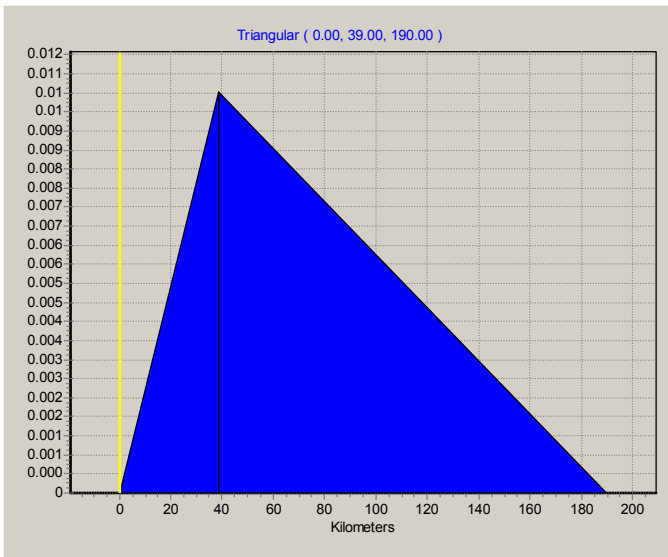


Figure 2.48. Distance distribution of recipient units for indirect contact (dairy cattle to dairy cattle). (Source: Sanderson, 2006)

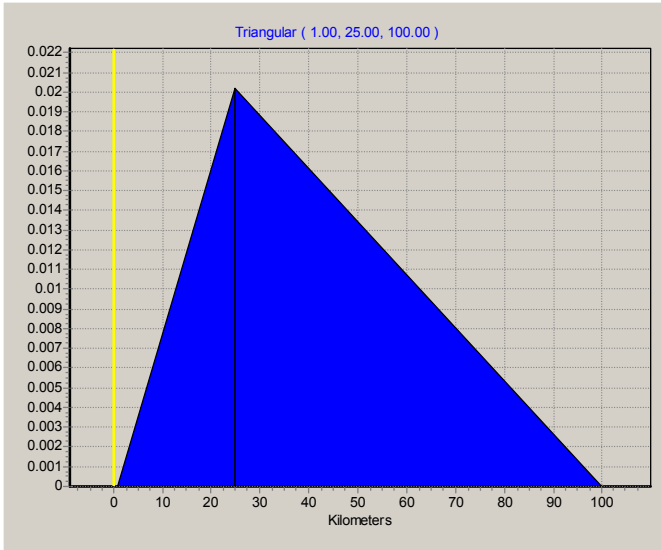


Figure 2.49. Distance distribution of recipient units for indirect contact (sheep to beef feedlot, sheep to cow-calf, and sheep to sheep). (Source: Sanderson, 2006)

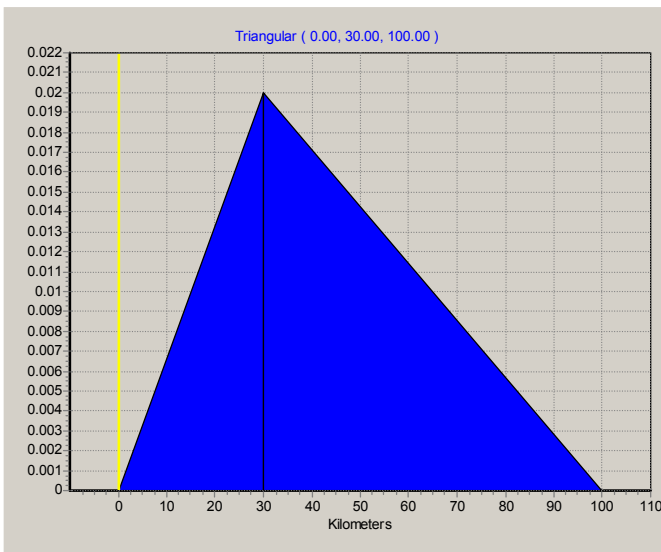


Figure 2.50. Distance distribution of recipient units for indirect contact (sheep to dairy cattle). (Source: Pendell, 2006)

Appendix IV: Disease detection

The figures were created from the North American Animal Disease Spread Model (NAADSM) version 3.1.24. They represent the relational function of model disease detection.

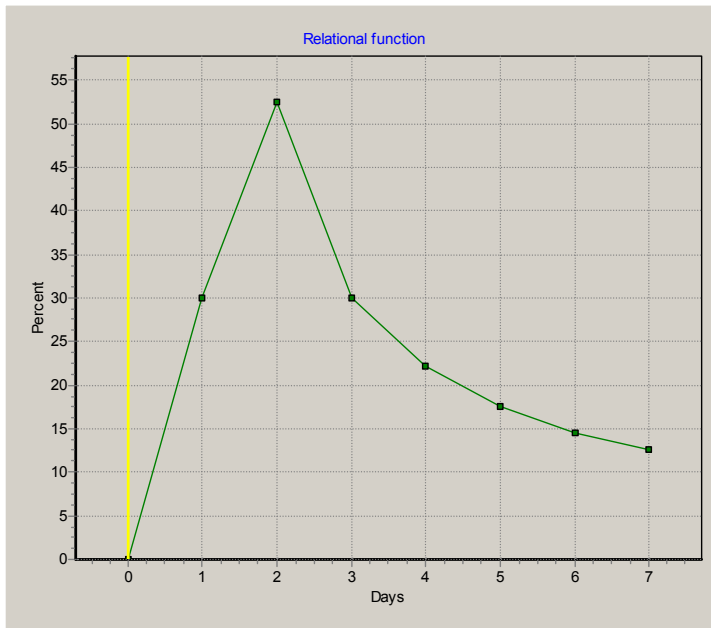


Figure 2.51. Probability of observing clinical signs, given the number of days that the unit is clinically infectious (Beef feedlot, cow-calf, and sheep). (Source: Hill, 2009)

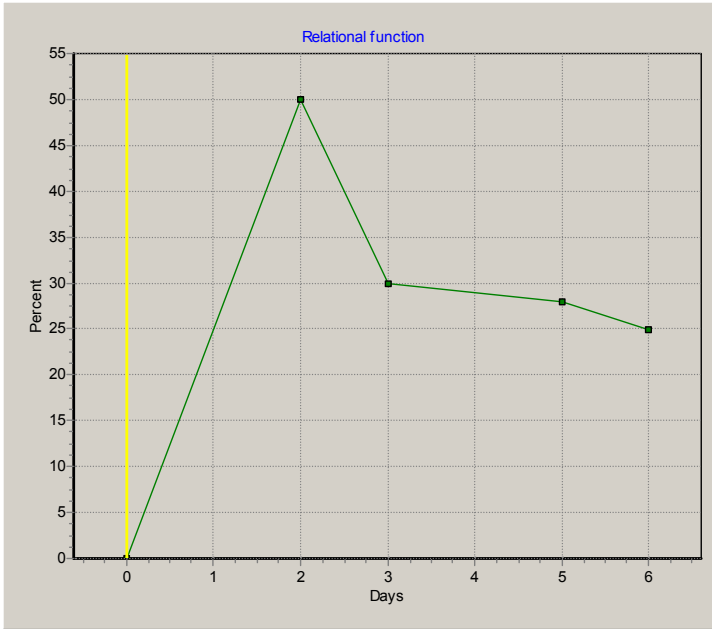


Figure 2.52. Probability of observing clinical signs, given the number of days that the unit is clinically infectious (Swine). (Source: Hill, 2009)

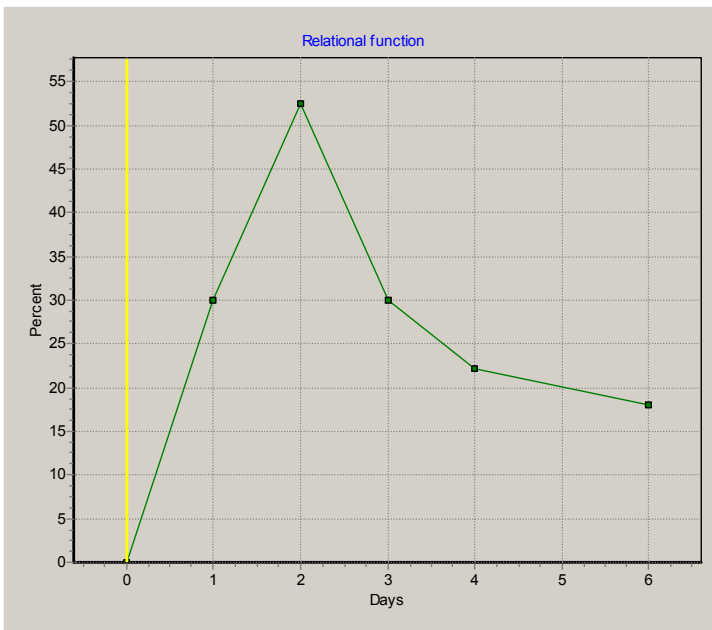


Figure 2.53. Probability of observing clinical signs, given the number of days that the unit is clinically infectious (Dairy cattle). (Source: Hill, 2009)

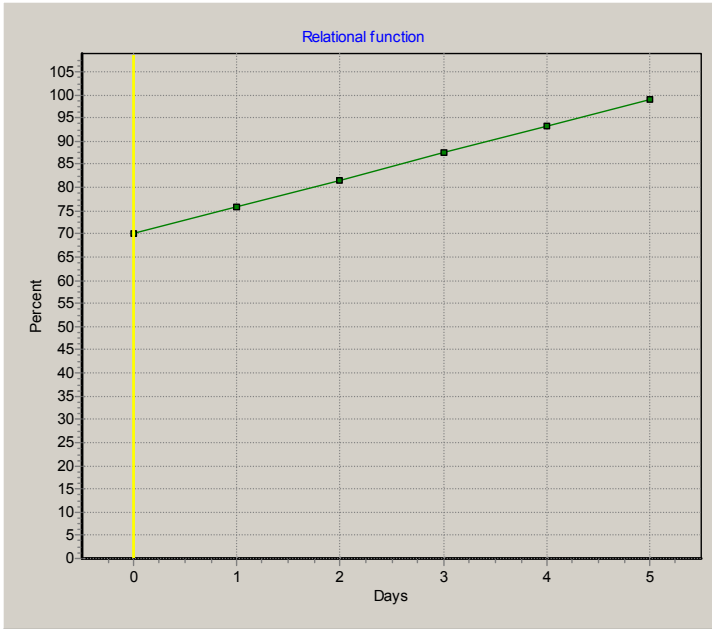


Figure 2.54. Probability of reporting an observed clinical unit, given the number of days since disease was first detected in any unit (All production types). (Source: Hill, 2009)

**CHAPTER 3: USES OF SIMULATION MODEL
TO ASSESS CONTROL STRATEGIES
FOR FOOT-AND-MOUTH DISEASE**

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Summary

A large area free of Foot-and-mouth disease (FMD) virus and having intensive livestock production, such as the central United States, may want to have a practical response plan in place for disease control and eradication if disease was introduced. For this simulation, the strategies of zoning for restricted animal movement, stamping out, and vaccination were applied to control the disease in an outbreak. The limited capacity of manpower for implementing the control plan in different scenarios was set realistically as a baseline scenario and five additional disease control scenarios. An epidemiological model of FMD spread was simulated, and the size and duration of the outbreaks were observed. In the baseline scenario, 11% of premises became infected with FMD virus and the duration of the epidemic was 115 days. Swine production units were the most likely to be infected, and the primary cause of disease spread was indirect contact. When compared to the baseline scenario restricted animal movement decreased the percentage of infected premises by 29.3%; decreases also occurred with initial ring vaccination on day seven (23.7%), trigger ring animal destruction (23.3%), initial ring vaccination on day 14 (23.0%), and additional animal destruction (21.2%). There was no significant difference (at $P < 0.05$) between the trigger ring animal destruction and initial ring vaccination on either day 7 or 14, but these three strategies were better than the additional animal destruction slightly but significantly ($P < 0.05$). All disease control strategy scenarios decreased the number of infected premises but did not shorten the duration of the epidemic. The best strategy to reduce epidemic size found in the study was zoning for restricted animal movement. Among all of strategies, the active disease phase ended within four to five months, and the outbreak control measures were set to end at 2 years,

but there were large numbers of livestock premises that were pending to be destroyed after FMD detection.

Keywords: Simulation model; Control strategies; Assess; Disease; Foot-and-mouth

1. Introduction

Of the viral diseases in cloven-hoofed animals, Foot and mouth disease (FMD) is an important contagious disease because of its rapid spread in high-value livestock. Cattle, buffaloes, pigs, sheep, goats, and deer are susceptible to FMD, but the disease is generally most severe in cattle and pigs (Geering et al., 2002). The United States (US) is an FMD-free country and has not experienced an outbreak since 1929 (Graves, 1979), therefore it is critical to know how different control measures would stop the spread of the disease if it was introduced. This can be accomplished by using simulation models.

The basic principles that should be applied to control and eradicate FMD are denying access of the virus to susceptible host animals, avoiding contact between infected and susceptible animals, reducing the number of infected or potentially infected animals in the livestock population, and reducing the number of susceptible animals (Geering et al., 2002). In practical terms, these principles could be implemented through zoning for control of animal movement, stamping out, and vaccination, and any disease eradication plan in the US could include these measures.

An intense livestock production area in the states of Colorado, Kansas, Nebraska, New Mexico, Oklahoma, and Texas was selected to assess disease controls. This region feeds approximately 78% of feeder cattle in the US (NASS, 2011), and introduction and

spread of FMD in this region could have devastating animal health and economic consequences (Pendell et al., 2007).

The objective of this study was to evaluate the efficiency of different limited strategies for FMD control in the central US. The simulated FMD outbreaks assessed disease incidence, epidemic duration and estimated number of destroyed and vaccinated animals.

2. Materials and Methods

Estimated conditions for disease spread were parameterized and capability levels of disease control were determined with different disease control strategies in the study area. The baseline scenario included only limited disease control. Restricted animal movement, additional capacity of animal destruction, and vaccination were added to additional scenarios to evaluate various control strategies. The scenarios were run in a stochastic simulator and the outbreak occurrences were recorded.

2.1 Simulation model

The North American Animal Disease Spread Model (NAADSM) was used to compare the effect of different FMD control strategies with the baseline scenario. NAADSM is a stochastic state-transition model for the spread of highly contagious diseases of animals. Parameters can be established to define model behavior for disease progression—direct contact, indirect contact, and airborne—and implementation of control measures such as destruction and vaccination (Harvey et al., 2007). The unit of interest was the geographical location of beef feedlot, cow-calf, dairy cattle, swine, and sheep production premises. This information was gathered from regional and national

authorities as well as the Farm Location and Animal Population Simulator (FLAPS). The FLAPS is a spatial modeling method used in ArcGIS and has been described by Freier et al. (2007). Using the process of premises gathering, the study area was composed of 102,283 livestock premises (approximately 37.7 million animals) in 413 U.S. counties in the states of Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas.

2.2 Model scenarios

The baseline scenario included limited disease control through restricted animal movement and destruction. Additional disease control strategies increased the possible capacity of implemented programs including restricted movement, additional and ring animal destruction, and ring vaccination. The control strategies were based on the availability of manpower and the distribution and size of livestock premises in the study area (Corso et al., 2009). Parameters for the scenarios were generated in another study conducted by the authors (Premashthira et al., 2011). This process was completed using literature reviews, statistical techniques, and expert opinions. The index case for all scenarios was simulated to start its latent period at a large beef feedlot operation in an intensive beef feedlot region. All simulations were allowed to run for period of two years (730 days). The additional limited disease control strategies were composed of 1) restricted animal movement, 2) additional animal destruction, 3) trigger ring animal destruction, 4) initial ring vaccination on day 7, and 5) initial ring vaccination on day 14. The baseline scenario and 5 additional limited disease control strategies are summarized in Table 3.1.

2.3 Output of models

Four hundred iterations were conducted for each model scenario in NAADSM. Results were summarized as total number of infected premises, duration of epidemic, estimated number of animals destroyed or vaccinated, and causes of infection. Median, mean, 75th percentile, and 95th percentile of the cumulative number of infected premises were presented as measures of the magnitude of the outbreak. Median, 75th percentile, and 95th percentile of the duration of the epidemic in days were presented to describe the length of the outbreak. Epidemic size as medians of daily cumulative infected premises on day 34, 41, and 48 were presented as change after the peak of outbreak. These three points in time were monitored because effects of specific vaccination strategies were expected to be apparent. In the model, the time from vaccination to onset of immunity was parameterized at 20 days. Thus, Day 34 was the first day of having herd immunity from the initial ring vaccination on day 14 and was one week after having herd immunity from the initial ring vaccination on day 7 strategies. Two weeks after this day were monitored on day 41, and 48. The estimated number of animals destroyed and vaccinated, in some scenarios, was presented by their medians.

2.4 Statistical analysis

Epidemic curves—median numbers of daily new premises infected with FMD virus—were fitted to common theoretical distributions by @Risk 5.0 (Palisade Inc., Newfield, NY). Distributions of size of epidemic—cumulative number of premises infected with FMD virus among 400 iterations in each scenario at the end of disease phase—were tested for normality using the Shapiro-Wilk test. Then, the nonparametric Kruskal-Wallis 1-way ANOVA by ranks for multiple comparisons of the size of

epidemic among different scenarios was performed. The Bonferroni correction for multiple comparisons was performed as post hoc analysis for all pairwise differences. Distributions of size of epidemic at day 34, 41, and 48 were tested for normality and difference of distributions using the same methods. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). For all analyses, type-I error probability was set at 0.05.

3. Results

3.1 Baseline scenario

For the baseline scenario (limited disease control), the median size of an epidemic was 11,283 premises (mean was 11,462 premises; 75th and 95th percentile were 13,560 and 17,111 premises, respectively) and median epidemic duration was 115 days (75th and 95th percentile were 132 and 176 days, respectively) (Table 3.2). Distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a lognormal distribution ($\mu = 24.90$, $\delta = 14.77$, and shift = +10.73). Of all infected premises, swine had the highest infected proportion (39.4%; Figure 3.3). The proportion of infected premises for beef feedlot, dairy, cow-calf, and sheep was 24.8, 24.0, 11.4, and 0.05 percent respectively. Indirect contact resulted in 82.0% of infections, and those caused by airborne transmission and direct contact were 13.4 and 4.6 percent respectively (Figure 3.4). Considering the cause of infection by production types, cow-calf was only one where the primary route of infection was airborne transmission (82.3%). Infections in the other production types were mainly caused by indirect contact (Table 3.3).

3.2 Restricted animal movement

When animal movement was restricted, the median size of an epidemic was 7,975 premises (mean was 8,151 premises; 75th and 95th percentile were 9,505 and 12,118 premises, respectively) and the median epidemic duration was 154 days (75th and 95th percentile were 200 and 242 days, respectively) (Table 3.2). The distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a weibull distribution ($\alpha = 2.11$, $\beta = 35.33$, and shift = +17.11). Of all infected premises, swine had the highest proportion (38.4%; Figure 3.3) of infections, followed by beef feedlot, dairy, cow-calf, and sheep at 25.5, 25.0, 11.1, and 0.05 percent respectively (Figure 3.3). In this scenario most infections were caused by indirect contact (83.7%), whereas airborne transmission and direct contact caused 14.2 and 2.1 percent respectively (Figure 3.4). Considering the cause of infection by production types, cow-calf was the only type where airborne transmission (89.2%) was the primary cause of infection. Infections in the other production types were mainly caused by indirect contact (Table 3.3).

Restricting animal movement reduced the magnitude of the outbreak from the baseline scenario 29.3% (reduction of the median number of infected premises) but the duration of the epidemic was 39 days longer than the baseline. This control strategy reduced the number of destroyed animals by 1.38 million from the baseline.

3.3 Additional animal destruction

The results for additional animal destruction revealed that the median size of an epidemic was 8,890 premises (mean was 9,300 premises; 75th and 95th percentile were 10,942 and 15,249 premises, respectively) and the median epidemic duration was 115 days (75th and 95th percentile were 132 and 178 days, respectively) (Table 3.2). The distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a gamma distribution ($\alpha = 3.97$, $\beta = 6.25$, and shift = +12.51). Of all infected premises, swine had the highest infected proportion (39.4%; Figure 3.3), followed by beef feedlot, dairy, cow-calf, and sheep at 24.8, 24.0, 11.8, and 0.05 percent respectively (Figure 3.3). Indirect contact caused the greatest proportion of infections (81.9%) followed by airborne transmission (13.5%) and direct contact (4.6%) (Figure 3.4). Considering the cause of infection by production types, cow-calf was the only type where airborne transmission (82.4%) resulted in the most infections. Infections in the other production types were mainly caused by indirect contact (Table 3.3). This strategy reduced the magnitude of the outbreak from the baseline scenario 21.2% (median number of infected premises reduction), but the duration of the epidemic was unchanged (115 days).

3.4 Trigger ring animal destruction

Trigger ring animal destruction for a three kilometer radius around each infected detected unit resulted in the median size for an epidemic of 8,649 premises (mean was 9,024 premises; 75th and 95th percentile were 10,551 and 14,609 premises, respectively) and the median epidemic duration was 116 days (75th and 95th percentile were 131 and

179 days, respectively) (Table 3.2). Distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a gamma distribution ($\alpha = 4.05$, $\beta = 6.20$, and shift =+12.42). Of all infected premises, swine had the highest infected proportion (39.4%; Figure 3.3), followed by beef feedlot, dairy, cow-calf, and sheep at 24.8, 24.0, 11.7, and 0.05 percent respectively (Figure 3.3). Most infections were caused by indirect contact (82.4%), followed by airborne transmission (13.4%) and direct contact (4.1%) (Figure 3.4). Considering the cause of infection by production types, cow-calf was the only one type to be most infected by airborne transmission (82.5%). Infections in the other production types were mainly caused by indirect contact (Table 3.3).

The trigger ring animal destruction had little effect on the number of infected premises (2.7% reduction) or epidemic duration (one day longer) as compared to the additional destruction strategy. The estimated number of animals destroyed in this scenario increased to 29.52 million compared to 29.49 million for the strategy of additional animal destruction.

3.5 Initial ring vaccination on day seven

When ring vaccination on day seven was considered, the median size of an epidemic was 8,608 premises (mean was 8,984 premises; 75th and 95th percentile were 10,579 and 14,460 premises, respectively) and the median epidemic duration was 115 days (75th and 95th percentile were 130 and 169 days, respectively) (Table 3.2).

Distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a weibull distribution ($\alpha = 1.88$, $\beta = 23.10$, and shift =+16.59). Of all infected premises, swine had the highest infected

proportion (39.4%; Figure 3.3), followed by beef feedlot, dairy, cow-calf, and sheep at 24.8, 24.0, 11.7, and 0.05 percent respectively (Figure 3.3). The highest proportion of infections was caused by indirect contact (82.0%), and airborne transmission and direct contact caused 13.4 and 4.6 percent of infections respectively (Figure 3.4). Considering the cause of infection by production types, cow-calf was the only one that was most infected by airborne transmission (82.3%). The other production types were mainly caused by indirect contact (Table 3.3).

The initial ring vaccination on day seven reduced the number of infected premises 23.7 percent from the baseline scenario, but resulted in the same duration of epidemic (115 days). Compared to baseline, this control strategy did not reduce the number of destroyed animals.

3.6 Initial ring vaccination on day 14

When the initial ring vaccination was conducted on day 14, the median size of an epidemic was 8,688 premises (mean was 8,944 premises; 75th and 95th percentile were 10,551 and 14,446 premises, respectively) and the median epidemic duration was 113 days (75th and 95th percentile were 133 and 167 days, respectively) (Table 3.2).

Distribution of the median number of daily new premises infected with FMD virus was skewed to the right (Figure 3.1) and was best fit with a weibull distribution ($\alpha = 1.86$, $\beta = 22.95$, and shift = +16.49). Of all infected premises, swine had the highest infected proportion (39.4%; Figure 3.3) followed by beef feedlot, dairy, cow-calf, and sheep at 24.8, 24.0, 11.7, and 0.05 percent respectively (Figure 3.3). The highest proportion of infections was caused by indirect contact (82.0%). Infections caused by airborne transmission and direct contact were 13.4 and 4.6 percent respectively (Figure 3.4).

Considering the cause of infection by production types, cow-calf was the only one that was most infected by airborne transmission (82.4%). Infections in the other production types were mainly caused by indirect contact (Table 3.3). The strategy of initial ring vaccination on day 14 increased the number of infected premises by 80 (0.01%) from the initial ring vaccination on day seven and had no effect on the epidemic duration (113 and 115 days). Compared to baseline, this control strategy had almost the same number of destroyed animals.

3.7 Estimated number of destroyed and vaccinated animals

Considering all scenarios the majority production type tagged for destruction was beef feedlot (Table 3.4). In the vaccination strategies 1,150 - 1,240 beef feedlot premises representing 5.0 – 5.3 million animals were vaccinated (Table 3.5). All scenarios set the outbreak to end in two years from when the index premises was exposed. Therefore many premises and animals would be destroyed after the end of outbreak. Two strategies using extra destruction actually decreased the number pending for destruction. The trigger ring animal destruction strategy decreased the queued number of beef feedlot and cow-calf animals to be destroyed, and the additional animal destruction strategy decreased the queued number of swine (Tables 3.6 and 3.7).

3.8 Distribution differences of size of epidemic

The Shapiro-Wilk normality test for all distributions of the number of daily new premises infected with FMD virus in all days of interest (day 34, day 41, day 48, and the end of disease phase), either raw or log-normal transformed data, identified non-

normality ($P < 0.0001$). Therefore all comparisons of epidemic size were tested using nonparametric statistics.

Using the nonparametric Kruskal-Wallis 1-way ANOVA by ranks for multiple comparisons, the distribution of size of the epidemic at the end of the disease phase in various scenarios were different ($P < 0.0001$). Using the same multiple comparisons method, the distribution of size of the epidemic at days 34, 41, and 48 were different ($P < 0.0001$ for all days of interest). This indicated that not all of the distribution of epidemic size were the same at day 34, 41, 48, and end of disease phase.

Using the Bonferroni correction for pairwise multiple comparisons of distribution of epidemic size, significant ($P < 0.05$) comparisons were indicated by different superscript letters within a column (Table 3.8). Baseline scenario differed significantly from all other scenarios on all days of observation ($P < 0.05$). Restricted animal movement differed from all other scenarios on all days of observation ($P < 0.05$) except on day 34. Additional animal destruction differed from all other scenarios on day 48 and at the end of disease phase ($P < 0.05$). On day 34 and 41, this scenario was not significantly different from either ring vaccination scenario ($P < 0.05$). Initial ring vaccination either on day 7 or 14 did not result in a significant difference on the effect of epidemic size ($P < 0.05$) (Table 3.8).

4. Discussion

Compared to the baseline scenario, all additional control strategies decreased the number of infected premises of FMD-susceptible livestock in the study area during the two-year outbreak period of the simulation model. This indicated that the magnitude of disease spread was less than the baseline scenario; however, these strategies did not decrease the duration of the epidemic.

The restriction of animal movement resulted in the lowest number of infected premises and a 29 percent decrease in infected premises as compared to baseline, but this disease control strategy had the longest duration of epidemic among all other scenarios. This result might be because the disease spread was controlled much more at the direct-contact level and would be more successfully detected within the ten-kilometer zone. Detected premises and direct contact traces were defined as the first and second priority for destruction; therefore more restricted movement helped reduce the number of premises infected by direct contact as compared to other scenarios. Because of limited manpower to stamp out animals, there might be more undetected premises from indirect contact than in other scenarios. The disease could spread over a longer distance and greater time in a less dense infection zone. In this animal movement strategy direct contact played less of a role, but indirect contact and airborne spread played greater roles in the cause of disease spread.

Both the additional destruction and trigger ring animal destruction strategies decreased by 21.2 and 23.3 percent the number of infected premises from the baseline scenario, respectively. Trigger ring animal destruction slightly decreased (0.5%) the proportion of infections caused by direct contact as compared to the additional animal

destruction strategy, but resulted in a slightly increased (0.5%) proportion of infections caused by indirect contact. According to production type, the highest number of animal destroyed in all scenarios was beef feedlots (16.3 million head in the baseline and 15.8 million head in the restricted animal movement. With capacity for destruction being equal, the magnitude of outbreak (number of infected premises) was slightly decreased by the trigger ring destruction as compared to the additional destruction.

Ring vaccination initiated earlier on day seven or later on day 14 after the first detection was assessed as the last two disease control strategies. These two scenarios resulted in nearly equal numbers of infected premises, but when compared to the baseline scenario the number of infected premises decreased by about 23 percent. The medians of epidemic duration for the seven-day and 14-day ring vaccination scenarios were 115 and 113 days respectively. These vaccination strategies did not decrease the duration from the baseline (115 days; Table 3.2). Within 143 and 141 days, there were 5.4 and 5.0 million cattle vaccinated in the seven-day and 14-day ring vaccination strategies respectively. Both vaccination strategies did not help decreasing the number of animal destroyed.

In developing the scenarios using additional control strategies, realistic estimations of manpower and the size and distribution of livestock premises in the central US were used. The swine and beef feedlot production types had the first and second priorities for destruction (the average herd sizes being 2,345 and 5,726 head respectively). In the baseline scenario, the capacity of destruction was set as three herds per day. The capacity of animal destruction scenarios was set as eight premises per day for both the general additional and ring destruction strategies. Even though the outbreak

in all scenarios was set as a two-year period, there were a high number of animals queued for destruction at the end of that time.

As verified in another study by the authors (Premashthira et al., 2011), indirect contact played major role (82-84%) in disease spread in the simulation model. Indirect contact was the major cause of disease spread in premises with a large average herd size such as in beef feedlots and swine production units. Any disease control and eradication program in the study area should therefore be more concerned about the spread of disease caused by indirect contact.

Several studies have used simulation models to assess FMD control measures, and they concluded that preemptive slaughter and ring vaccination consistently decreased the size or duration of an epidemic (Bates et al., 2003; Schoenbaum and Disney, 2003; Le Menach et al., 2005). In this study, a decrease in the size of the epidemic as assessed by the cumulative number of infected premises was found in the destruction and vaccination strategies. However, the restricted animal movement strategy decreased the size of the epidemic more than did the destruction and vaccination strategies. Moreover, these strategies did not reduce the duration of the epidemic. The results in this study differ from previous studies because limitation and prioritization of disease control activities were included in the model. NAADSM allows us to limit the manpower capacity for disease control. Our model scenarios had very low capacity compared to all susceptible and infected premises; for example, 3-8 premises per day for destruction and 10 premises per day for vaccination, while the average number of newly infected premises was 52-98 premises per day.

This study involves 102,283 premises in the central US. Any limitations of manpower could result in the omission of many infected premises, which were out of operation priority such as indirect contact, from the disease control program. Some infected premises would not be detected or would be delayed in being detected, so they possibly would be omitted from the restricted movement program. Also, some FMD-infected and detected premises would not be destroyed or vaccinated because of the limited capacity to handle all the premises.

5. Tables

Table 3.1

Descriptions of baseline scenario and other disease control scenarios as different foot-and-mouth disease control strategies for assessing the hypothetical outbreaks in the central United States using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep, using population data from 2006-2008.

	Scenario					
	Baseline	Restricted animal movement	Additional animal destruction	Trigger ring animal destruction	Initial ring vaccination on day 7	Initial ring vaccination on day 14
Short description	Limited disease control	Strengthen the restriction of animal movement.	Add capacity for animal destruction.	Add capacity for animal destruction in premises 3 kilometers around detected unit.	The ring vaccination program starts at day 7 after first detection.	The ring vaccination program starts at day 14 after first detection.
Effect on movement rate in 10 km zone radius after detection	30% of pre-outbreak for direct contact and 50% of pre-outbreak for indirect contact (on day 14)	0% of pre-outbreak for direct contact and 30% for indirect contact (on day 5)	Same as baseline	Same as baseline	Same as baseline	Same as baseline
Destruction capacity	3 premises per day	Same as baseline	8 premises per day	8 premises per day	Same as baseline	Same as baseline
Destruction priority	1) detected premises 2) direct contact premises	Same as baseline	Same as baseline	1) detected premises 2) direct contact premises 3) 3 kilometers around detected premises	Same as baseline	Same as baseline
Production type priority of destruction	1) swine 2) beef feedlot 3) dairy 4) cow-calf 5) sheep	Same as baseline	Same as baseline	1) beef feedlot 2) cow-calf 3) swine 4) dairy 5) sheep	Same as baseline	Same as baseline
Vaccination in 10 km zone radius after detection	Do not vaccinate.	Do not vaccinate.	Do not vaccinate.	Do not vaccinate.	Capacity is 10 premises per day. The ring vaccination program starts at day 7 after first detection. The production type priority of vaccination is 1) beef feedlot 2) cow-calf 3) dairy 4) swine 5) sheep	Capacity is 10 premises per day. The ring vaccination program starts at day 14 after first detection. The production type priority of vaccination is 1) beef feedlot 2) cow-calf 3) dairy 4) swine 5) sheep

Table 3.2

Simulation results for cumulative number of infected premises, duration of epidemic, and estimated number of destroyed animals of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

Scenario	Cumulative number of infected premises				Duration of epidemic (days)			Estimated number of destroyed animals (x 1 million)
	Median	Mean	P75	P95	Median	P75	P95	
Baseline (limited disease control)	11,283	11,461	13,560	17,111	115	132	176	29.50
Restricted animal movement	7,975	8,151	9,505	12,118	154	200	242	28.12
Additional animal destruction	8,890	9,300	10,942	15,249	115	132	178	29.49
Trigger ring animal destruction	8,649	9,024	10,551	14,609	116	131	179	29.52
Initial ring vaccination on day 7	8,608	8,984	10,579	14,460	115	130	169	29.58
Initial ring vaccination on day 14	8,688	8,944	10,551	14,446	113	133	167	29.50

Table 3.3

Simulation results for proportion of infected premises by causes of infection in each production type (beef feedlot, cow-calf, dairy cattle, swine, and sheep) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data from 2006-2008.

Scenario	Proportion of infected premises (%) by causes of infection				
	Causes of infection	Beef feedlot	Cow-calf	Dairy	Swine
Baseline					
<i>Airborne</i>	1.9	82.3	1.0	7.8	0.0
<i>Direct contact</i>	3.9	0.0	7.0	5.0	0.0
<i>Indirect contact</i>	94.2	17.7	92.0	87.2	100.0
Restricted animal movement					
<i>Airborne</i>	2.8	89.2	1.2	8.5	0.0
<i>Direct contact</i>	2.9	0.0	4.4	0.7	0.0
<i>Indirect contact</i>	94.3	10.8	94.4	90.9	100.0
Additional animal destruction					
<i>Airborne</i>	1.9	82.4	1.0	7.8	0.0
<i>Direct contact</i>	3.8	0.0	7.0	5.0	0.0
<i>Indirect contact</i>	94.3	17.6	92.0	87.2	100.0
Trigger ring animal destruction					
<i>Airborne</i>	1.9	82.5	1.0	7.8	0.0
<i>Direct contact</i>	3.8	0.0	7.0	3.8	0.0
<i>Indirect contact</i>	94.2	17.5	92.0	88.4	100.0
Initial ring vaccination on day 7					
<i>Airborne</i>	1.9	82.3	0.9	7.7	0.0
<i>Direct contact</i>	3.9	0.0	7.0	5.0	0.0
<i>Indirect contact</i>	94.2	17.7	92.0	87.3	100.0
Initial ring vaccination on day 14					
<i>Airborne</i>	1.9	82.4	1.0	7.8	0.0
<i>Direct contact</i>	3.8	0.0	7.1	4.9	0.0
<i>Indirect contact</i>	94.3	17.6	92.0	87.3	100.0

Table 3.4

Simulation results for estimated number of destroyed animals in each production type (beef feedlot, cow-calf, dairy cattle, swine, and sheep) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data from 2006-2008.

Scenario	Estimated number of destroyed animals					Total
	Beef feedlot	Cow-calf	Dairy	Swine	Sheep	
Baseline	16,390,261	225,425	1,975,928	10,910,488	853	29,502,955
Restricted animal movement	15,821,945	113,241	1,939,670	10,246,895	782	28,122,533
Additional animal destruction	16,364,225	225,680	1,974,165	10,926,559	860	29,491,489
Trigger ring animal destruction	16,378,791	221,743	1,974,578	10,946,191	853	29,522,155
Initial ring vaccination on day 7	16,419,966	223,313	1,975,949	10,964,057	862	29,584,147
Initial ring vaccination on day 14	16,391,412	222,023	1,976,160	10,912,006	861	29,502,462

Table 3.5

Simulation results for estimated number of vaccinated beef feedlots of two scenarios as foot-and-mouth disease control strategies by vaccination (initial ring vaccination on day 7 and on day 14) in the central United States, using population data from 2006-2008.

Scenario	Number of beef feedlots vaccinated	
	heads	premises
Initial ring vaccination on day 7 (day7 -day143)	5,352,069	1,240
Initial ring vaccination on day 14 (day 14 -day141)	5,043,000	1,150

Table 3.6

Simulation results for estimated number of animals to be destroyed following the two-year period from when the index premises was exposed (queue) in each production type (beef feedlot, cow-calf, dairy cattle, swine, and sheep) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data from 2006-2008.

Scenario	Estimated number of animals to be destroyed after 2 years (queue)				
	Beef feedlot	Cow-calf	Dairy	Swine	Sheep
Baseline	16,240,102	225,425	1,975,928	4,858,756	853
Restricted animal movement	15,638,158	113,241	1,939,670	4,799,599	782
Additional animal destruction	9,479,914	225,680	1,974,165	112,405	860
Trigger ring animal destruction	202,234	3,039	1,974,578	6,380,505	853
Initial ring vaccination on day 7	16,280,514	223,313	1,975,949	4,998,072	862
Initial ring vaccination on day 14	16,248,537	222,023	1,976,160	4,949,697	861

Table 3.7

Simulation results for estimated number of premises to be destroyed following the two-year period from when the index premises was exposed (queue) in each production type (beef feedlot, cow-calf, dairy cattle, swine, and sheep) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data from 2006-2008.

Scenario	Estimated number of premises to be destroyed after 2 years (queue)				
	Beef feedlot	Cow-calf	Dairy	Swine	Sheep
Baseline	2,841	1,359	2,771	2,431	6
Restricted animal movement	2,769	1,219	2,741	2,114	5
Additional animal destruction	1,670	1,359	2,770	58	6
Trigger ring animal destruction	36	34	2,770	3,013	6
Initial ring vaccination on day 7	2,850	1,359	2,772	2,441	7
Initial ring vaccination on day 14	2,842	1,353	2,771	2,426	6

Table 3.8

Simulation results for medians of daily cumulative infected premises on day 34, 41, 48, and the end of disease phase of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

Scenario	Number of iteration	Medians of daily cumulative infected premises			
		Day 34	Day 41	Day 48	End of disease phase
Baseline	400	6,334 ^A	8,375 ^F	9,939 ^L	11,283 ^P
Restricted animal movement	398	1,490 ^{B,E}	2,840 ^G	4,102 ^M	7,975 ^Q
Additional animal destruction	400	3,911 ^C	5,837 ^H	7,229 ^N	8,890 ^R
Trigger ring animal destruction	400	3,781 ^D	5,691 ^{I,J,K}	7,135 ^O	8,649 ^S
Initial ring vaccination on day 7	400	4,045 ^C	5,699 ^H	7,167 ^O	8,608 ^S
Initial ring vaccination on day 14	400	3,809 ^{C,D,E}	5,711 ^{H,I,K}	7,172 ^O	8,688 ^S

^{A-S} Within a column, values with different superscript letters differ significantly ($P < 0.05$) as determined by Bonferroni correction for multiple comparisons.

6. Figures

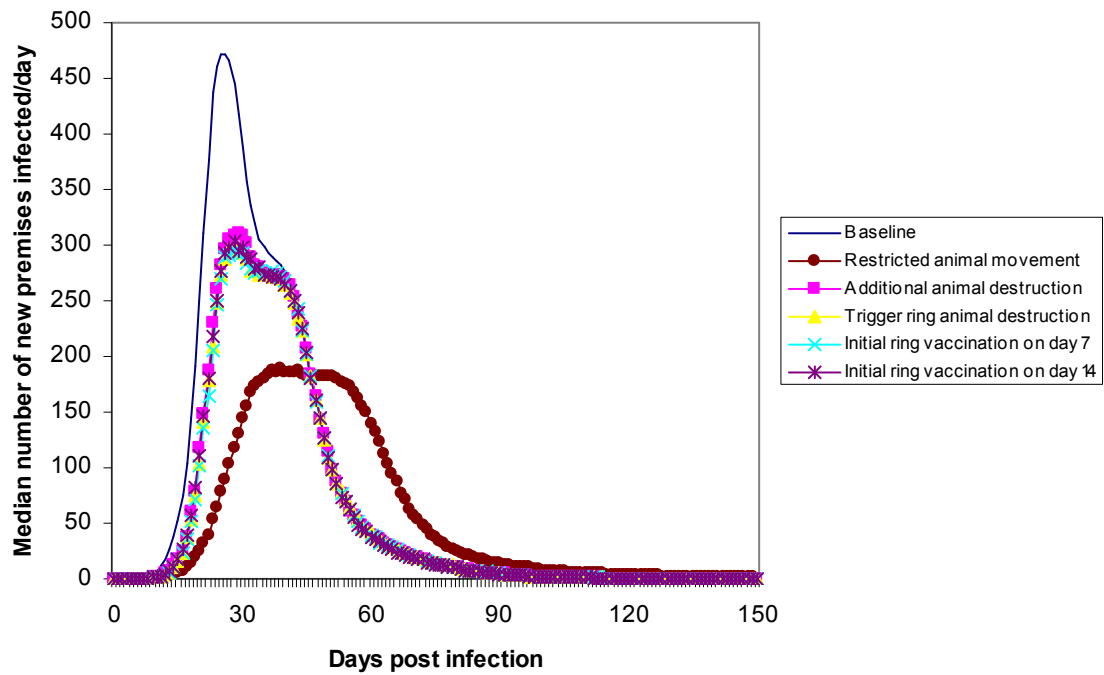


Figure 3.1. Simulation results for relationship between days post infection and median number of daily new premises infected with foot-and mouth disease virus of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

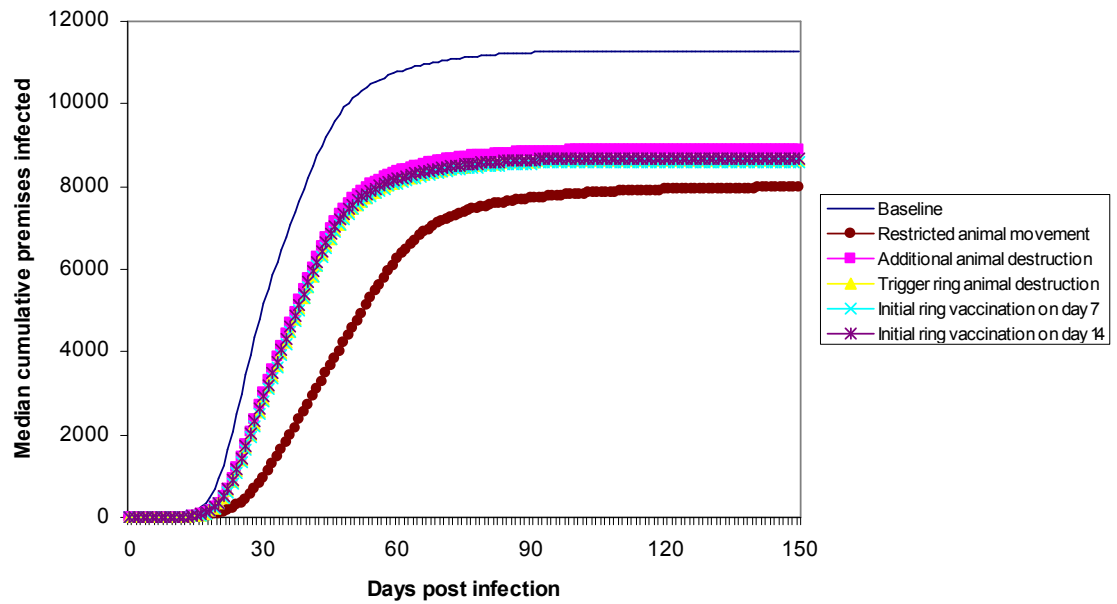


Figure 3.2. Simulation results for relationship between days post infection and median cumulative infected premises with foot-and mouth disease virus of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

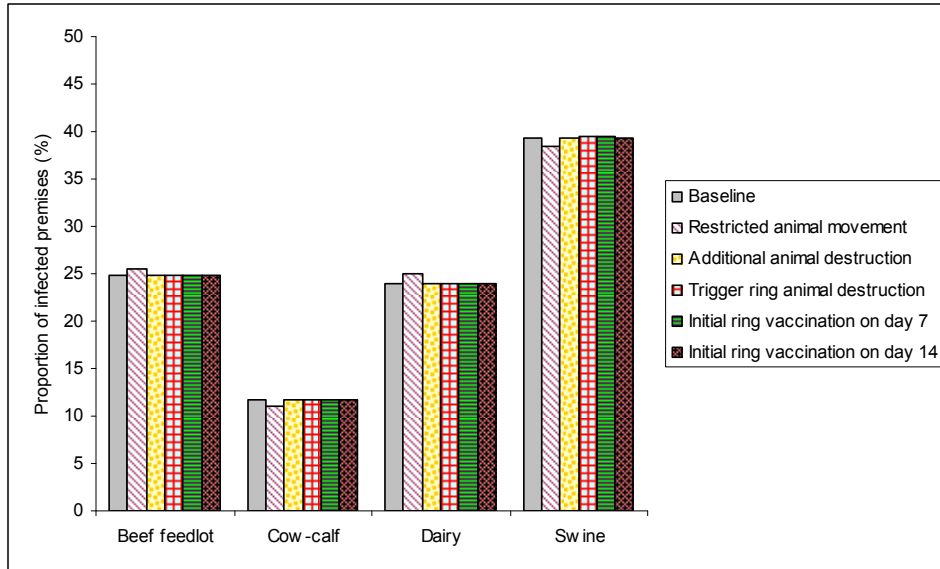


Figure 3.3. Simulation results for proportion of premises infected with foot-and-mouth disease virus by production types (beef feedlot, cow-calf, dairy cattle, and swine) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data from 2006-2008.

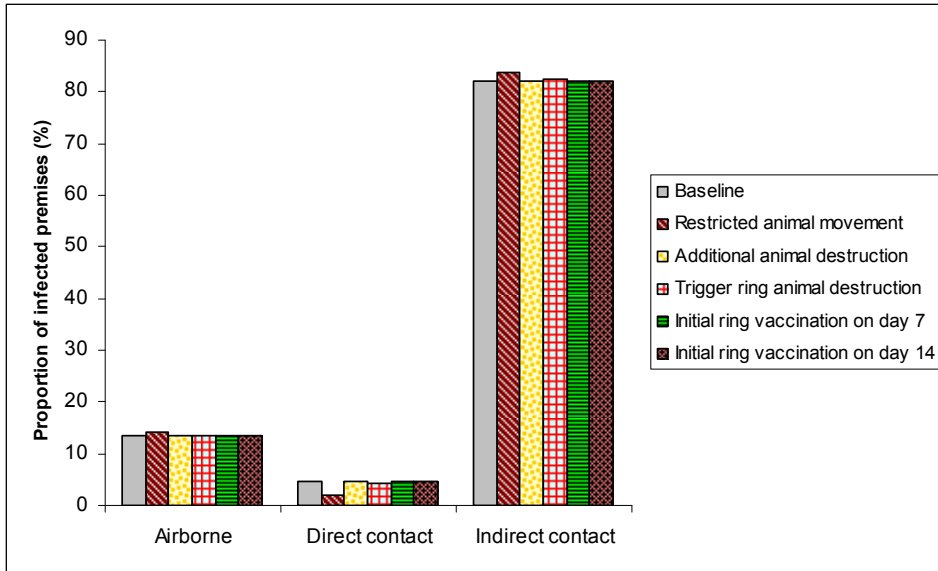


Figure 3.4. Simulation results for proportion of premises infected with foot-and-mouth disease virus by causes of infection (airborne, direct contact, or indirect contact) of baseline scenario and other scenarios as different disease control strategies of foot-and-mouth disease in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, and swine from 2006-2008.

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**CHAPTER 4: QUANTITATIVE SPATIAL METHODS TO
DETERMINE THE FOOT-AND-MOUTH DISEASE
OUTBREAK AREA FOR A HYPOTHETICAL OUTBREAK
ORIGINATING IN THE CENTRAL UNITED STATES**

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Summary

In cloven-hoofed animals such as cattle, buffalo, sheep and pigs, foot-and-mouth disease (FMD) is one of the most highly contagious viral diseases. The United States has been FMD-free since 1929. Any area free of FMD virus may want to simulate a hypothetical outbreak in order to observe the spatial trend of FMD spread. A large area in the central United States includes the major cattle feeding region of the country, therefore the effect of a hypothetical FMD introduction and spread in the region is interesting to model to examine the area influenced by the outbreak. An epidemiologic simulation model of an FMD outbreak in the central United States was implemented and the resulting geographic locations of infected premises were determined. Considering the county level, it was found that in an outbreak almost ninety percent of the area was infected with FMD virus. Quantitative spatial methods such as regular density analysis, kernel density estimation, and variogram function can help identify important outbreak areas from the simulated infected points. Two hot spots of high density infection were found in eastern Kansas and eastern Nebraska, northeast of the index case. Spatial similarity of FMD infection was 166.7 kilometers measured the range among counties with increasing distances. Spatial cross-correlation and spatial autoregressive models describe the correlation of selected variables of interest. Animal populations counted as premises or herds were strong-positive spatially correlated with the number of infected premises. At the county level, high influential factors for having high number of infected premises are number of dairy, beef feedlot, and swine premises. Premises density is the most influential factor to predict the infected density in a county. Geographical information systems can help with visualizing the outbreak area in maps. The findings of

spatial occurrence will be used as a foundation for the epidemiologic and economic impacts of FMD in the central United States.

Keywords: Quantitative spatial methods; Disease; Foot and mouth; Outbreak area; Central United States

1. Introduction

Foot-and-mouth disease (FMD) is a highly contagious animal viral disease in cloven-hoofed animals that may have rapid and unexpected national and international spread. Introduction of the FMD virus into disease-free herds, areas, or countries is likely to spread very rapidly with high morbidity rates (Geering et al., 2002). The United States (US) has not experienced an FMD outbreak since 1929 (Graves, 1979), therefore spatial analysis and visualization of a hypothetical outbreak in a critical area will be useful for estimating the impact of the disease. An intense livestock production area is found in the states of Colorado, Kansas, Nebraska, New Mexico, Oklahoma, and Texas; approximately 78% of cattle fed in the US are located in this area (NASS, 2011). Introduction and spread of FMD in this region could have devastating animal health and economic consequences (Pendell et al., 2007).

Determining the geographical boundaries of an outbreak region is essential step in controlling the spread of the disease. There are three main methods used to identify the outbreak region: 1) geographical location of premises, 2) epidemiological simulation modeling, and 3) quantitative spatial analysis including visualization in the form of maps or plots. The number of livestock farm sites, or premises, was brought together from

many sources in the study area. The primary sources being 1) State reports that were required to receive environmental permits and 2) the farm location and animal population simulator (FLAPS) which is an ArcGIS software that uses the county-level National Agriculture Statistics Service (NASS) data. The geographical location, production type, and maximum herd size were obtained for each study premises. In epidemiological simulation modeling, a stochastic model simulator is used to determine which premises are infected and uninfected in repeated iterations. This can help in identifying outbreak spots for subsequent spatial analysis. Quantitative spatial analysis and visualization of the simulation results using a geographical information system (GIS) at the county level help identify an outbreak area. Spatial trend in a potential FMD outbreak could be analyzed by several approaches such as density estimation, hot spot analysis, spatial continuity of distance of infection, and variations of the disease spread and their correlation to variables of interest.

The main objective of this study was to determine the geographic region affected by a simulated outbreak in the event FMD was introduced into a major cattle feeding area such as the central US. The second objective was to describe the spatial trend and variation of FMD spread in a hypothetical outbreak.

2. Materials and Methods

2.1 Study area and premises gathering

The study area was composed of 413 US counties in the states of Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas. Population data of FMD-susceptible livestock species (cattle, pigs, and sheep) were collected, including latitude

and longitude of their premises sites, using the decimal degree system. Based on differences in likelihood of potential disease progression and spread as well as dissimilar animal management operations, the livestock premises were classified into five different production types: beef feedlot, cow-calf, dairy cattle, swine, and sheep.

The number of premises included within the study area was gathered from a variety of sources. There are three methods by which the states reported the location of the premises. Kansas, New Mexico, Oklahoma, and Texas reported the geographic location of livestock premises as latitude and longitude. Colorado reported the premises by postal address, so Google Earth was used to locate the geographical site of livestock premises in Colorado. Nebraska reported the geographical locations using the Public Land Survey System (PLSS) that describes land in the United States using a rectangular coordinate system. The geographical area in Nebraska was converted to an estimated point location by first locating the central point of the rectangle for the first premises. In case of having extra premises in the same rectangle, the subsequent premises within the same rectangle were selected at the points between the center and the corners. Finally, all geographical locations of premises from the three methods were harmonized to the decimal degree latitude and longitude system. Additionally, the sheep premises within Colorado were collected as secondary data from Mayo (2006).

Data from the CAFOs were obtained through the Open Records Act. The maximum number of head at each premises, in which the majority being beef feedlots, was collected from state agencies since these operations (e.g., confined animal feeding operation or CAFO) are required to receive environmental permits. The location, size, and number of small livestock operations were not available since they were not included

in the environmental permit records. The geospatial information for these livestock operations (cow-calf, dairy cattle, and swine) was generated by a spatial modeling method called Farm Location and Animal Population Simulator (FLAPS) in ArcGIS software, using the county-level National Agriculture Statistics Service (NASS) data (Freier et al., 2007). The output of FLAPS produced the list of premises including their farm type, geographical location, and premises size.

2.2 Steps in epidemiological simulation modeling

An epidemiological model was constructed and simulated using the North American Animal Disease Spread Model (NAADSM). The NAADSM is a stochastic state-transitional model for the spread of highly contagious diseases of animals. NAADSM users can establish parameters to define model behavior in terms of disease progression; direct contact, indirect contact, and airborne dissemination; and implementation of control measures. This model is being used to evaluate outbreak scenarios and potential control strategies for exotic animal diseases in the US, Canada, and elsewhere (Harvey et al., 2007).

A baseline scenario was constructed using the estimated parameters that were obtained from the literature, statistical analysis, and expert opinions based on experiences from related research and work in the US. The baseline scenario simulated the spread of an FMD outbreak in the central US with limited disease control implementation. An index case was located in a large beef feedlot in southwest Kansas. The simulation included 400 iterations and each iteration simulated a period of 730 days (2 years). Geographical location and information for FMD-infected and -uninfected premises in the

scenario were collected and used to analyze the spatial distribution of the simulated outbreaks.

2.3 Spatial analysis and visualization

2.3.1 Base maps

Base maps used in the analysis were from the US Census Bureau website at <http://www.census.gov/geo/www/index.html> (U.S. Census Bureau, 2010). The shape files for county boundaries within the six states—Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas—were downloaded and projected to an identical coordinate system.

2.3.2 Geographical coordinates of infected and uninfected premises

Four hundred iterations of the baseline scenario were run by NAADSM, a stochastic model simulator. One hundred of the 400 simulated iterations were systematically selected for analysis. Although 400 iterations were simulated, the large amounts of required spatial data associated with each simulation prohibited us from analyzing all these runs. Thus, we assumed the sequence of simulation outputs are not correlated, and that sampling of 100 runs would be representative of the variability among 400 runs in the baseline scenario. Geographical points and data for infected and uninfected premises gathered from the baseline scenario were grouped by counties. Among the 100 systematically sampled iterations the average number of infected premises, including their variance in each county, was calculated. The premises were of mixed production types.

2.3.3 Susceptible population distribution

Using the pre-run baseline scenario the susceptible study population and its basic statistics were summarized by a table, histograms, and category maps. The table summarized the number of counties in each of the states included in the study. The category maps and histograms displayed the distribution of county land area in square kilometers, number of premises and animals in each county, as well as premises density and animal density in each county. The category maps by county boundary were created in ArcMap and the histograms by R software (R Development Core Team, 2008).

2.3.4 Outbreak estimation and visualization

The infected and uninfected premises from the 100 simulated iterations were analyzed and visualized spatially in ArcGIS.

Average number of infected premises (\hat{N}_i) at the county level

In county i , the average number of infected premises (\hat{N}_i) was calculated by the following formula.

$$(1) \hat{N}_i = \frac{1}{100} \sum_{j=1}^{100} N_j,$$

where 100 is number of iterations of the baseline scenario, and N_j is number of infected premises in county i during the j^{th} ($j=1, \dots, 100$) iteration.

Proportion of infected premises at the county level (\hat{P}_i)

The proportion of infected herds in county i (\hat{P}_i) is calculated by

$$(2) \hat{P}_i = \frac{\hat{N}_i}{S_i},$$

where S_i is number of susceptible premises in county i .

Variance of proportion of infected premises at the county level ($\hat{V}(\hat{P}_i)$)

The variance of proportion of infected premises (\hat{P}_i) in county i ($\hat{V}(\hat{P}_i)$) is approximated by

$$(3) \hat{V}(\hat{P}_i) = \frac{\hat{P}_i \hat{Q}_i}{S_i - 1},$$

where $\hat{Q}_i = 1 - \hat{P}_i$.

Proportion of infected premises at the state level (\hat{P}_s)

The proportion of infected herds in state s (\hat{P}_s) is calculated by

$$(4) \hat{P}_s = \frac{\sum A_{si} \hat{P}_{si}}{A_s},$$

where A_{si} is the area of each county in square kilometers (km^2), \hat{P}_{si} is the estimated proportion of infected premises in county i within state s , and A_s is the summation of A_{si} in state s .

Variance of proportion of infected herds in the state level ($V(\hat{P}_s)$)

The variance of proportion of infected premises in state s ($V(\hat{P}_s)$) is calculated by

$$(5) V(\hat{P}_s) = \left(\frac{1}{A_s} \right)^2 \sum A_{si}^2 V(\hat{P}_{si}).$$

2.4 Kernel Density Estimation

Kernel density estimation (KDE) analyzes the properties of a point event distribution and has been widely used for hotspot analysis and detection. The objective of KDE is to produce a smooth density surface of point events over space by passing a moving window over the spatial data at each location and estimate the density of points in the window. Sample points are weighted proportional to their distances from the center of the window (Lin et al., 2011). Using KDE with geographical data and a sample of controls, the relative risk function over a geographical region can estimate effectively the spatial distribution of disease cases (Bithell, 1990).

Common kernels used to estimate the density at a given location include the Gaussian, uniform, triangle, and Epanechnikov which is parabolic in shape (Lake et al., 2009). Silverman (1986) describes the kernel method in several dimensions and illustrates the advantage of this method which is having higher differentiability properties than normal and Epanechnikov kernels. In addition, the several dimensions kernel can be calculated more quickly than the normal kernel.

The multivariate kernel density estimator using kernel K , bandwidth h or radius of the moving window in d -dimensional space is defined by

$$(6) \hat{f}(x) = \frac{1}{nh^d} \sum_{i=1}^n K \left\{ \frac{1}{h} (x - X_i) \right\},$$

where X_1, \dots, X_n is assumed as the given multivariate data set whose underlying density is to be estimated (Silverman, 1986).

There are some publications of kernel density estimation application in geographical epidemiology; for example, Bithell (1990) and Mukherjee et al. (2002). Bithell (1990) made use of a two-dimensional Poisson process to estimate the density of cases of childhood leukemia. Bithell defined the relative function as a ratio of the density of cases of childhood leukemia and controls. Mukherjee et al. (2002) used the technique of density estimation on cases of goiter in the Muzaffarpur district of Bihar, a state of India. The authors found that the risk of developing goiter varies spatially along the Indo-Nepal border and the Sitamarhi headquarters.

The FMD-infected premises coordinates were collected from the baseline scenario from the 400 simulated iterations by NAADSM. All 400 iterations from the baseline scenario were integrated to estimate KDE. The size of bandwidth was set as 100,000 meters and the number of equally spaced grid coordinates in the x and y direction as 50 grids per axis. The spatial library for R created by Reich and Davis (2007a) was used to perform the KDE operation. The average value of KDE of the FMD outbreak was illustrated as a map in ArcGIS. The KDE's variance, lower limit, upper limit, range, skewness, and coefficient of variation were illustrated by perspective maps and contour maps by R software.

2.5 Spatial continuity

A variogram is a common technique used to describes how spatial continuity changes as function of distance and direction. Variograms are preferred by geostatisticians to describe spatial continuity in a set of data (Reich and Davis, 2007b).

The sample variogram is defined by

$$(7) \gamma(h) = \frac{1}{2N(h)} \sum_{i=1}^{N(h)} (y_i - y_j)^2,$$

where $N(h)$ is the number of data pairs separated by distance h , y_i is the observed value at location s_i and y_j is the observed value at location j . The sample variogram models were fit to three theoretical variogram models: exponential, spherical, and Gaussian. Akaike Information Criterion (AIC) (Akaike, 1969) was used to identify the best fitting variogram model. The spatial library for R created by Reich and Davis (2007a) was used to perform the operation.

The corresponding variogram will generally increase as the distance between the pairs of points increases. As the distance increases, the variogram will reach a plateau. The distance at which the variogram reaches the plateau is called the range. The range describes the distance at which observations become spatially independent. The plateau of the variogram is called the sill. The sill describes the variance of data. The vertical jump from 0 at the origin to the small value of the variogram at extremely small separation distances is called the nugget effect (Reich and Davis, 2007b).

From the results of baseline scenario, the average numbers of FMD-infected premises in each county were calculated. The coordinates of the central points of each county were located for measuring the spatial continuity of the average number of infected premises using a variogram.

2.6 Spatial autocorrelation

Spatial autocorrelation is frequently encountered in ecological data of distributions of organisms and their environment (Lichstein et al., 2002). Bonham et al. (1995) used spatial autocorrelation and cross correlation statistics to study the spatial relationship of blue grama (*Bouteloua gracilis*) with other site characteristics of a mixed grass community in southern Arizona. Moran's I statistics measure the correlation between neighboring of study area units. The diagonal elements of this correlation matrix were Moran's I statistics, while the off-diagonal elements were cross-correlation statistics referred to as Moran's Bivariate I_{yz} (Bonham et al., 1995), also called bimoran's I . The estimates of spatial autocorrelation and cross-correlation statistics for all variables were presented in a matrix along with estimates of the linear correlation coefficient \textcircled{R} .

This study applied spatial autocorrelation and cross-correlation to analyze FMD infection and associated factors from county-level simulation modeling. A binary spatial weights matrix was used to describe the spatial continuity of neighboring counties. If two counties shared a common border, they were considered neighbors. The number of infected premises, infected density, and proportion of infected premises were used as infection assessments. County land area, premises density, animal density, and animal population in different groups were used as factors.

2.7 Spatial autoregressive model

Using the results from baseline scenario, ordinary least square models were considered that describe the dependence of variable Y on the k -independent X variables by a simple linear relationship:

$$(8) Y_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_k X_{ik} + \varepsilon_i, i = 1, \dots, n \text{ (Reich and Davis, 2007b),}$$

where β_0 is intercept or the estimated average value of dependent variable (Y_i) when the independent variables (X_i) are zero, and β_i are the regression coefficients.

The dependent variables (Y_i), i.e., the FMD infection assessments, were the number of infected premises and the infected density at the county level. The independent variables (X_i) were county land area, premises density, animal density, beef feedlot population, cow-calf population, dairy cattle population, and swine population at the county level.

After fitting the OLS models, the residuals were inspected to determine if they were spatially independent. If the residuals in the OLS models were spatially correlated, this indicated that the assumption of independent errors was violated (Lichstein et al., 2002). The error could perhaps be modeled with a spatial autoregressive model, spatial lag model, or a combined model. The spatial lag model differs slightly from the spatial autoregressive model because the spatial lag model models the spatial correlation using neighboring values, while the spatial autoregressive model describes the spatial correlation in the error term (Reich and Davis, 2007b).

Spatial autoregressive model (SpatAR) is defined by

$$(9) Y_i = \beta_0 + \beta_1 X_{i1} + \dots + \beta_k X_{ik} + \varepsilon_i,$$

where Y_1, \dots, Y_n are data, β_0 is intercept or the estimated average value of dependent variable (Y_i) when the independent variables (X_i) are zero, β_1, \dots, β_k are the regression coefficients, $\varepsilon_i = \lambda W \varepsilon_j + \nu$, W is spatial weight matrix, $\nu \sim N(0,1)$, and ε_j are spatially correlated errors.

Spatial lag model (SpatLag) is defined by

$$(10) Y_i = \beta_0 + X_{i1}\beta_1 + \dots + X_{ik}\beta_k + \rho \sum_{j=1}^n W_{ij}Y_j + \varepsilon_i ,$$

where $-1 \leq \lambda, \rho \leq 1$ are measured the spatial correlation in the data.

A combination of spatial autoregressive and spatial lag model (SpatCmb) is defined by

$$(11) Y_i = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k + \rho WY_j + \varepsilon_i \text{ (Reich and Davis, 2007b),}$$

where $\varepsilon_i = \lambda W\varepsilon_j + \nu$.

3. Results

3.1 Study area and basic statistics

Among the six states, 100 percent of the counties in Kansas were included in the study area (Figure 4.1). Sixty-six percent of the total number of counties in the six states were included in the study (413 of 626). A high density of premises appeared in the eastern part of the study area and southeast of the approximate index case (Figure 4.2). The highest density of animals tended to be in the center of study area and in some counties to the south and north of the index case point (Figure 4.3). A frequency distribution of county land area in square kilometer indicated a right skew distribution (Figure 4.4). Regardless of production types, the frequency distributions of the number of premises, number of animals, density of premises, and animal density were also highly skewed to the right indicating a large number of low density counties and a few high density counties (Figure 4.5, 4.6, 4.7, and 4.8 respectively).

3.2 Area of a centrally-originating FMD outbreak simulated

From the systematic random selection of 100 out of the total 400 iterations of the simulation model, 370 out of 413 counties (89.6%) were affected with an average of at least one FMD-infected premises in each county (Figure 4.9).

The majority of infected counties had an average of infected premises of fewer than approximately 40 herds (Figures 4.10 and 4.11). The highest average number of infected premises, greater than 83 herds, was found in the east-northeast section of the map in Kansas and Nebraska.

The proportion of infected premises at the county level had a U-shaped distribution with high frequency of counties with no or 100% infection (Figure 4.12). A map demonstrates that the high proportion of infected premises scatters to the north, south, and southeast of the map (Figure 4.13). The largest geographical group with its high proportion was shown to be in Nebraska. Additionally, Figure 4.14 illustrates the standard deviation of proportion of infected herds at the county level.

To initially check the spatial dependency of infected premises with other factors, scatter plots were created. To illustrate the county land area, number of initial susceptible premises, and number of initial susceptible animals versus the number of infected herds (Figures 4.15, 4.16, and 4.17). These factors are possibly spatially dependent with the number of infected premises.

From the simulation of the baseline scenario, Nebraska had the highest proportion of its area infected (Table 4.2 and Figure 4.18), while New Mexico, Colorado, and Kansas had a lower proportion of infected area.

3.3 Kernel density estimation

The high density areas were found northeast of the index case point (Figure 4.19). Two hot spots were discovered in eastern Kansas and eastern Nebraska. Considering the contour maps and perspective maps (Figures 4.20 and 4.21), the high density of infection area moved from the lower limit KDE around the index case to the average and upper limit KDE in a northeast direction. The high variance of density is also found northeast of the outbreak origin.

The average value of KDE illustrated nine levels of density of FMD infection (Figure 4.19). Regarding these levels, the high and medium levels (levels 1-6, density value greater than 0.015) were within 75 counties in Kansas, 52 counties in Nebraska, and one county in Texas. Otherwise, 285 counties of all six states were found to have a low level of average value KDE. The hot spots of high density infection (level 1, density level greater than 0.05) included 19 counties in Kansas and 2 counties in Nebraska (Table 4.3).

3.4 Spatial continuity

Considering the lowest AIC, the best variogram model for the number of infected premises was the spherical model. With regard to the center points of the counties, the range of distance that shares spatial dependency of FMD infection is 166.7 kilometers with a low nugget effect (Table 4.4, Figure 4.22). The low nugget effect indicates strong spatial dependencies in the data. The minimum, average, and maximum distance of center points among the 413 counties were 20.6, 604.5, and 1866.1 kilometers. At the

county level there were some small-size counties that shared spatial dependency, but the majority of study counties, especially the large-area counties, did not.

3.5 Spatial autocorrelation

Moran's *I* statistic, the estimate of spatial autocorrelation, indicated that the animal population was randomly distributed throughout the study area (Table 4.5). That is, the spatial autocorrelation of the animal population (head count by county) was not statistically significant. In contrast, all other factors about population, density, county land area, and infection assessments exhibited a positive significance.

3.6 Spatial autoregressive model

The OLS model explained the number of infected premises (model 2) after number of sheep premises was excluded because its estimated value was not significant (model 1)(Table 4.6). This model had r-square of 0.9755 indicating the regression line was an almost perfect fit of the data. From model 2 the most influential factors for having a high number of infected premises at the county level were number of dairy premises, number of beef feedlot premises, and number of swine premises, respectively. The number of cow-calf premises had very low magnitude of coefficient in the model.

To explain infected density, OLS model, model 3, was constructed (Table 4.6) and the residuals of spatial correlation were plotted (Figure 4.23). R-Square of the model was 0.5, indicating that the model explained 50 percent of the variability observed in a dependent variable such as infected density. The residuals (Figure 4.23) of model 3 exhibited spatial correlation, and an attempt was made to model the error with spatial autoregressive, spatial lag, and combined models. Considering the AIC, the combined

model of spatial autoregressive and spatial lag (SpatCmb) is the best model to explain the infected density of counties. The infected density was depended on premises density, animal density, independent errors, and some values from neighbors. The most influential factor to predict the infected density is premises density.

4. Discussion

The index case was located in a large beef feedlot premises in southwest Kansas because it was expected to have a high potential for initiating and spreading infection into the area. From the results of the baseline scenario stochastic modeling, 370 out of 413 study counties were included in the hypothetical outbreak of FMD infection originating from a central location. If FMD virus was introduced into the study region, it would spread to almost 90 percent of the area. This result indicated that FMD would spread widely in the central United States.

When the proportion of infected premises at the county level was considered as an outbreak measurement, the trend in the distribution looked different as compared to what was seen with the number of infected premises. The distribution had two high peaks at the lowest and highest proportions. The map illustrated that the high proportions were found in the northern and southern regions of the map. This pattern was probably emerged because the number of susceptible premises away from the map center was much lower than it was in the middle. This study illustrates that the outbreak measurement should be concerned with the number of infected premises rather than the infected proportion, because the measurement of the infected number is related to the distribution of the susceptible number while infected proportion is not.

Two hot spots of infected density in eastern Kansas and eastern Nebraska were indicated by KDE. The outbreak started approximately from the center of the study area, but the high density of infection spread to areas that were composed of high premises density (eastern Kansas) and high animal density (eastern Nebraska). KDE levels (Table 4.3) also indicated that the high and medium levels of infected density were mostly located in Kansas and Nebraska.

From the estimate of spatial cross-correlation statistics, Moran's *I* statistic indicated that most population factors that were counted as premises exhibited a significant positive spatial autocorrelation with their own kind. This was unlike when the population was counted as animal head. County land area exhibited negative-spatial correlation to most infection assessment and population factors. This finding indicated that smaller-size counties correlated with higher population numbers and FMD infection. The number of infected premises, one of the infection assessments, was probably spatially influenced by premises and animal density, premises population for all production types, and premises population for beef feedlot, cow-calf, dairy cattle, and swine, but negative-spatially influenced by county land area. This is similar to when infected density is considered as infection assessment. Otherwise, the proportion of infected premises was negative-spatially influenced by many factors, except independently with all types of animal populations, beef feedlot populations, and swine populations. This technique was frequently encountered in ecological data of plants but this study had attempted to apply in epidemiological data of an infectious disease of livestock.

The OLS model to explain the number infected premises had a very high coefficient of determination. The model also revealed that the most influential factors for having a high number of infected premises at the county level are the number of dairy, beef feedlot, and swine premises, respectively. Surprisingly, cow-calf premises, which comprised 89.6 percent of the total, were a factor that had very little influence on the hypothetical outbreak. This might be because the cow-calf operations had the lowest density population, therefore disease transmission parameters to and from cow-calf units were set as lower likelihood compared to other production types. In model 2 (OLS model) and 6 (combined model of spatial autoregressive and spatial lag model), the county land area had negative coefficients in the models, while the premises density in model 6 had a positive coefficient. This might be because study counties having a large area frequently had low premises density and were settled far away from the intense area of infection.

This study was attempted to determine the geographical region in central US affected by a simulated outbreak of FMD. The limitations of the approach were the lack of surrounding livestock population data. The simulated outbreak had to be assumed spreading within 413 counties of study area; although there was high possibility of spreading out of the area and the outbreak area determined would be unlike the findings in the study.

In conclusion, the currently FMD-free central United States was considered as an influential area for a hypothetical FMD outbreak. The spread of FMD might expand throughout most of the area, but the highest intensity of infection occurred specifically in counties having a high density of susceptible premises. This result might assist decision

makers in prioritizing FMD control strategies in counties having higher livestock premises density first in order to reduce the infection magnitude. Moreover, considering in the premises density in each county might be more efficient for controlling the disease than examining animal density.

The limitation of the study, as defined by the assumptions of the model, was that all premises in the same production type had the same disease parameters and that there were homogenous contact rates between specific pairs of production types. The animal population even in the same production type will vary in its distribution and would have different parameters and rates.

5. Tables

Table 4.1

Number of counties in each of the 6 states in the Central United States included in a hypothetical outbreak of foot-and-mouth disease, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008.

State	Total number of counties	Number of study counties	Percent
Colorado	64	47	73.4
Kansas	105	105	100.0
Nebraska	93	90	96.8
New Mexico	33	11	33.3
Oklahoma	77	49	63.6
Texas	254	111	43.7

Table 4.2

Proportion of infected premises at the state level in a hypothetical outbreak of foot-and-mouth disease in 6 contiguous central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008.

State	Number of study counties	\hat{P}_s ^a	LowerCI ^b	UpperCI ^c	%SE ^d
Colorado	47	0.13	0.11	0.15	16.58
Kansas	105	0.14	0.13	0.14	3.11
Nebraska	90	0.88	0.86	0.90	2.18
New Mexico	11	0.11	0.11	0.12	4.23
Oklahoma	49	0.27	0.26	0.29	4.65
Texas	111	0.63	0.62	0.65	2.46

^a Proportion of infected premises at the state level.

^b Lower confidence limit for 95% confidence interval of \hat{P}_s .

^c Upper confidence limit for 95% confidence interval of \hat{P}_s .

^d Standard error percentage.

Table 4.3

Number of counties by average value of kernel density estimate (KDE) levels of a hypothetical foot-and mouth disease infection in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008.

State	KDE level (1 is highest and 9 is lowest)									Total
	1	2	3	4	5	6	7	8	9	
Colorado	-	-	-	-	-	-	-	3	44	47
Kansas	19	8	9	6	10	23	18	8	4	105
Nebraska	2	7	12	8	9	14	7	6	25	90
New Mexico	-	-	-	-	-	-	-	-	11	11
Oklahoma	-	-	-	-	-	-	19	16	14	49
Texas	-	-	-	-	-	1	16	19	75	111

Table 4.4

Descriptive statistics of the fitted variogram models for number of infected premises of a hypothetical foot-and mouth disease outbreak at county-level in the central United States encompassing 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008.

Variogram Model	AIC ^a	Range (km ^b)	Sill	Nugget
Spherical	264.68	166.73	1610.35	18.73
Exponential	317.44	134.71	1648.42	410.98
Gaussian	266.93	123.86	1606.32	43.27

^a Akaike Information Criterion

^b Kilometers

Table 4.5

Spatial autocorrelation and cross-correlation analysis and associated factors in a hypothetical foot-and mouth disease outbreak at county-level in the central United States encompassing 413 counties in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008.

Infection assessment			Factors											Units of factors
Number of infected premises	Infected dens.	Proportion of infected premises	County land area	Premises dens.	Animal dens.	Premises pop.	Animal pop.	Beef feedlot pop.	Cow-calf pop.	Dairy pop.	Swine pop.	Sheep pop.		
<i>0.23</i> ¹ +++	-0.10 ---	0.26 +++	-0.16 ---	0.27 +++	0.10 +++	0.20 +++	0.04 NS	0.20 +++	0.19 +++	0.16 +++	0.17 +++	-0.08 ---	Number of infected premises	Premises
	<i>0.30</i> +++	-0.06 --	-0.18 --	0.26 +++	0.09 +++	0.19 +++	0.03 NS	0.23 +++	0.17 +++	0.17 +++	0.20 +++	-0.11 ---	Infected dens.	Premises per sq km
		<i>0.48</i> +++	-0.16 ---	-0.29 ---	0.06 ++	-0.30 ---	0.03 NS	-0.02 NS	-0.31 ---	-0.19 ---	-0.01 NS	-0.13 ---	Proportion of infected premises	-
			<i>0.29</i> +++	-0.14 ---	-0.11 ---	-0.08 ---	-0.07 ---	-0.14 ---	-0.07 ---	-0.06 --	-0.15 ---	0.19 +++	County land area	sq km
				<i>0.40</i> +++	0.06 +++	0.36 +++	0.04 +	0.16 +++	0.35 +++	0.26 +++	0.17 +++	-0.09 ---	Premises dens.	Premises per sq km
					<i>0.06</i> +	0.03 NS	0.03 NS	0.09 +++	0.03 NS	0.03 NS	0.06 ++	-0.07 ---	Animal dens.	Head per sq km
						<i>0.35</i> +++	0.04 NS	0.11 +++	0.35 +++	0.22 +++	0.12 +++	-0.07 ---	Premises pop.	Premises
							<i>0.02</i> NS	0.03 NS	0.03 NS	0.01 NS	0.01 NS	-0.04 -	Animal pop.	Head
								<i>0.22</i> +++	0.09 +++	0.10 +++	0.17 +++	-0.05 --	Beef feedlot pop.	Premises
									<i>0.36</i> +++	0.22 +++	0.11 +++	-0.07 ---	Cow-calf pop.	Premises
										<i>0.16</i> +++	0.10 +++	-0.03 NS	Dairy pop.	Premises
											<i>0.13</i> +++	-0.09 ---	Swine pop.	Premises
												<i>0.32</i> +++	Sheep pop.	Premises

1 Moran's I or bimiran's I of binary spatial weights matrix of boundary-shared counties
 +++ = positive correlated significant, $\alpha = 0.01$
 ++ = positive correlated significant, $\alpha = 0.05$
 + = positive correlated significant, $\alpha = 0.1$
 --- = negative correlated significant, $\alpha = 0.01$
 -- = negative correlated significant, $\alpha = 0.05$
 - = negative correlated significant, $\alpha = 0.1$
 NS = not significant, $\alpha > 0.1$

dens. = density
 pop. = population
 sq km = square kilometers
Italic number = spatial autocorrelation

Table 4.6

Spatial regression models for estimating FMD infection (n=413 neighborhood counties) in a hypothetical foot-and mouth disease outbreak at the county level in the central United States in six states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep data from 2006-2008. The numbers in parentheses are the estimated standard errors.

Model	1	2*	3	4	5	6*
Type	OLS	OLS	OLS	SpatAR	SpatLag	SpatCmb
Dependent variable	IP	IP ^a	ID	ID	ID	ID ^b
Intercept	-1.6155 (0.0109)	-1.6294 (0.0097)	0.0060 (0.0002)	0.0055 (0.0014)	0.0029 (0.0955)	0.0031 (0.0640)
Coefficients						
AR	-0.3773 (0.0263)	-0.3660 (0.0225)	-0.0012 (0.0027)	-0.0010 (0.0151)	-0.0009 (0.0222)	-0.0008 (0.0309)
BF	1.1761 (0.0000)	1.1767 (0.0000)				
CC	0.0046 (0.0001)	0.0045 (0.0001)				
DR	1.2833 (0.0000)	1.2836 (0.0000)				
SW	1.0708 (0.0000)	1.0704 (0.0000)				
SH	0.0558 (0.8373)					
PD			0.0682 (0.0000)	0.0675 (0.0000)	0.0620 (0.0000)	0.0654 (0.0000)
AD			0.0001 (0.0000)	0.0001 (0.0000)	0.0001 (0.0000)	0.0001 (0.0000)
λ				0.3182 (0.0000)		0.2511 (0.0018)
ρ					0.2252 (0.0009)	0.1370 (0.0070)
Degree of freedom	406	407	409	408	408	407
R-Square	0.9756	0.9755	0.5000	0.5656	0.4664	0.5436
AIC	2694.185	2692.228	-2289.016	-2312.394	-2305.14	-2723.74
Likelihood ratio^c				23.378 (0.0000)	18.1194 (0.0000)	29.7268 (0.0000)
Moran's I on residuals^d	0.0183 (0.478)	0.018 (0.4723)	0.1726 (0.2365)	-0.0039 (0.9645)	0.0608 (0.0597)	-0.0288 (0.4331)
Rank^e			4	2	3	1

* are the final models

^aFull model: $IP = \beta_0 + \beta_1 AR + \beta_2 BF + \beta_3 CC + \beta_4 DR + \beta_5 SW + \varepsilon$, where IP=number of infected premises; AR=county land area (square kilometers); BF= number of beef feedlot premises; CC=number of cow-calf premises; DR=number of dairy premises; SW=number of swine premises.

^bFull model: $ID = \beta_0 + \beta_1 AR + \beta_2 PD + \beta_3 AD + \rho W\gamma + \varepsilon_{ID}$, where, $\varepsilon_{ID} = \lambda W\varepsilon + v$; ID= infected density; AR=county land area (square kilometers); PD=premises density (premises per square kilometers); AD=animal density (head per square kilometers); W=spatial weights matrix; $-1 < \lambda, \rho < 1$, measures of spatial correlation; ε =spatially correlated errors from the regression model, $v \sim N(0,1)$ = spatially independent errors. ^cTesting the hypothesis that the spatial model is an improvement over the OLS model. ^dTesting the hypothesis that the residuals are spatially independent. ^eRanking based on the Akaike Information Criterion (AIC).

6. Figures

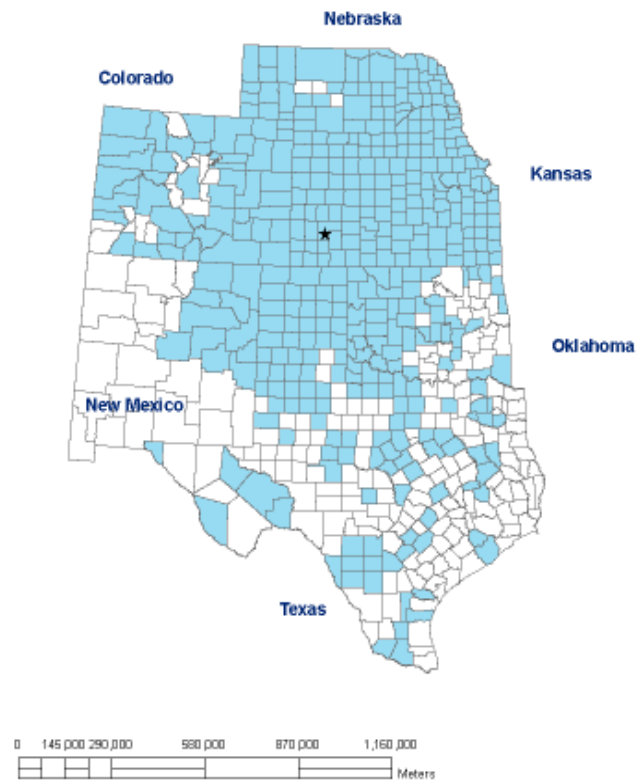


Figure 4.1. Study area of a hypothetical outbreak foot-and-mouth disease in 6 states in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The shaded counties identify the 413 counties used in this study, while the star represents the approximate location of the index case of the hypothetical outbreak.

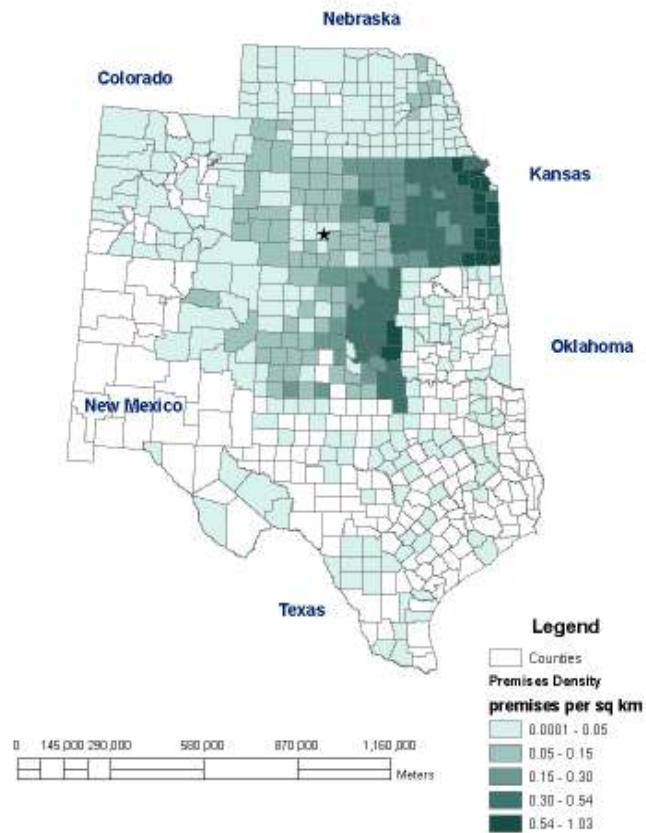


Figure 4.2. Premises density (premises per square kilometer) at the county level of a hypothetical outbreak foot-and-mouth disease in 413 counties in 6 states in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

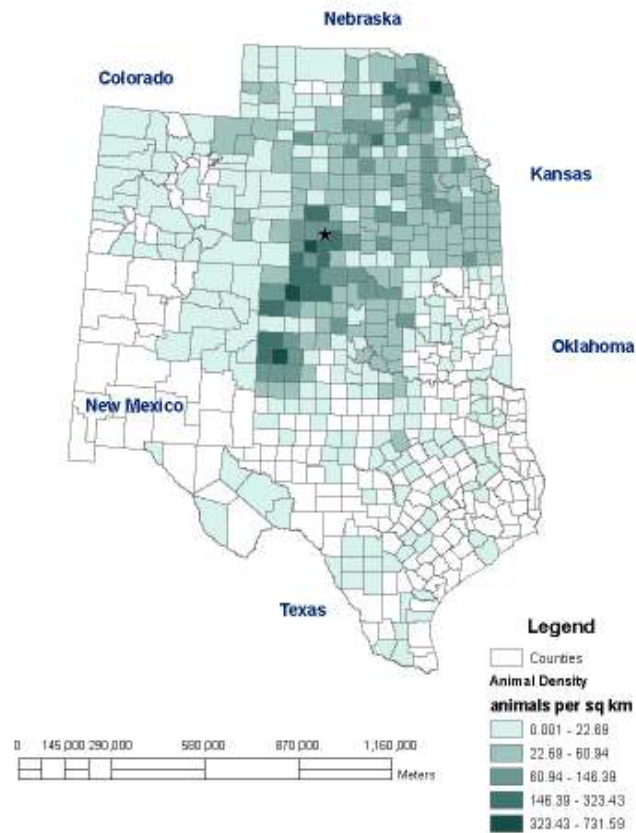


Figure 4.3. Animal density (animals per square kilometer) at the county level of a hypothetical outbreak foot-and-mouth disease in 413 counties in 6 states in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

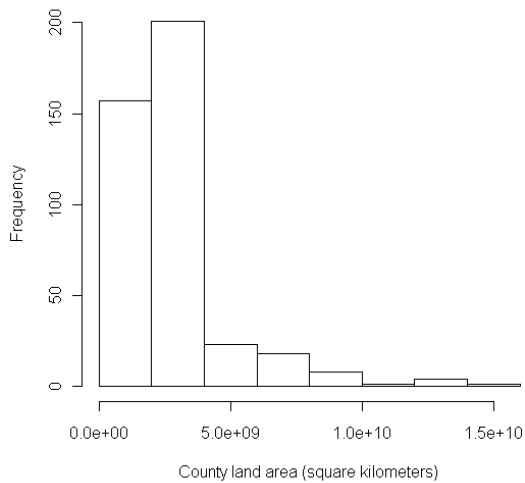


Figure 4.4. Frequency distribution of county land area (square kilometers) at the county level of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

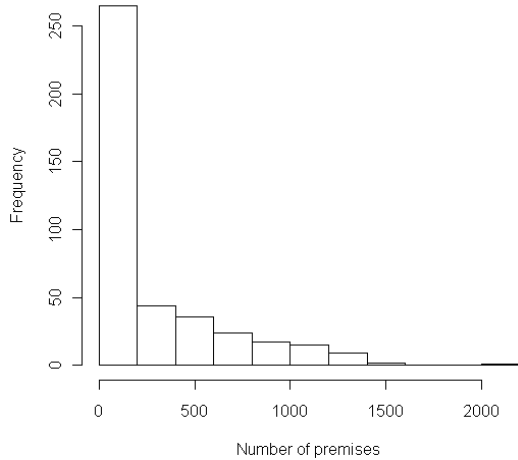


Figure 4.5. Frequency distribution of the number of premises at the county level of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

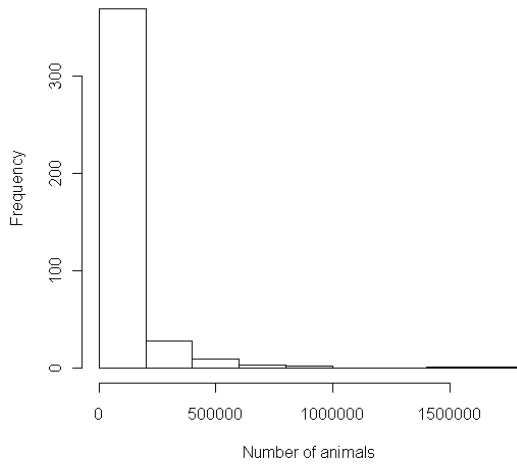


Figure 4.6. Frequency distribution of the number of animals at the county level of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

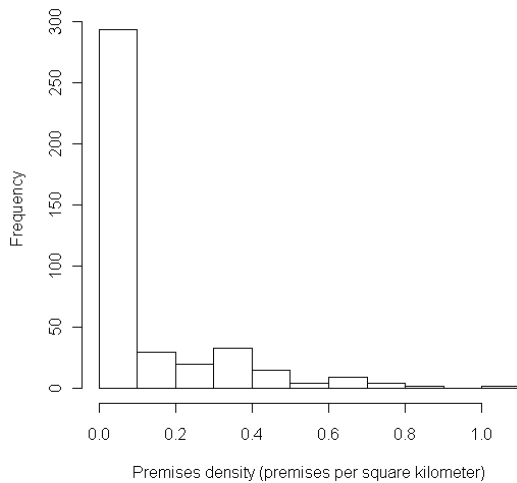


Figure. 4.7. Frequency distribution of premises density (premises per square kilometer) at the county level of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

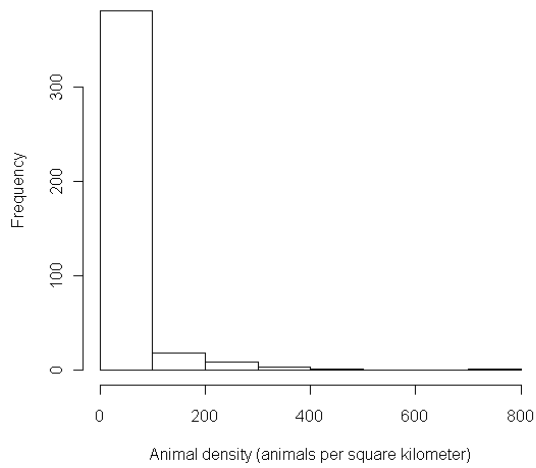


Figure. 4.8. Frequency distribution of animal density (animals per square kilometer) at the county level of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

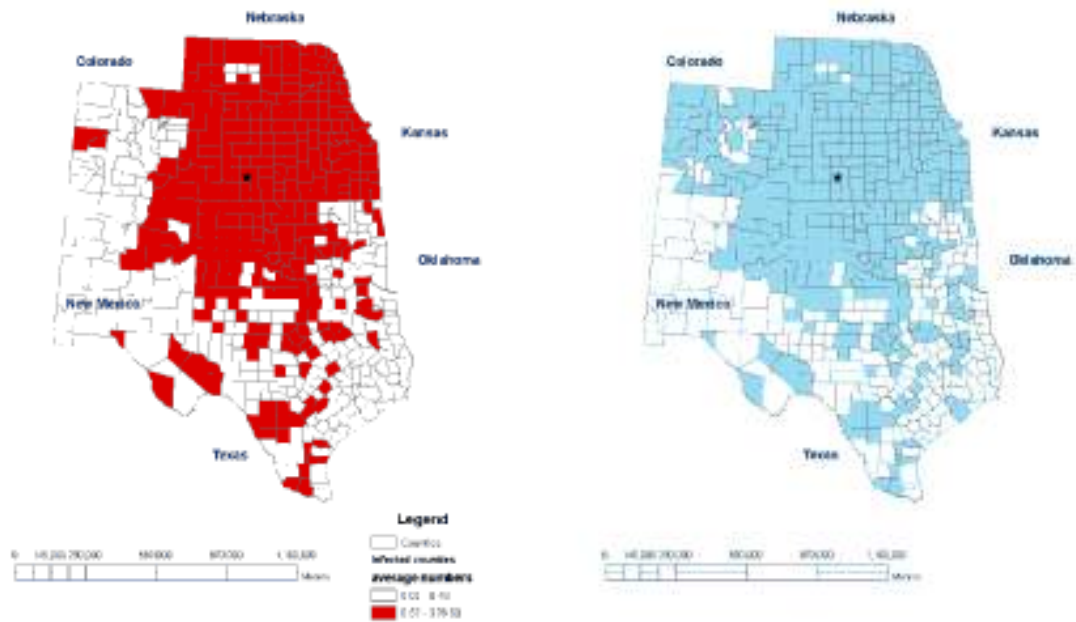


Figure 4.9. Infected counties (left, from simulation result) and susceptible counties (right) of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The stars represent the approximate location of the index case of the hypothetical outbreak.

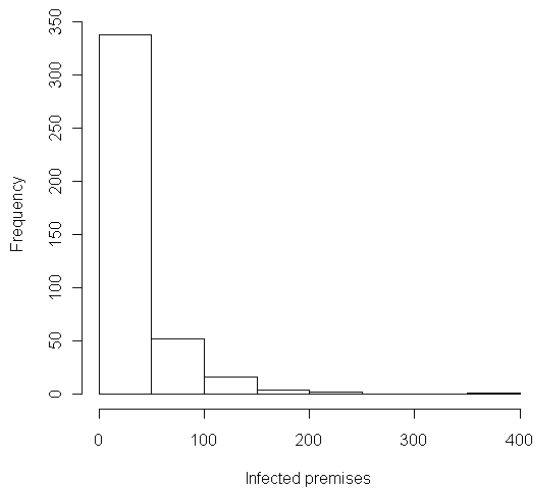


Figure 4.10. Frequency distribution of the average number of infected premises at the county level from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

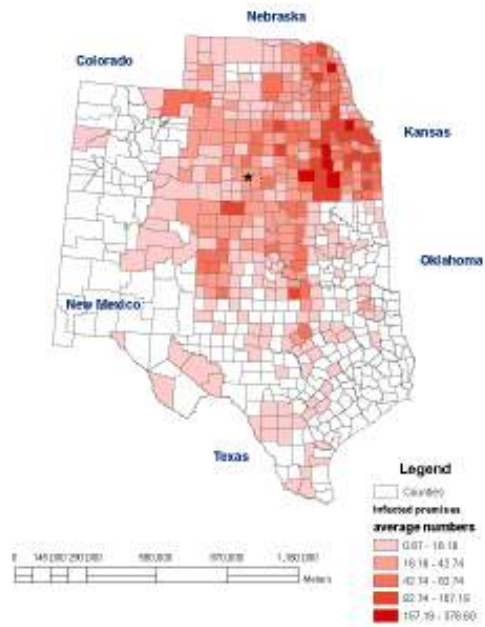


Figure 4.11. Average number of infected premises in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

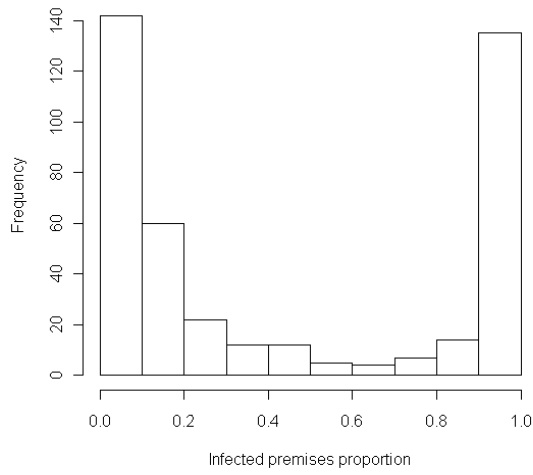


Figure. 4.12. Frequency distribution proportion of infected premises at the county level from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

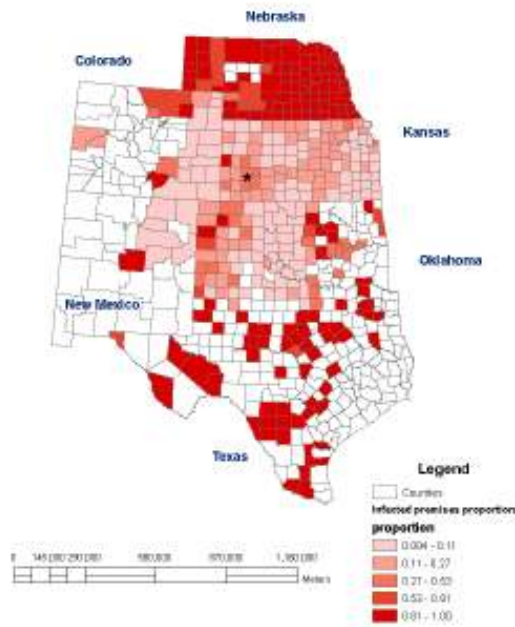


Figure 4.13. Number of infected premises proportion in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

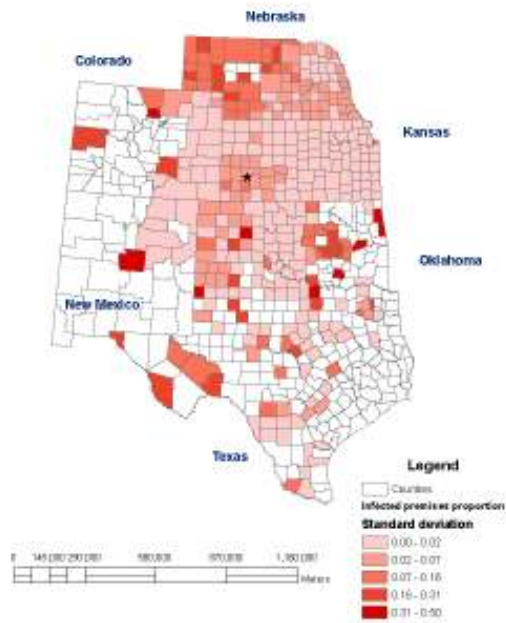


Figure 4.14. Standard deviation of the infected premises proportion in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

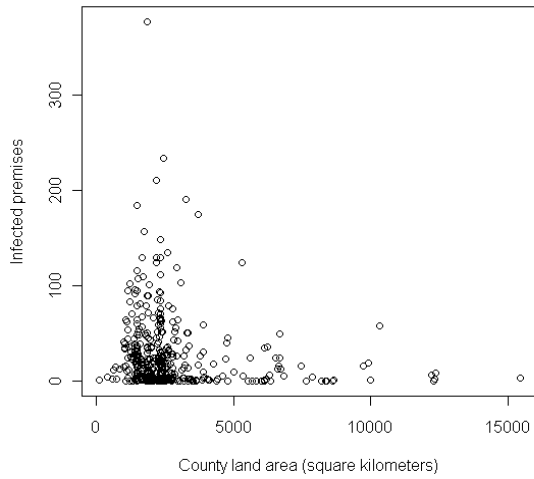


Figure 4.15. Plot of county land area (square kilometers) versus infected premises in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

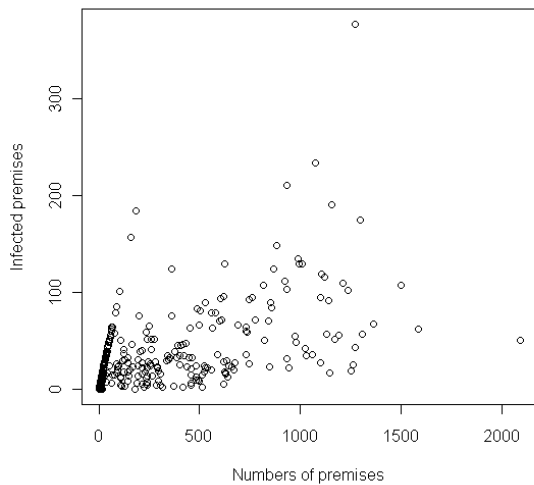


Figure 4.16. Plot of the number of initial susceptible premises versus the number of infected herds in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

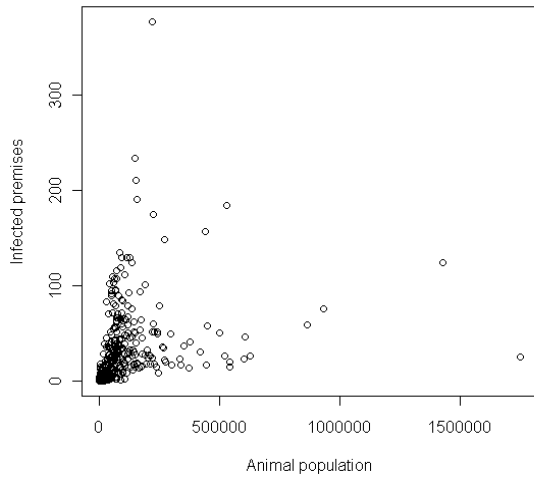


Figure 4.17. Plot of the number of initial susceptible animals versus infected premises in each county from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas), using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

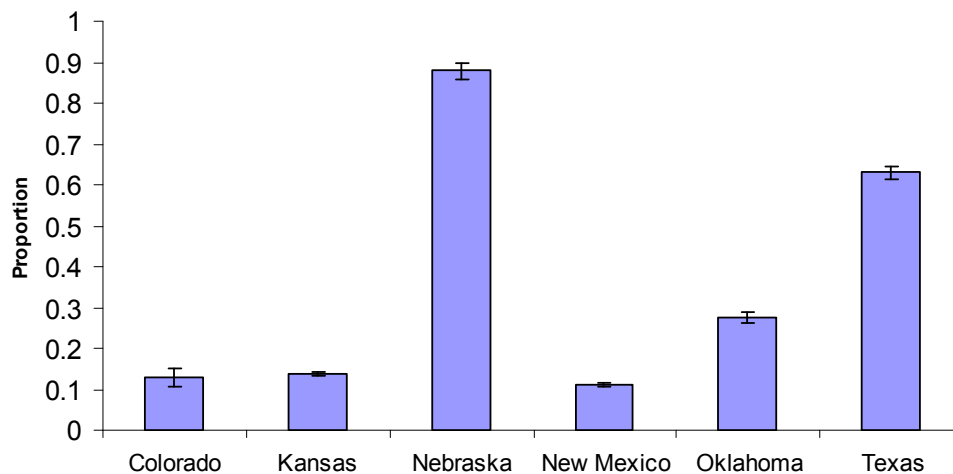


Figure 4.18. Average proportion of infected premises (weighted by area) at the state level from simulation result of a hypothetical outbreak of foot-and-mouth disease in 413 counties in 6 states, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

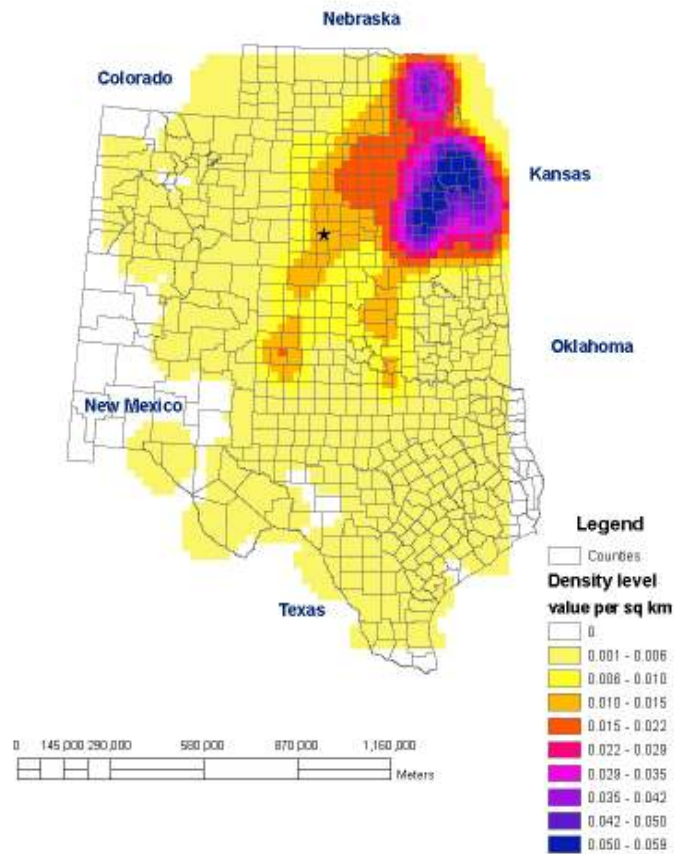


Figure 4.19. Kernel density estimate of a hypothetical outbreak of foot-and-mouth disease infection at the premises level from 400 iterations of simulation result in 413 susceptible counties in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008. The star represents the approximate location of the index case of the hypothetical outbreak.

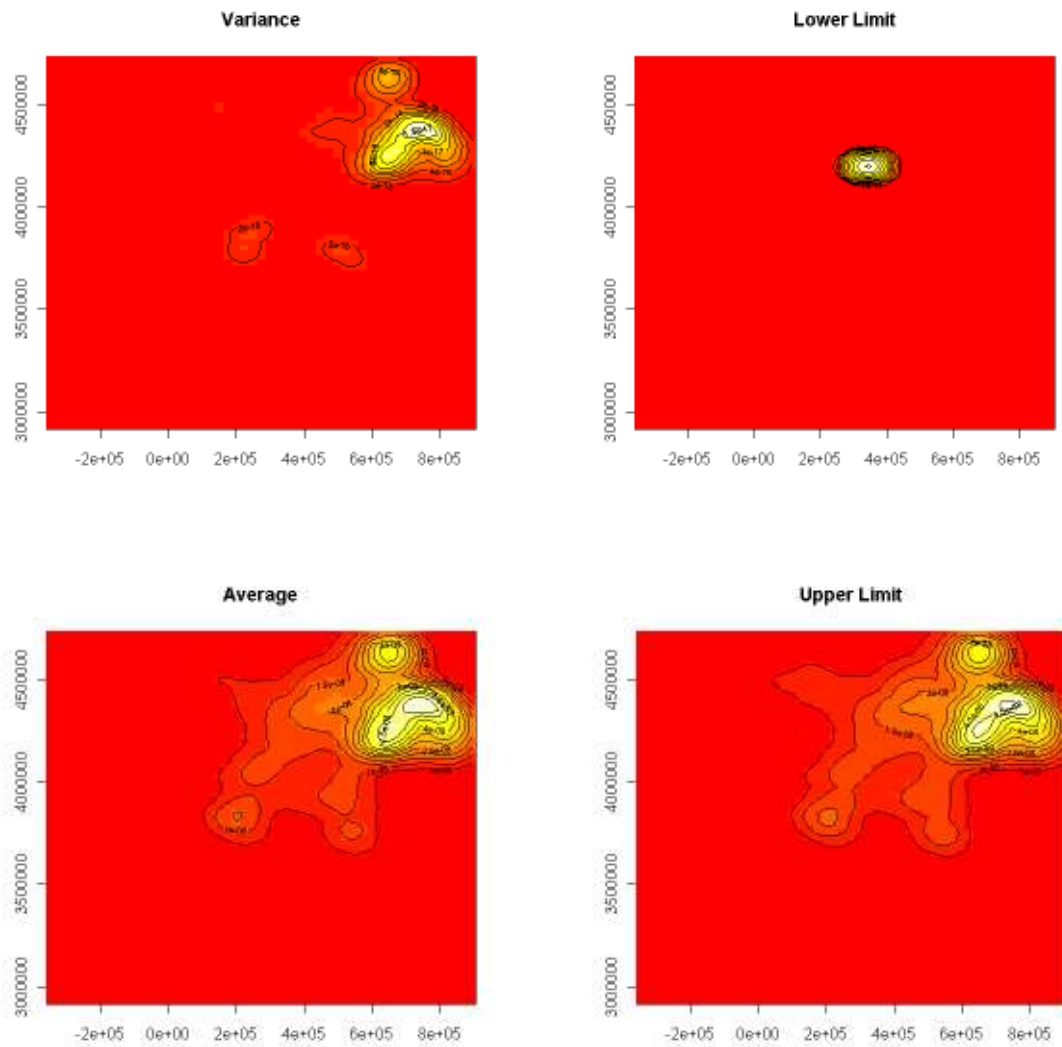


Figure 4.20. Contour maps of kernel density estimate of a hypothetical outbreak of foot-and-mouth disease infection at the premises level from 400 iterations of simulation result in 413 susceptible counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas) in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

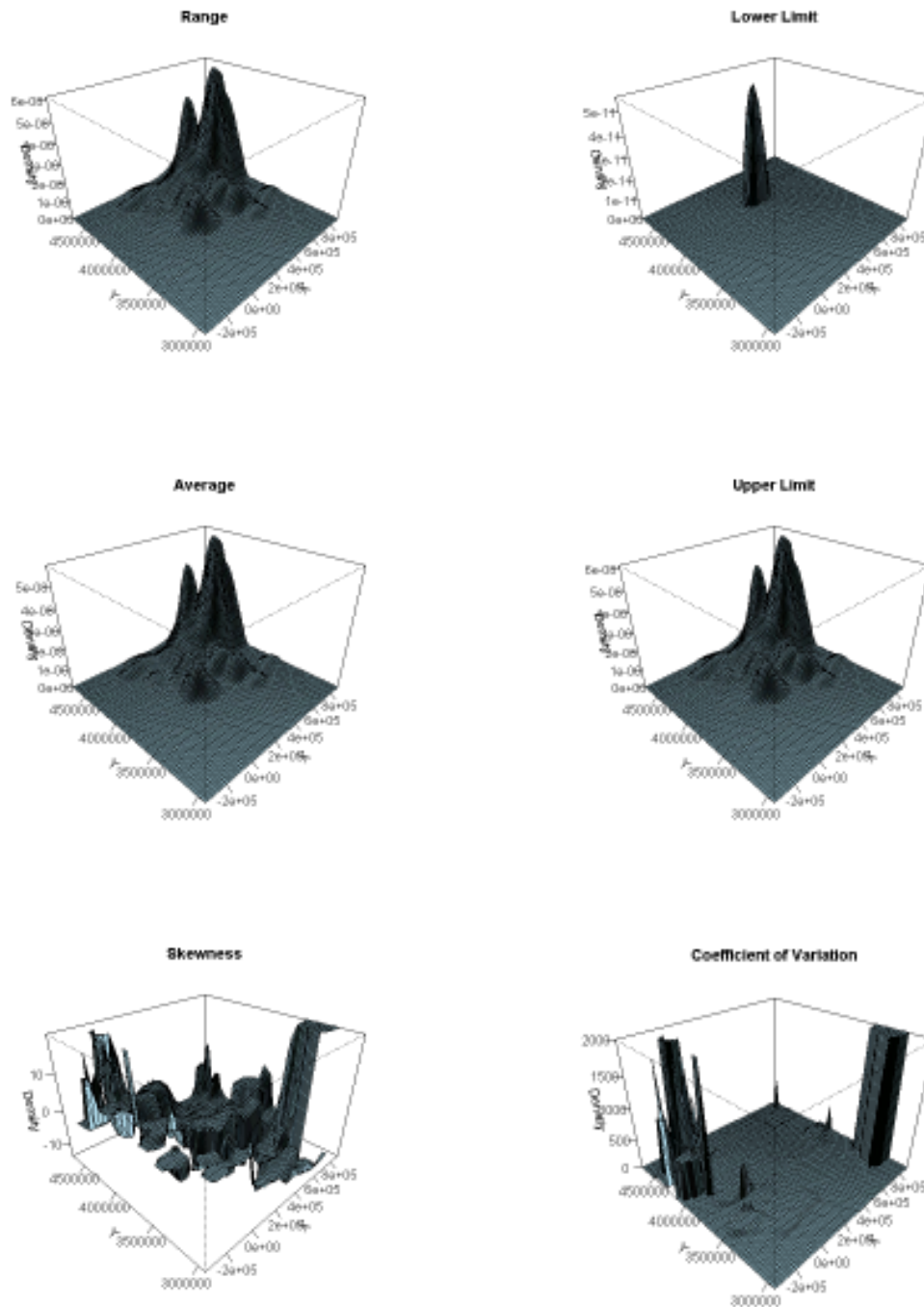


Figure 4.21. Perspective maps of kernel density estimate of a hypothetical outbreak of foot-and-mouth disease infection at the premises level from 400 iterations of simulation result in 413 susceptible counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas) in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

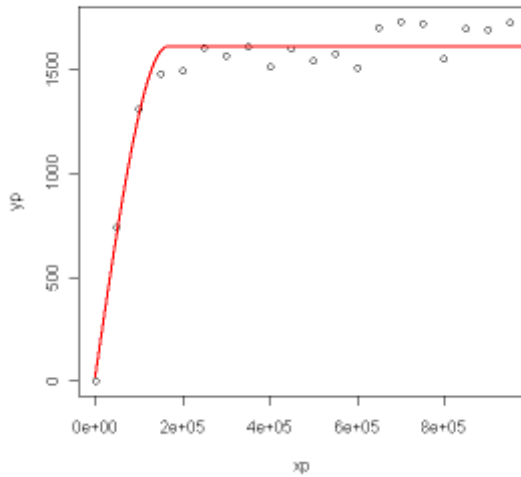


Figure 4.22. Spherical variogram model for number of infected premises at the county level of simulation result a hypothetical outbreak of foot-and-mouth disease infection at the county level of simulation result in 413 susceptible counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas) in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

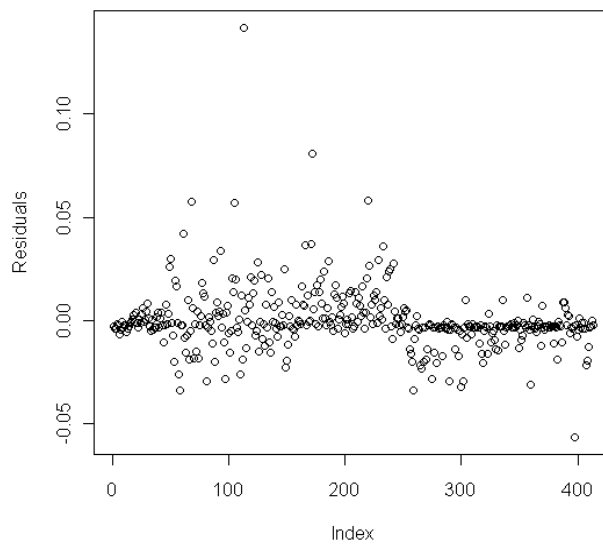


Figure 4.23. Residual plot of the ordinary least square model of foot-and-mouth disease infected density at the county level of simulation result from a hypothetical outbreak of simulation result in 413 susceptible counties in 6 states (Kansas, Colorado, Nebraska, New Mexico, Oklahoma, and Texas) in the central United States, using population data of beef feedlot, cow-calf, dairy cattle, swine, and sheep from 2006-2008.

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CHAPTER 5: CONCLUSION

The objective of this comprehensive review and research was to determine a hypothetical outbreak of foot-and-mouth disease (FMD) in the central United States using different limited disease control measures. The research findings demonstrated that the hypothetical FMD outbreak would spread throughout most of the area, and the limited disease control measures would decrease the number of affected premises but not shorten the duration of infection phase. The estimated number of infected premises was dependent on the number of livestock premises at the county level. The research framework is summarized regarding the order and flow of the review and study process in Figure 5.1.

The comprehensive review of epidemiological simulation modeling and spatial analysis for FMD control strategies explored these techniques and applications. The review stimulated some ideas for the parameter generation process for the FMD simulation model. These ideas were used to initiate a study on FMD simulation modeling and spatial analysis as described in Chapters 2-4. The review suggested a large-scale spatial analysis for FMD simulation modeling is preferred; therefore, the premises were identified as the unit of interest in the hypothetical outbreak in the central United States.

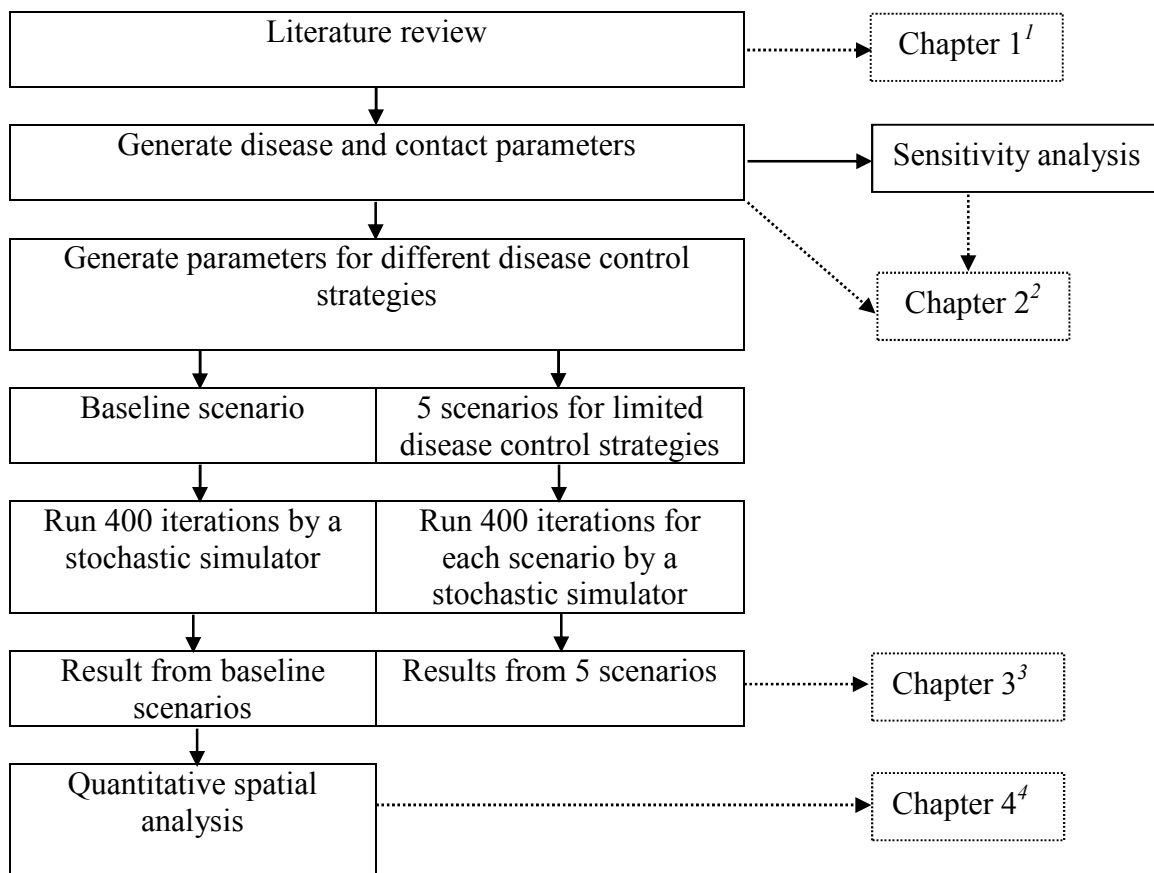


Figure 5.1. Research framework on “Uses of quantitative spatial analysis and epidemiological simulation modeling for assessing control strategies for foot-and-mouth disease”

¹Chapter 1: Epidemiological simulation modeling and spatial analysis for foot-and-mouth disease control strategies: A comprehensive review

²Chapter 2: Simulation models of an outbreak of foot-and-mouth disease in the central United States: Parameter generation process

³Chapter 3: Uses of simulation model to assess control strategies for foot-and-mouth disease

⁴Chapter 4: Quantitative spatial methods to determine the foot-and-mouth disease outbreak area for a hypothetical outbreak originating in the central United States

The parameter generation process was an attempt to generate reasonable and practical disease stage duration and disease transmission parameters for FMD in a hypothetical outbreak in the central United States. The parameter generation was run by the North American Animal Disease Spread Model (NAADSM). The 102,283 study premises of five production types of FMD-susceptible herds in Kansas, Colorado Nebraska, New Mexico, Oklahoma, and Texas were gathered from many sources and by a simulator. Herd-level disease stage parameters were gathered from published literature and a software package simulator. Disease transmission parameters were estimated and derived from expert opinion. Important input parameters were analyzed through sensitivity analysis by comparing the output of disease spread from various values of specific input disease or contact parameters. The most important finding was that disease spread was sensitive to indirect contact parameters in both contact rates and distances, but was not sensitive to direct contact. This finding led us to consider that primary cause of disease spread within the simulated outbreak would be from indirect contact more than direct contact.

Using limited control as the baseline scenario, the simulation model compared additional control strategies for FMD to the baseline. Each scenario of five strategies was run 400 iterations by NAADSM. With regard to the number of infected premises of livestock, restricted animal movement was the best strategy, as it reduced the magnitude of the outbreak by 29.3% from the baseline scenario. However, this strategy lengthened the duration of the epidemic by 39 days. Other strategies such as additional animal destruction, trigger ring animal destruction, initial ring vaccination on day seven and on day 14 also helped reduce the magnitude of the outbreak, but they did not shorten the

epidemic duration. All of these limited disease control strategies estimated that a large number of infected animals would need to be destroyed after the disease phase ended. If the capacity of manpower were the same as in the model, it would take several years to destroy all queued infected animals.

Quantitative spatial methods to determine the FMD outbreak area found that almost ninety percent of the county area was infected with FMD virus. The high density affected areas were found northeast of the index case point (in southwest Kansas). Spatial similarity of FMD infection was 166.7 kilometers measured the range among counties with increasing distances. The spatial autocorrelation of number of infected premises and infected density exhibited a significantly positive association to premises density, animal density, and number of susceptible premises, but not to the number of susceptible animals in each county. The most influential factors for having a high number of infected premises at the county level were number of dairy premises, number of beef feedlot premises, and number of swine premises, respectively. The most influential factor to predict the infected density is premises density.

To our knowledge, this is the first study attempting to integrate epidemiological simulation modeling and quantitative spatial analysis in the study region. The results showed that the central United States must be considered as an important area for FMD spread. In this large area disease control strategies such as restricted animal movement, animal destruction, and ring vaccination would help reduce magnitude of the outbreak. They would not, however, help shorten the duration of the epidemic duration if manpower is limited. The aim of this study was to provide recommendations based on the best available data to people who make FMD control and eradication plans in the

central United States area. Ultimately, decision-makers must implement the plan in a practical way.