DISSERTATION

CONSTRUCTION AND EVALUATION OF EPIDEMIOLOGIC SIMULATION MODELS FOR THE WITHIN- AND AMONG-UNIT SPREAD AND CONTROL OF INFECTIOUS DISEASES OF LIVESTOCK AND POULTRY

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ABSTRACT

CONSTRUCTION AND EVALUATION OF EPIDEMIOLOGIC SIMULATION MODELS FOR THE WITHIN- AND AMONG-UNIT SPREAD AND CONTROL OF INFECTIOUS DISEASES OF LIVESTOCK AND POULTRY

Epidemiologic modeling is an increasingly common method of estimating the potential impact of outbreaks of highly contagious diseases, such as foot-and-mouth disease (FMD) and highly pathogenic avian influenza (HPAI), in populations of domesticated animals. Disease models are also used to inform policy decisions regarding disease control methods and outbreak response plans, to estimate the possible magnitude of an outbreak, and to estimate the resources needed for outbreak response. Although disease models are computationally sophisticated, the quality of the results of modeling studies depends on the quality and accuracy of the data on which they are based, and on the conceptual soundness and validity of the models themselves. For such models to be credibly applied, they should realistically represent the systems they are intended to reflect, should be based to as great an extent as possible on valid data, and should be subjected to careful and ongoing scrutiny.

Two key steps in the evaluation of epidemiologic models are model verification and model validation. Verification is the demonstration that a computer-driven model is operating correctly, and conforms to its intended design. Validation refers to the process of determining how well a model corresponds to the system that it intended to represent. For a veterinary epidemiologic model, validation would address issues such as how well the model represents the dynamics of the disease in question in a population to which the model is applied, and how well the model represents the application of different measures for disease control. Among the steps

that can be taken by epidemiologic modelers to facilitate the processes of model verification and validation are to clearly state the purpose, assumptions, and limitations of a model; to provide a detailed description of the conceptual model for use by everyone who might be tasked with evaluation of a model; document steps already taken to test the model; and thoroughly describe the data sources and the process used to produce model input parameters from data.

The realistic representation of the dynamics of spread of disease within individual herds or flocks can have important implications for disease detection and surveillance, as well as for disease transmission between herds or flocks. We have developed a simulation model of within-unit (within-herd or within-flock) disease spread that operates at the level of the individual animal, and fully incorporates sources of individual-level variation such as variability in the durations of incubating and infectious periods, the stochastic nature of disease spread among individuals, and the effects of vaccination. We describe this stochastic model, along with the processes employed for verification and validation. The incorporation of this approach to modeling of within-unit disease dynamics into models of between-unit disease spread should improve the utility of these models for emergency preparedness and response planning by making it possible to assess the value of different approaches to disease detection and surveillance, in populations with or without some existing level of vaccine immunity.

Models rely not only on realistic representations of the systems of interest, but also on valid and realistic information. For spatially explicit models of the spread and control of disease in populations of livestock and poultry, this means a heavy reliance upon valid spatial representations of the populations of interest, including such characteristics as the geographic locations of farms and their proximity to others in the population. In the United States, limited information regarding the locations of actual farm premises is available, and modeling work

often makes use of artificially generated population datasets. In order to evaluate the accuracy and validity of the use of such artificially generated datasets, we compared the outcomes of mechanistic epidemiologic simulation models that were run using an empirical population dataset to those of models that made use of several different synthetic population datasets. Although we found generally good qualitative agreement among models run using various population datasets, the quantitative differences in model outcomes could be substantial. When quantitative outcomes from epidemiologic models are desired or required, care should be taken to adequately capture or describe the uncertainty in model-based outcomes due to the use of synthetic population datasets.

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DEDICATION

For Theodore and Andrew: may they never be defeated, but if defeated, may they never be discouraged. And also for Cindy who, all these years later, still puts up with far too much.

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1. Introduction, literature review, and study objectives

Epidemiologic modeling is an increasingly common method of estimating the potential impact of outbreaks of highly contagious diseases, such as foot-and-mouth disease (FMD) and highly pathogenic avian influenza (HPAI), in populations of domesticated animals. In this chapter, our goals are as follows: to describe epidemiologic models and discuss the reasons for their construction and use; to explore the differences, strengths, and limitations among various types of epidemiologic models; to provide a review of FMD and HPAI with specific emphasis on disease epidemiology; to review recent epidemiologic modeling studies of the spread and control of FMD and HPAI in populations of livestock and poultry; and to establish the context for the work described in subsequent chapters.

1.1. The motivation for building epidemiologic models

Epidemiologic models are members of a class identified by some authors as "process models" (Hurd and Kaneene, 1993; King and Soskoline, 1988). A process model is a simplified, quantitative representation of a real system or process, which attempts to describe or illustrate how that system or process operates. In the case of epidemiologic models, the primary process of interest is the spread of disease in a population over time. Epidemiologic process models might be quite simple or relatively complex, depending on the purpose for which they are intended. Simple process models have been constructed to explore the dynamics of infectious disease in susceptible, randomly mixing populations. Pioneering work by Kermack and McKendrick (1927, 1932, 1933), for example, contributed to development of the threshold theorem of epidemics: in a simple mathematical model that considered only the rate of disease spread among individuals in a population, Kermack and McKendrick demonstrated that, for an

epidemic to occur, a certain proportion of the population must be susceptible to disease. Below this threshold density, an epidemic is not expected to occur.

More complex processes might involve any of several mechanisms responsible for disease spread in animal populations, such as the nature and frequency of interaction among members of an animal population or physical mechanisms by which causal agents of infectious disease are transmitted. Relatively complex epidemiologic process models have been constructed that attempt to account for multiple mechanisms of disease spread in heterogeneous animal populations (*e.g.*, Bates et al., 2003c, 2003d; Patyk et al., in preparation). Several of these more complex models are discussed in more detail below. In other cases, epidemiologic systems might be concerned with interactions between two or more populations, such as host and parasite populations, or populations of disease vectors and animal species susceptible to disease. Epidemiologic systems of interest often also involve interventions made to limit further spread of disease.

Each of the contributing elements of a real system might be termed a *component* of that system. Quantitative process modeling allows investigators to study the often dynamic nature of the interactions among these components (Anderson and May, 1991; Hurd and Kaneene, 1993) and to examine how the alteration of individual components of a system might affect the overall outcome of that system. Models are particularly useful for the demonstration of the potential effects of such alterations when it is not practical, or even possible, to experimentally alter the real system. In veterinary epidemiology, it is neither possible nor desirable to experimentally determine the extent of a regional or national disease outbreak or to test large-scale mitigation strategies under actual field conditions. Disease models provide an alternative experimental framework in which the extent of an outbreak or the effects of various large-scale mitigation

strategies can be explored. Models may be used to assess how a system might respond to different events or interventions, for example, to investigate disease spread under different seasonal conditions or to compare the efficacy of different disease control strategies in different regions and populations. Modeling has the added advantage of being far less expensive than experience with actual disease outbreaks (Garner and Lack, 1995; Schoenbaum and Disney, 2003).

Additionally, through the process of constructing a epidemiologic model, the understanding of the system being modeled is often improved: Teclaw (1979) pointed out that "models not only mimic real systems in a more comprehensible way, but may go beyond description and lead to conclusions contrary to intuition." Similarly, the systematic process of model building often identifies gaps in existing knowledge about components of the system under investigation. The identification of such gaps can then be used to guide useful field or laboratory research (Taylor, 2003).

1.2. Types of epidemiologic models

Epidemiologic models may take any of several forms. This section presents a simple taxonomy for some of the types of models that have appeared in the epidemiologic and veterinary epidemiologic literature. The list of types of models addressed here is by no means exhaustive. There is no clear set of rules that distinguishes models of one type from another, and there are many models that defy the broad characterizations presented. It is still helpful, however, to draw some conceptual, if not always clear, lines between the various categories and to keep in mind that models of different types can often be used to complement one another.

1.2.1. Differential calculus-based mathematical models

Some models, such as differential calculus models, are based on sets of formulas or equations that describe the system of interest in a rigorously mathematical way. Analytical approaches can then be used to determine solutions for these systems, thus producing model outcomes. The models of Kermack and McKendrick (1927, 1932, 1933) are models of this type (see Figure 1-1). More recent applications of this type of model in veterinary epidemiology have been described (Bavinck et al., 2009; Miller, 1976; Smith and Dunipace, 2011; Thornley and France, 2009), some of which are discussed in more detail in subsequent sections.

These models are generally deterministic in nature: they make use of single values to represent model parameters, and they give exactly one estimate of the outcome, produced analytically, which typically represents the "typical" or average expected situation. Because model parameters are represented with single values, rather than distributions, deterministic models cannot directly account for natural biological variability among individuals in a population. Such models also fail to account for stochasticity. As Carpenter (2011) points out, this limitation can have considerable consequences for the validity of such models: "in the early stages of an epidemic, especially in a small population with a low contact rate, deterministic models fail to accurately portray the 'boom or bust' situation of epidemics, *i.e.*, given an identical scenario sometimes an epidemic dies out while other times it takes off and becomes explosive." Deterministic mathematical models also generally fail to account for spatial relationships that exist among the elements of certain populations, such as a population of farm premises. For these reasons, among others, some investigators prefer to use stochastic, spatially explicit models. Two general types of stochastic spatially explicit models are described in sections 1.2.2 and 1.2.3.

1.2.2. Spatial kernel-based mathematical models

A second class of mathematical models is based on the concept of a *spatial kernel*. In such models, populations of interest are characterized by their spatial or geographic distributions. Such models have been used, for example, to consider disease spread among a population of livestock or poultry premises, each of which is represented in spatial context generally as a point location. The spatial kernel represents the probability of disease spread between an infectious and a susceptible unit (*i.e.*, premises) based on the distance between the two units (Keeling, 2005; Keeling et al., 2001; Rorres et al., 2010, 2011; Tildesley et al., 2012). Spatial kernel functions are generally empirical, derived from outbreak data. Keeling et al. (2001), for example, created a spatial kernel to represent the spread of foot-and-mouth disease (FMD) in the United Kingdom (UK) in 2001 during an outbreak in progress. Rorres et al. (2010, 2011) have generated a similar spatial kernel, based on historical information collected during an outbreak of highly pathogenic avian influenza (HPAI) in the eastern United States (US). These spatial kernels are then used to stochastically simulate the spread of disease throughout the population of interest. This approach does not distinguish among different mechanisms that might lead to infection: all such mechanisms are incorporated into the spatial kernel (Keeling, 2005).

Spatial kernel-based models rely on information regarding outbreak *outcomes*: they rely on data collected either during or after an outbreak to generate a spatial kernel. [Models that rely on information about outbreak outcomes have been called "top-down" models by some authors (*e.g.*, Singer et al., 2011). This is in contrast to "bottom-up" models, discussed in the following section.] The kernel is then applied by analogy: spatial kernels produced based on one outbreak have been applied to other populations based on the assumption that the circumstances contributing to disease spread are analogous in the two situations. Tildesley et al. (2012) used a spatial kernel generated during the 2001 outbreak of FMD in the UK to evaluate options for

disease control in the event of an FMD outbreak in Pennsylvania. Similarly, Keeling et al. (2001) used a spatial kernel generated in the early phases of the 2001 UK FMD outbreak to estimate the continued impact of the outbreak in its later stages. This spatial kernel has also been applied retrospectively to evaluate alternative measures for FMD control in the UK outbreak (Keeling et al., 2003; Tildesley et al., 2006).

Although these models have the advantage that they can be parameterized relatively quickly in the face of an outbreak (Keeling, 2005; Rorres et al., 2011a), they have several limitations. First and foremost is their reliance on outcome data: the utility of such models in advance of an outbreak for planning purposes is limited to situations analogous to those in which outbreaks have occurred. It would be inappropriate, for example, to apply the method of Tildesley et al. (2012) to evaluate measures for FMD control in the western United States: the UK-based spatial kernel is very likely wholly inappropriate to application in a population with very different demographics, geographic distributions, and other characteristics. A second limitation is that of the quality of information used to generate the spatial kernel. Data from early stages of outbreaks in progress are likely not to be high-quality. This in turn may influence the accuracy of model results.

Third, because the spatial kernel does not distinguish between different mechanisms of disease spread, they can provide little insight regarding the impacts of those mechanisms, or of the effects of disease control measures targeted to specific mechanisms of disease spread. To realistically address questions regarding specific components of an epidemiologic system, it is necessary to construct models that represent the mechanisms behind those components.

1.2.3. Mechanistic simulation models

An alternative to the mathematically-oriented modeling approaches discussed above is the use of computer-driven simulation models that attempt to mimic the actual processes that occur within a system: in an epidemiologic simulation model, for example, the frequency of movement of animals among farm or ranch premises might be recreated to mimic this mechanism of disease spread. These models are intended to emphasize "realism rather than mathematical rigour" (Miller, 1976), in the sense that analytical, closed-form solutions to sets of equations are not sought. Instead, the representation of individual components of a system is used to determine the emergent properties of the system as a whole. For this reason, models of this type are sometimes referred to as "bottom-up" models (Singer et al., 2011): model building begins at the bottom, with the representation of basic components, and builds toward the outcome of interest. Most mechanistic simulation models are stochastic and can thus be used to represent the entire range of possible outcomes from a single set of starting conditions: best case, typical, and worst case outcomes.

Mechanistic simulation models still require information, but the information required pertains to system inputs, rather than outcomes: that is, these models do not rely on data from a disease event. Such information is generally more readily available. Consequently, epidemiologic simulation models of disease spread and control find their greatest utility in regions or countries that are currently free from the disease of interest, and for which no obvious analogous outbreak situations exist.

An additional advantage associated with mechanistic models is that they are often more transparent to non-specialists. In the construction of epidemiologic simulation models, the attempt is often made to represent complex systems in ways that are readily understandable, and easily communicated to policy makers, response planners, and other stakeholders. Each of the

components of a complex system can be separated and described in ways that are accessible to the intended audience, and in ways that are recognizable as real-world phenomena. These characteristics are critical for the conceptual validity of models, as discussed in chapter 2.

Numerous mechanistic simulation models have been applied to questions in veterinary epidemiology (Bates et al., 2003c; Dickey et al., 2008; Harvey et al., 2007; Patyk et al., in preparation; Schoenbaum and Disney, 2003; Sharkey et al., 2008; Truscott et al., 2007; Yoon et al., 2006). Additional examples of all three types of models described above are presented and discussed in section 1.4, following a brief review of the biology and epidemiology of FMD and HPAI in section 1.3.

1.3. Biology and epidemiology of foot-and-mouth disease and highly pathogenic avian influenza

1.3.1. Foot-and-mouth disease

Foot-and-mouth disease (FMD) is a highly contagious disease that affects many important livestock species. Since 2000, FMD has been reported in most major areas of the world with the exceptions of North America, Australia, and central Europe (Food and Agriculture Organization of the United Nations, 2012).

The causal agent of FMD is a picornavirus in the genus *Aphthovirus*, of which seven serotypes, designated O, A, C, SAT 1, SAT 2, SAT 3, and Asia 1, are currently recognized (Alexandersen et al., 2003). FMD virus (FMDV) consists of a single strand of positive sense RNA, surrounded by a capsid composed of multiple copies of four structural proteins (Acharya et al., 1989). Replication of viral RNA in infected host cells occurs via an intermediate negative sense RNA molecule, which is then used as a template for the synthesis of new positive sense viral RNA (Monaghan, 2004).

Among known susceptible species are cattle, swine, sheep, goats, African and Indian buffalo, American bison, and Bactrian camels, among others (Alexandersen et al., 2003; Larska et al., 2009; Maroudam et al., 2008; Rhyan et al., 2008; Thomson et al., 2003; Vosloo et al., 2007). Host specificity is determined partly by viral strain: even within serotypes, species-specific strains occur. A porcinophilic strain of serotype O was responsible for a 1997 outbreak of FMD in Taiwan that had little to no effect on cattle in the country (Lee et al., 2009; Yang et al., 1999), while another strain of the same serotype caused the outbreak among cattle and sheep in the United Kingdom in 2001 (Gibbens et al., 2001; Haydon et al., 2004).

FMD is particularly notable for its potential for rapid, extensive spread in naïve populations, its potential to cause animal health emergencies of international scope, and for its severe economic consequences (OIE, 2011). An FMD outbreak on the island of Taiwan in 1997 resulted in the infection of animals on 6147 farms. Over 4 million swine were slaughtered as part of a disease control campaign, and over 21 million doses of vaccine were dispensed. Direct costs associated with the outbreak have been estimated at over $378 million, while the total estimated cost to the swine industry in Taiwan was assessed at $1.6 billion. Taiwan had been free of FMD for over 68 years prior to the 1997 outbreak, which is thought to have started with the smuggling of infected animals or animal products into the country (Chen et al., 1999; Yang et al., 1999).

More recently, an epidemic of FMD occurred in the United Kingdom in 2001, 34 years after the most recent previous major epidemic (Ferguson et al., 2001a). The epidemic led to the detection of over 2000 infected premises and the destruction of over 6.5 million animals (Haydon et al., 2004). Before the epidemic ended, FMD had spread to Ireland, France, and the

Netherlands (UK Department for Environment Food and Rural Affairs, 2002). Economic losses in the UK alone have been estimated at $10.7 to $11.7 billion (Thompson et al., 2002).

Mechanisms of transmission of FMD have been characterized. Direct animal-to-animal contact resulting in transfer of the virus from infected to susceptible animals is the most common form of transmission. Physical contact with excretions and secretions (vesicular fluid, milk, urine, feces, semen) and fecal-oral transmission can result in disease spread. Ruminants in particular are susceptible to disease transmission via inhalation of aerosolized secretions (Alexandersen et al., 2003; Bates et al., 2003d; Donaldson, 1987). The movement of infected sheep through markets prior to the detection of disease is thought to have been a major contributor to the 2001 FMD outbreak in the UK (Mansley et al., 2003). Indirect contact by contaminated personnel, vehicles, and other equipment can contribute to the spread of disease (Alexandersen et al., 2003; Bates et al., 2003d). Indirect contact by vehicles and equipment is believed to have played a major role in an outbreak of FMD that occurred in Uruguay in 2001 (European Commission, 2001; Reeves et al., 2006). Some investigators believe that, under certain climatic conditions, it may be possible for FMD to be transmitted over long distances (potentially across many kilometers) by airborne dissemination (Bates et al., 2003d; Donaldson et al., 2001), although this hypothesis remains controversial.

Although the last reported case of FMD in the United States occurred in 1929 (Mohler and Snyder, 1930), the disease continues to be a substantial threat to US animal agriculture. International trade of livestock and animal products and the continuing increase in international travel make the inadvertent introduction of FMD more probable. In recent years, concern about the potential for intentional introduction of FMD through acts of bioterrorism has also risen substantially (Bates et al., 2003d; Kostova-Vassilevska, 2004; Wilson et al., 2001).

The economic implications, particularly for international trade, of an outbreak of FMD in the US would be considerable. The occurrence of FMD in a country or region previously recognized as free from disease provides ample reason for other countries to discontinue trade with the infected country or region (Kitching, 2000). Detection of one animal infected with bovine spongiform encephalopathy in the US resulted in the immediate closure of US beef export markets in Japan, Korea, Mexico, and Canada, and in the estimated loss to the US beef industry in 2004 of $3.2 to $4.7 billion (Coffey et al., 2005). Recent studies show that the economic impact of an outbreak of FMD in the US could be severe (Ekboir, 1999; Paarlberg et al., 2008; Pendell et al., 2007).

Measures for disease prevention (such as import restrictions and mandatory quarantine of live animals to be transported across national boundaries) provide a first line of defense, but the possibility of introduction of FMD will always exist. Consequently, appropriate contingency planning is essential (Geering and Lubroth, 2002).

The primary objective of contingency planning for FMD, particularly in countries or regions that are currently free of FMD, is rapid containment of the disease, to be followed by eradication (Geering and Lubroth, 2002; USDA-APHIS-VS, 2010). Once freedom from disease can be demonstrated after an outbreak, international trade may resume. The central challenge for the development of contingency and response plans is to provide an economically feasible course of action that will minimize the consequences of an incursion of FMD as effectively and efficiently as possible.

Foot-and-mouth disease is characterized clinically by the appearance of often severe vesicular lesions in and around the mouth and on the feet; lameness; drooling; and reluctance to feed, stand, or walk (Alexandersen et al., 2003). These signs are often more pronounced in

swine and cattle than in sheep or goats (Alexandersen et al., 2003; Kitching and Hughes, 2002; Kitching et al., 2005), and, as noted above, may vary with the strain of the virus. Although a variety of diagnostic tests for FMD exist (*e.g.*, Alexandersen et al., 2003; Clavijo et al., 2004; Fu et al., 2011; Grubman and Baxt, 2004), initial detection of FMD and detection of herds subsequently infected during an outbreak are often made on the basis of clinical signs of disease (Gibbens et al., 2001; Kitching et al., 2005; Mansley et al., 2011), with subsequent confirmation by diagnostic test (Alexandersen et al., 2003; Kitching et al., 2005).

Among the measures that have been used for the control of FMD outbreaks are quarantine and localized restriction of animal movements; depopulation of detected, infected herds; preemptive depopulation of herds known to have had contact with detected, infected herds; preemptive depopulation of herds based on proximity to detected, infected herds; vaccination of susceptible animals in proximity of infected herds; or nation-wide emergency vaccination of susceptible livestock (Geering and Lubroth, 2002; USDA-APHIS-VS, 2010). Each of these measures has implications for animal health and welfare; the state of local, regional, and national economies; and international trade. Contingency plans must consider which of these measures, either alone or in combination with others, will yield the best possible results. The scale on which these practices is applied is an additional consideration, particularly in the face of limited resources.

1.3.2. Highly pathogenic avian influenza

Avian influenza is a viral disease that affects many species of wild and domesticated birds. Among the susceptible species are chickens, turkeys, ducks, quail, pheasants, geese, and many wild bird species (Alexander, 2007; Artois et al., 2009; Humberd et al., 2006; Makarova et al., 2003).

Influenza viruses are negative-sense single-stranded viruses in the family Orthomyxoviridae. Three genera of *Influenzavirus* are recognized, and are referred to as type A, B, or C. Influenza viruses of type A are known to infect birds. Subtypes of type A viruses are distinguished from one another based on the characteristics of two antigenic glycoproteins found in the outer coat of the virus particle, hemagglutinin and neuraminidase. Subtypes are named based on the forms of hemagglutinin and neuraminidase present, for example, "H5N1" or "H7N7". Sixteen forms of the hemagglutinin glycoprotein and nine forms of neuraminidase have been characterized in influenza A viruses known to infect birds. All forms of hemagglutinin and neuraminidase glycoproteins and nearly all combinations have been found in birds (Alexander and Brown, 2009; Alexander, 2007). Recently, a seventeenth antigen type of hemagglutinin, found in fruit bats, was characterized (Tong et al., 2012).

Strains of avian influenza are further classified based on their pathogenicity. So-called "highly pathogenic" strains are those which have been shown to cause at least 75% mortality in four-to-eight-week-old susceptible chickens (Alexander and Brown, 2009), but the severity of clinical disease and the level of mortality associated with each strain varies considerably by host species (Alexander, 2007; Perkins and Swayne, 2003). Chickens and turkeys, for example, are highly susceptible to highly pathogenic H5 strains and show high levels of mortality, while ducks infected with the same H5 strains show little clinical disease and low levels of mortality (Alexander and Brown, 2009; Alexander et al., 1986; Jeong et al., 2009). Considerable variability has been shown in infected wild species as well (Artois et al., 2009). Among the other clinical signs of disease in birds are the following: neurological signs, such as paresis, paralysis, tremors; diarrhea; pulmonary edema and congestion; and lesions of various internal organs (Ellis et al., 2004; Perkins and Swayne, 2001).

Mutation of low-pathogenic strains of influenza in birds can give rise to highly pathogenic strains. All known highly pathogenic strains are either H5 or H7 subtypes. Because these subtypes are known to give rise to highly pathogenic strains, all H5 and H7 infections, whether low-pathogenic or highly pathogenic, are notifiable diseases according to the World Organization for Animal Health (OIE) and the USDA (Alexander and Brown, 2009; OIE, 2011; USDA-APHIS, 2011).

Primary infection of domestic poultry with avian influenza is often due to contact with infected wild birds (Alexander, 2007; Artois et al., 2009; Easterday et al., 1997; Stallknecht and Brown, 2008; Swayne, 2008a, 2008b), but the vast majority of subsequent spread of disease within domestic poultry populations is due to the spread of infective feces by various fomites. Large quantities of virus are excreted in feces, which can result in contamination of food or water, and infection by either fecal-oral or fecal-cloacal routes. The H5N1 strain of avian influenza is an exception, in that it is also transmitted via respiratory mechanisms (Alexander, 2007).

Between flocks of domestic poultry, indirect contact (movement of personnel and equipment) is thought to be the major source of transmission (Alexander, 2007; Capua and Marangon, 2006; Capua et al., 2003). Disease spread by the transport of live or dead birds has also been implicated in past outbreaks (Halvorson, 2009). Some investigators have posited that localized spread of disease by airborne mechanisms or flying insects can take place (Alexander, 2007), but long-distance airborne transmission is not believed to occur (Capua and Marangon, 2006).

The likelihood of spread of avian influenza in poultry populations is dependent on the population density of poultry and on the levels of biosecurity practiced in poultry flocks. Early

detection and rapid diagnosis have been recognized as key factors in disease control (Alexander and Brown, 2009; Capua and Marangon, 2006). Depopulation of infected domestic flocks, either alone or coupled with preemptive depopulation of neighboring flocks, has been used for control of avian influenza outbreaks (Alexander and Brown, 2009; Bavinck et al., 2009; Halvorson, 2009; Sims et al., 2003; Stegeman et al., 2004).

Initial detection of highly pathogenic avian influenza in commercial flocks is often based on observation of unusually high levels of within-flock mortality. Baseline levels of mortality in commercial flocks are often observed and considered normal during poultry production (*e.g.*, Elbers et al., 2004; Vieira et al., 2009; Xin et al., 1994), but mortality beyond baseline levels has been used to establish thresholds of mortality above which reporting of potential disease is either recommended or, in some cases, mandated (Elbers et al., 2004; Vieira et al., 2009). Thresholds of 0.2% to 5% daily mortality, observed over 1 or 2 consecutive 24-hour periods, have been employed in practice (Elbers et al., 2004, 2007).

Historically, the use of vaccination for the control of avian influenza has been discouraged, in part because of the potential difficulty in detecting or correctly diagnosing disease in infected vaccinated flocks (Alexander, 2007; Savill et al., 2006b), and due to concern that vaccinated birds might act as subclinical carriers of infection (Capua and Marangon, 2006). Vaccination has been used, however, in outbreaks of avian influenza in Mexico and Pakistan (Alexander and Brown, 2009; Naeem and Siddique, 2006). The use of emergency vaccination (*i.e.*, vaccination carried out in the face of an outbreak to control the disease) is thought to be a potentially useful control measure, if carried out in concert with other biosecurity and disease surveillance measures (Capua and Marangon, 2006).

Outbreaks of avian influenza in the US, the Netherlands, and the recent outbreak of an Asian strain of H5N1 illustrate some of the difficulties associated with the control of the disease.

A low-pathogenic strain of H5N2 avian influenza was first noted in Lancaster County, Pennsylvania in the spring of 1983. Signs of disease included respiratory difficulties in infected birds and decreased egg production, but only low levels of mortality. By the fall of that year, a highly pathogenic strain had emerged, with mortality approaching 90% in infected flocks. Control of disease was complicated by the simultaneous circulation of low-pathogenic and highly pathogenic strains until the decision was made to depopulate all flocks that showed signs of infection with H5N2, whether low- or high-pathogenic, in February 1984. The outbreak resulted in the detection of 65 infected flocks in Pennsylvania, Virginia, Maryland, and New Jersey, and the deaths of 17 million birds, either due to disease or to depopulation (Alexander and Brown, 2009; Halvorson, 2009).

An outbreak of H7N7 HPAI occurred in the Netherlands in 2003. Initial disease control measures included depopulation of detected infected flocks and preemptive depopulation of all flocks within 1 km of known infected premises. As the epidemic continued, however, only complete depopulation of areas with dense poultry populations was found to be effective. The epidemic resulted in the infection of 255 flocks, the depopulation of 1255 commercial and 17,421 noncommercial flocks, and the culling of 30 million birds (Bavinck et al., 2009; Stegeman et al., 2004). The experience caused Stegeman et al. (2004) to conclude that "outbreaks of HPAI viruses are difficult – if not impossible – to control with usual measures in poultry-dense areas, and effective control could be achieved only by depopulation of the whole affected area."

In 1996, a new strain of H5N1 was isolated in Guandong province, China. The strain is thought to have been circulating in domestic ducks in China from that time, leading to several outbreaks in the late 1990's and early 2000's. An outbreak in Hong Kong in 2002 led to the slaughter of nearly 1 million birds (Sims et al., 2003). Since that time, the strain has spread westward throughout Asia into Europe and Africa (Alexander and Brown, 2009; Artois et al., 2009). Infection of humans by this strain can also occur (Beigel et al., 2005). Since 2003, close to 600 cases of human infection with H5N1 have been reported. Of those, 60% resulted in death (Centers for Disease Control and Prevention, 2012).

1.4. Recent disease modeling efforts

Epidemiologic modeling for the purposes of evaluating control and mitigation strategies for diseases like FMD and HPAI in the US has been carried out for many years: Miller (1976) described a relatively simple model for this purpose over 30 years ago. More recently, improved computational capabilities have led to a substantial increase in the application of modeling techniques (Bates et al., 2003a, 2003b, 2003c; Dickey et al., 2008; Harvey et al., 2007; Patyk et al., in preparation; Sanderson et al., 2009; Schoenbaum and Disney, 2003; Sharkey et al., 2008; Truscott et al., 2007; USDA-APHIS-VS-CEAH, 2009).

1.4.1. Modeling foot-and-mouth disease in the US

Schoenbaum and Disney (2003) presented a flexible epidemiologic simulation model for the evaluation of alternative FMD mitigation strategies in the US. Hypothetical data and information from expert opinion were used to construct epidemiologic models. Epidemiologic modeling results were coupled with economic analyses to determine optimal control strategies. Among the economic implications considered were total direct government costs associated with outbreaks, domestic loss impacts, and impacts of international trade losses. Schoenbaum and

Disney concluded that preemptive depopulation of herds near infected premises was not a suitable control strategy under the conditions considered. Preemptive depopulation of herds identified as having had contact with infected premises was shown to be generally cost-effective and led to shorter disease outbreaks than depopulation of only known infected herds. The authors also concluded that the use of vaccination for disease control would be more expensive than depopulation. Finally, the authors concluded that "the choice of best mitigation strategy depended on herd demographics and the rate of contact among herds".

While Schoenbaum and Disney (2003) considered hypothetical scenarios thought to be representative of US livestock populations in different regions, Bates et al. (2001; 2003; 2003a, 2003b) took a different approach and collected detailed information on contact rates and distances among herds in a relatively small study region. In contrast to the results of Schoenbaum and Disney, Bates et al. concluded that vaccination could be a cost-effective measure for disease control: vaccination of all susceptible livestock within 50 km of detected infected premises reduced the average number of herds infected during an outbreak by 41%. Bates et al. (2003) noted that vaccination "may be a cost-effective strategy... if vaccinated animals are not subsequently slaughtered and there is no future adverse economic impact, such as trade restrictions." Schoenbaum and Disney (2003) made the explicit assumption that vaccinated animals would have to be destroyed in order to resume normal international trade and considered this factor in their economic analysis.

In recent years there has been considerable enhancement, evaluation, and application of the model originally developed by Schoenbaum and Disney (2003). In 2002, the Emergency Management Working Group of the North American Animal Health Committee reviewed several existing models, examined the assumptions made in these models, and identified several

areas for improvement (USDA-APHIS-VS-CEAH, 2002). These suggestions led to the development of the *North American Animal Disease Spread Model* (*NAADSM*), described by Harvey et al. (2007), based in part on the original efforts of Schoenbaum and Disney (2003). *NAADSM* is well characterized (Harvey et al., 2007; Hill and Reeves, 2006), thoroughly tested, and has been subjected to repeated scrutiny by many independent evaluators. Over 80 experts from 11 countries have participated in detailed reviews of *NAADSM* since 2002 (Dubé et al., 2008; USDA-APHIS-VS-CEAH, 2002, 2004), and a complete description of the mechanisms included in *NAADSM* has been published for review by the scientific and regulatory communities (Harvey et al., 2007).

Dickey et al. (2008) reported on the importance of considering heterogeneous contact rates among premises of different types in epidemiologic simulation modeling: model results differed considerably when all farm premises were treated as an "average" type than when differences in management practices and contact rates among farms of different types were considered. This characteristic was anticipated by Bates et al. (2003a) and Harvey et al. (2007): both of these models explicitly allow the simulation of heterogeneous contact rates among farms of different types. Dickey et al. reiterated the importance of the collection and application of data specific to regions of the US where epidemiologic modeling would be used.

Pendell et al. (2007) constructed an economic framework that integrated *NAADSM* to analyze the regional impacts of FMD under three alternate disease introduction scenarios in southwest Kansas. The authors concluded that the potential economic impact of an outbreak was heavily dependent upon the type and location of the initially infected premises. Depending on the type and location of the initially infected premises, the authors estimate the losses in Kansas

might range from $35 million to $1 billion. Pendell et al. had access to some data concerning the locations of livestock premises, but relied on expert opinion for contact rates and distances.

Similarly, Paarlberg et al. (2008) used an integrated system consisting of an epidemiologic model (*NAADSM*) and an economic model of the US agricultural sector to examine the potential impact on the US economy of an outbreak of a foreign animal disease like FMD. They considered a scenario in which FMD is introduced by contaminated feed into four small swine operations. The authors estimated total losses to livestock-related enterprises of between $2.8 billion and $4.1 billion, which extended over a period as long as 4 years. Paarlberg et al. relied heavily on expert opinion for the development of their epidemiologic models.

Ward et al. (2009) conducted simulation modeling of an FMD incursion in an 8-county area in Texas characterized by large, intensive feedlot operations. Information about direct rates of contact among operations was collected with a survey (Loneragan et al., 2006), the results of which have not been published in an accessible form. Expert opinion was used to estimate the frequency of indirect contact. Ward et al. reported that early detection of disease had the greatest impact on reducing severity of simulated outbreaks, while vaccination had little or no effect.

More recently, Sanderson et al. (2009) reported on the effect of movement controls, increased biosecurity, and vaccination on the potential epidemiologic impact of an FMD incursion in the state of Kansas. The authors concluded that indirect contact was the major source of disease transmission, and that local vaccination around infected premises did not contribute to the effective control of disease spread. This conclusion is driven largely by expert-opinion-based assumptions regarding the effects, frequency, and distances of indirect contacts among farm premises, a limitation readily acknowledged by the authors. This study and the discrepancies in results between studies relying on expert opinion again highlight the need for

more accurate information about the number and range of premises-to-premises contacts: in order for epidemiologic modeling techniques to provide valid, credible results, and to make meaningful contributions to animal health emergency response planners and policy makers, more information about the contact networks that exist among farm premises is needed.

Most models of FMD have been concerned with spread of disease between premises. Relatively little attention has been devoted to the within-herd spread of disease. An exception is a study conducted by Carpenter et al. (2004), which made use of a simple stochastic model of spread of FMD within a hypothetical dairy herd. Of particular interest to the study was the extent of disease spread within the herd by the time clinical signs could be detected. Using their model, the authors showed that, by the time 1% of a dairy herd of 1000 animals showed clinical signs of FMD, 65% to 97% of the herd would already be infected.

1.4.2. Modeling highly pathogenic avian influenza

The scale of the units of interest in modeling investigations of HPAI varies widely. Unlike models of FMD, which have rarely considered the spread of disease within herds, within-flock spread of HPAI has been more often of interest in modeling studies (Bos et al., 2007, 2009, 2010; Savill et al., 2006b, 2008; Tiensin et al., 2007). Between-flock models at the regional or national level have been constructed to explore disease dynamics of past outbreaks (Bavinck et al., 2009; Rorres et al., 2010, 2011; Smith and Dunipace, 2011) and to evaluate disease surveillance and control strategies (Alba et al., 2010; Dorea et al., 2010; Patyk et al., in preparation; Sharkey et al., 2008; Truscott et al., 2007). Although beyond the scope of the current report, even a global-scale model of the spread of HPAI has been proposed (Rao et al., 2009).

1.4.2.1. Models of within-flock spread of HPAI

Several mathematical models of within-flock spread of HPAI have been constructed, with a particular emphasis on disease detection. Dorea et al. (2010), for example, constructed a relatively simple, deterministic model of the within-flock spread of disease to determine the likely time of detection of disease within infected flocks. On the basis of their model, the authors reported that detection of disease within infected flocks based on observed levels of mortality would most likely occur five days after infection. This model was based on parameters that described the durations of the latent and infectious phases of HPAI in infected chickens and the rate of within-flock transmission of disease. By contrast, Bos et al. (2007), using a slightly different stochastic mathematical model, concluded that 11 to 15 days could elapse between infection and detection of disease based on observed levels of mortality. Bos et al. used data from the 2003 outbreak of H7N7 HPAI in the Netherlands to inform their model. Parameters used to represent disease state durations and transmission were the same in both reports. The difference in outcomes for time to detection is likely due to the mortality threshold employed in each study. Dorea et al. assumed that disease detection would occur when a threshold of 0.2% mortality on a given day was observed. This value was based on responses to a questionnaire, in which poultry producers indicated the degree of mortality that they would have to observe before taking further action (Vieira et al., 2009). Bos et al. used the higher threshold for detection of 0.5% mortality on 2 consecutive days. This higher threshold was based on legislation in place in the Netherlands for mandatory reporting of disease.

In a similar study, Savill et al. (2008) suggested that, in flocks in which birds are housed in cages, the use of a mortality threshold based on within-cage mortality for disease detection would be more sensitive than use of overall within-flock mortality. All three reports relied on mathematical and statistical models of the within-flock transmission rate of HPAI from an

experimental disease transmission study (van der Goot et al., 2005). Similar estimates have also been determined from field outbreak data (Bos et al., 2009, 2010; Tiensin et al., 2007).

Savill et al. had earlier used the same model to demonstrate the implications of the use of vaccination on detection of disease in HPAI-infected flocks (Savill et al., 2006b). In the study, they suggested that at least 90% of vaccinated birds had to be protected in order to reduce the probability of an outbreak by 50%. The authors conclude that, for a vaccination program to be successful, the vaccine must not only be highly effective but must also be coupled to sensitive disease detection mechanisms. The authors also suggested that the use of unvaccinated sentinel birds in vaccinated flocks could improve the sensitivity of disease detection.

1.4.2.2. Models of between-flock spread of HPAI

Several investigators have used models of HPAI based on past outbreaks to investigate disease dynamics in a population of flocks. Two recent studies have used nonspatial, mathematical models to examine the role of backyard flocks in HPAI outbreaks. Bavinck et al. (2009), relying on data collected during the H7N7 outbreak in the Netherlands in 2003, suggested that backyard flocks were less susceptible to infection than commercial flocks and had little influence on the course of the epidemic, and that it may not be necessary in the future to depopulate backyard flocks.

In a study based on a 2004 outbreak of H7N3 in British Columbia, Smith and Dunipace (2011) similarly acknowledge that the influence of backyard flocks during that outbreak seemed to be "modest at best" but suggested that their influence could not be disregarded. Contrary to Bavinck et al., Smith and Dunipace suggested that the need to either depopulate or vaccinate backyard flocks should be considered when estimating the overall effort required for disease control.

Spatially explicit mathematical models of the spread of HPAI based on past outbreaks have also been constructed. Rorres et al. (2010, 2011) described methods for estimating spatial kernels from limited data, and applied these methods to estimate spatial kernels based on the 1983-1984 epidemic of H5N2 HPAI in the eastern United States. According to the authors, their purpose "was to deal with the problem of how to determine model parameters based on the varieties of data that are actually available during and after an epidemic" (Rorres et al., 2011). They tout the "simplicity" of their model, in that it represents spread of disease with only two parameters which could be relatively quickly generated from available information in the face of an outbreak. Although the authors demonstrate that the parameters they developed can be used to recreate outbreaks that fit the historical outbreak and acknowledge that models can be "useful adjuncts to all the other arguments that go into selecting one control strategy rather than another" (Rorres et al., 2011), neither of these reports attempted to provide information regarding potential control strategies for HPAI.

Boender et al. (2007) demonstrated an application of spatial-kernel-based models for HPAI. Using a spatial kernel derived from data collected during the 2003 H7N7 epidemic in the Netherlands, they constructed a model to produce a map of the Netherlands that differentiated between areas thought to be of high and low risk during potential future outbreaks. According to the authors, high-risk areas were those in which local-area spread alone could lead to major outbreaks. Such areas are likely those characterized by dense poultry populations. The authors did not report on the actual density of poultry populations, nor did they compare their model-based risk map to a map that reflected only population density.

Mechanistic simulation models of the spread of HPAI have also been constructed. Using the outcome of their deterministic model of within-flock spread of disease (see section 1.4.2.1),

Dorea et al. (2010) then constructed a stochastic model of between-flock spread to estimate the number of secondary exposures of premises to HPAI. Using population information from two counties in the state of Georgia, Dorea et al. estimated that, before detection of disease on a primary infected premises, premises on average would spread disease to two to three additional farms.

The model of Dorea et al. (2010) was not used to estimate impacts beyond the number of premises infected by one initially infected farm. Three additional models have been developed to address issues of larger scope. Two of these simulate the spread and control of HPAI in Great Britain (Sharkey et al., 2008; Truscott et al., 2007), and one simulates the spread and control of HPAI in the US state of South Carolina (Patyk et al., in preparation).

With a stochastic simulation model, Truscott et al. (2007) simulated the spread of HPAI among 23,516 premises in Great Britain. The authors attempted to represent direct and indirect contacts that would occur within networks based on shared connections, such as slaughter facilities or connections between premises that were part of the same poultry company. The model also simulated local-area transmission of disease. According to this study, although typical approaches for disease control, including the imposition of movement restrictions of people and poultry and the depopulation of infected premises, were sufficient to control most outbreaks, more strident measures were necessary in the case of larger outbreaks. In this simulation, when outbreaks exceeded 20 premises, additional control measures were used. The most effective interventions in case of these large-scale outbreaks were the use of preemptive depopulation of all poultry within 10 km of known infected premises, or the nationwide use of vaccination. Although simulation results indicate that the use of depopulation would be more

effective, the authors suggest that logistical constraints and the expense associated with such a major depopulation effort make nationwide vaccination the more attractive option.

Likewise, Sharkey et al. (2008) presented model results that indicated that most outbreaks of HPAI in Great Britain would be small: in 73% of cases, outbreaks were restricted to the initially infected premises. This model accounted for multiple mechanisms of disease transmission, including transport of animals, indirect contact, and local-area spread of disease. In their simulations, local-area spread contributed to 54% of all disease spread, with the remainder produced by indirect contact among premises. They concluded, however, that "large outbreaks cannot occur with local transmission alone". Regardless of the control strategy employed, 99% of all simulated outbreaks ended within 100 days. Among the strategies used were the depopulation of known infected premises, reduction of movement among premises, imposition of surveillance zones of 3 km and 10 km, and tracing of contacts that occurred among premises. Neither preemptive depopulation nor vaccination were considered in this study. Given the critical importance of these two control measures in this population (according to Truscott et al., 2007), a more direct, detailed comparison of control strategies and model parameters would be useful.

Finally, the report of Patyk et al. (in preparation) is the currently the most detailed relatively large-scale model of the spread and control of HPAI in the United States. The authors established a set of parameters to represent disease transmission by direct contact, indirect contact, and local-area spread, as well as a typical set of disease control measures. In a population of 786 commercial premises and 5353 backyard premises, this model produced a number of infected flocks from 1 (indicating that disease did not spread beyond the initially infected premises) to 483, with a median of 17 infected flocks. The maximum outbreak duration

observed was 123 days. This study did not include a comparison of multiple control strategies, but the authors alluded to its potential utility for such a purpose.

1.5. Objectives of the current study

1.5.1. Evaluation of epidemiologic models

"Modeling, although seemingly objective, should be seen as a subjective activity in which the world view of the modeler is an integral part of the process" (Haywood and Haywood, 2002). Every model is based on a set of decisions made by the modelers. These decisions are dependent partly on the nature of the research questions that a model is used to address, but there is also a considerable degree of subjectivity involved in the construction and application of models. In the examples presented above, we have seen subjective decisions regarding the form of model to use (*e.g.*, spatial-kernel-based or simulation), the degree of realism and complexity that the models incorporate, the mechanisms of disease spread believed to be important and the degree of differentiation between such mechanisms, and the control measures evaluated with models (*e.g.*, depopulation, vaccination, or both). These choices naturally influence conclusions drawn from model-based investigations.

The subjectivity inherent in the construction and use of models complicates the assessment of the utility of such models: just as model development involves elements of subjectivity, so too does the evaluation of models and model-based conclusions. For veterinary epidemiologic models to be credible, and therefore credibly applied, they must be transparent and critically evaluated. In chapter 2, we discuss various approaches that have been employed in the evaluation of veterinary epidemiologic models, and present a set of guidelines intended to aid those who will be charged with performing such evaluations.

1.5.2. Building a more realistic model of within-unit effects of disease and vaccination

"While it is advisable that models be only as complex as needed, it is often necessary to modify simplifying assumptions and thus increase model complexity to better reflect reality" (Carpenter, 2011). A model might be considered "more complex" than other "simpler" (but less realistic) models because it requires more parameters, but there are other critical considerations. Models that require few parameters are not necessarily "simple" if those parameters represent theoretical abstractions rather than real-world events. Furthermore, in many instances, less effort is required to collect relevant information to generate several model parameters that represent observable, measureable qualities than it is to generate a single parameter that represents a less tangible phenomenon. For example, the models of Schoenbaum and Disney (2003) and Harvey et al. (2007) make the simplifying assumption that the durations of the latent, subclinically infectious, and clinically infectious disease states can be treated as unit-level characteristics. Data available to directly inform such a unit-level characteristic, however, are scarce or nonexistent. By contrast, the model of Bates et al. (2003c) considers animal-level durations for disease states, and simulates within-unit spread of disease. Although this is more "complex" in the sense that more computation must be carried out by the model, information for the parameters themselves is more readily obtained (*e.g.*, Burrows, 1968; Mardones et al., 2010).

In the examples presented above, although within-unit spread has been modeled in the context of disease detection, few veterinary epidemiologic models of the between-unit spread and control of disease explicitly consider within-unit spread. In chapter 3, we show that a consideration of within-unit spread is important for models that will be used to evaluate approaches for disease detection and surveillance. We describe a stochastic, individual-based model of within-unit spread of disease, which also includes representations of disease mortality and the effects of vaccination. We also illustrate the application of this model for the within-unit

spread and detection of foot-and-mouth disease (FMD) and highly pathogenic avian influenza (HPAI). Although this model requires more parameters than "simpler" models, the data required to inform those parameters are more easily obtained, more transparent, and more credible.

We also describe our application during construction of this model of the guidelines presented in chapter 2, to ensure that it can be fully evaluated by its users, other modelers, field epidemiologists and veterinary practitioners, and decision-makers.

1.5.3. A comparison of model outcomes based on different sources of population data

"Any model ultimately depends for its validity on the accuracy and completeness of the data underpinning it" (Taylor, 2003). Regardless of the form that epidemiologic models take, they all share a common requirement for empirical data. Although a simulation model based on incomplete or theoretical input information may yield useful hypotheses for further research, for model results to be useful to response planners and decision makers, the model must be based on valid, if not completely accurate, input data.

Unfortunately, for efforts to model diseases of livestock and poultry in the United States, detailed, accurate data concerning the farm populations of interest (including the number, sizes, and locations of farms) are not available. In most instances, a surrogate for actual farm population datasets must be used.

In chapter 4, we evaluate several methods that have been developed to generate such surrogate datasets, and show how they affect the outcomes of a model of the spread and control of HPAI in commercial poultry flocks in South Carolina. The aim is to show whether, and if so, how, model results can be credibly applied when they are based on population demographics that are known not to be accurate.

The diagram above illustrates the conceptual foundation of the Kermack and McKendrick model of disease spread. In this model, the population of interest is divided into three classes. Initially, most individuals in the population are susceptible to disease. The size of this class is designated *S*. As susceptible individuals become infected, they join the infectious class (*I*). The rate of infection of susceptible individuals is influenced by the number of infectious individuals in the population together with an additional transmission parameter *β*. As infected individuals recover (at rate *γ*), they join the recovered class (*R*). Once recovered, this model assumes that individuals are immune to reinfection by the disease. This simple model further assumes that the population is closed, *i.e.*, that no new individuals enter the population through birth or immigration, and no individuals leave through to emigration or death.

The dynamics of this system can be represented by the following set of differential equations, which describe the rate of change over time of each of the three classes in the population:

$$\frac{dS}{dt} = -\beta SI$$ The size of the susceptible class decreases as susceptible individuals come into contact with infectious individuals, influenced by the transmission parameter.

$$\frac{dI}{dt} = \beta SI - \gamma I$$ The size of the infectious class increases with newly infected susceptible individuals, and decreases as infectious individuals recover.

$$\frac{dR}{dt} = \gamma I$$ The size of the recovered class increases as previously infectious individuals recover.

Figure 1-1. The differential equations-based model of Kermack and McKendrick (1927).

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2. Approaches for evaluating veterinary epidemiologic models: verification, validation, and their limitations[1]

Summary

The evaluation of models of the spread and control of animal diseases is crucial if these models are to be used to inform decisions about the control or management of such diseases. Two key steps in the evaluation of epidemiologic models are model verification and model validation. Verification is the demonstration that a computer-driven model is operating correctly, and conforms to its intended design. Validation refers to the process of determining how well a model corresponds to the system that it is intended to represent. For a veterinary epidemiologic model, validation would address such issues as how well the model represents the dynamics of the disease in question in the population to which this model is applied, and how well the model represents the application of different measures for disease control.

Just as the development of epidemiologic models is a subjective, continuous process, subject to change and refinement, so too is the evaluation of models. The purpose of model evaluation is not to demonstrate that a model is a "true" or "accurate" representation of a system, but to subject it to sufficient scrutiny so that it may be used with an appropriate degree of confidence to aid decision-making.

To facilitate model verification and validation, epidemiologic modelers should clearly state the purpose, assumptions and limitations of a model; provide a detailed description of the conceptual model; document those steps already taken to test the model; and thoroughly describe the data sources and the process used to produce model input parameters from those data.

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2.1. Introduction

Computer-driven epidemiologic modeling is an increasingly common technique for assessing the potential consequences and possible spread of animal diseases. Modeling of animal diseases has been used to estimate the possible magnitude of an outbreak and the resources needed for a response, and to inform policy decisions on measures for disease control (Bates et al., 2003a, 2003c; Ferguson et al., 2001a, 2001b; Garner et al., 2010; Keeling et al., 2001, 2003; Portacci et al., 2009; Schoenbaum and Disney, 2003). Epidemiologic models may take several forms. Some are based on analytical formulas that describe the system of interest in a rigorously mathematical way (Ferguson et al., 2001a, 2001b; Keeling et al., 2001, 2003; Thornley and France, 2009). Others employ computer-driven simulation to mimic the actual mechanistic processes at work within a system (Bates et al., 2003b; Garner and Beckett, 2005; Harvey et al., 2007).

Regardless of their form, all models – especially models which are intended for use by response planners and policy-makers – require careful evaluation. For models to be effectively used in these instances, a sufficiently high level of credibility of the model and its results must be achieved so that decision-makers and other stakeholders can have a justifiable degree of confidence in their application. By the same token, careful evaluation of models can identify and clarify their limitations and weaknesses, temper tendencies toward over-reliance on apparently "objective" model-produced outcomes, and minimize their misapplication.

Methods for model evaluation are quite diverse; as several authors have noted, there is no single standard or approach that can be applied to all models (Kleijnen, 1999; McCarl, 1984). At a very basic level, as the mathematical or computational complexity of epidemiologic models increases, it is essential to demonstrate that the mathematical framework or software used for a

model is free from major errors which would threaten the accuracy of the calculations that the model produces. Some approaches for evaluating models are, by necessity, qualitative. Any assessment of the conceptual quality of a model, for example, is fundamentally qualitative in nature. In some instances, it may be possible to use quantitative or statistical approaches to demonstrate correspondence between a model and a natural system, although the use of such quantitative methodologies does not necessarily ensure that a model is conceptually sound.

The aim of this paper is to describe approaches for evaluating epidemiologic models intended to inform management or policy decisions on animal diseases, with an emphasis on two approaches that have been called "verification" and "validation". Our specific objectives are as follows:

- to briefly define and describe the processes of model verification and validation
- to discuss several approaches used to address the challenging issue of validating epidemiologic models intended to inform emergency response plans
- to illustrate practical approaches to model verification and validation, based our experiences as members of the research team behind the *North American Animal Disease Spread Model* (*NAADSM*) (Harvey et al., 2007)
- and, finally, to present a set of suggestions for steps that could be taken to improve the credibility and acceptance of epidemiologic models for the management of animal diseases.

2.2. Model context, development, and evaluation

Figure 2-1 illustrates a conceptual series of steps in the process of model development and application. Several of these steps deal explicitly with the evaluation of models, but almost every stage in the figure implies some form of appraisal of the model under development. Decisions

made at the outset of model development about the specific purpose of a model and the questions which it is being designed to answer will affect the ways in which the model's utility and credibility are assessed.

First and foremost, models must be evaluated in the context of the problems that they are intended to answer (Law and McComas, 2001; Overton, 1977; Sargent, 2009). The criteria for judging a model that is intended to inform broad questions in a qualitative way will be quite different from those used to evaluate a model that claims to offer specific predictive capabilities.

Secondly, for results of modeling investigations to be credible, the models must be built upon reliable data (Rykiel, 1996; Taylor, 2003). Models based on incomplete or theoretical input data may yield useful hypotheses for further research and evaluation, but the limitations of such models should be clearly and expressly stated. The more complete the input data for a model are, the more likely it is that the model's output will be credible.

Thirdly, just as the conceptual development of models is, in many respects, a subjective undertaking, so too is the evaluation of models. Individual modelers must weigh the relative importance of different aspects of epidemiologic systems, and may come to different conclusions about how to represent various processes in their models, or even about which processes to represent. Any assessment of the credibility of a model must consider these subjective design decisions.

Fourthly, Figure 2-1 makes the distinction between a conceptual model or model framework, and a specific model that applies a particular conceptual framework, together with a particular data set or set of parameter values, to represent a specific situation. *The North American Animal Disease Spread Model*, for example, is a framework for the development of epidemiologic simulation models, which has been used to build specific models of a variety of

diseases in different settings and populations, such as foot and mouth disease (FMD) (Pendell et al., 2007; USDA-APHIS-VS-CEAH, 2009), Aujezsky's disease (pseudorabies) (Portacci et al., 2009), and highly pathogenic avian influenza (HPAI) (Patyk et al., in preparation), among others. Both the conceptual framework and the particular instances in which the framework are used need to be evaluated. The utility of the former does not necessarily rely upon the latter, but the quality of specific models is highly dependent on both the conceptual framework and the data used for their construction.

Finally, Figure 2-1 illustrates that the process of model development and evaluation is cyclical and iterative. Evaluation is not a single, discrete step, and "is not something to be attempted after the simulation model has already been developed, and only if there is time and money remaining" (Law and McComas, 2001). Model evaluation should instead be considered ongoing: model assumptions should be reassessed continually as new sources of information become available.

The assessment of the computational correctness of a model has been called "verification". Verification deals with questions such as: "Does the computer program perform all calculations correctly?" and: "Does the program match exactly what the designers intended?" The assessment of how well a model conforms to or exemplifies the system that it is intended to represent is sometimes referred to as "validation" (Kleijnen, 1999; Sargent, 2009; Schlesinger, 1979). Validation is intended to address the question, "Is a model an adequate representation of the real system?" (For the remainder of this paper, we will follow these definitions for "verification" and "validation", but note that these definitions are not universally applied. For example, Oreskes et al. (1994) use the terms "verification" and "validation" to denote somewhat different concepts.)

Together, verification and validation efforts can help investigators to ascertain the overall quality and credibility of a model.

2.3. Model verification

Model verification refers to the process of determining whether the model, as implemented in software, conforms to the desired conceptual model (Sargent, 2009). In other words, verification provides an assessment of whether the software implementation of the model is working correctly. Among the criteria by which a model's verification status might be assessed include its correctness (the "extent to which a model meets its specifications") and its reliability (the "extent to which a model can be expected to perform its intended function with required precision") (McCall et al., 1977; Scholten and Udink ten Cate, 1999). Any model used for scientific research or for decision support should be expected to meet a high standard for such characteristics.

Model verification, although straightforward in concept, can be time-consuming, particularly as models become more complex. Sargent (2009) and Scheller et al. (2010) present useful discussions of some of the software engineering practices that can facilitate the construction of verified models, particularly for larger projects, and several authors have provided detailed descriptions of approaches to verification (Knepell and Arangno, 1993; Whitner and Balci, 1989). In this paper, we focus on two central aspects of model verification that have a direct impact upon the credibility of epidemiologic models regardless of their form, size or scope: producing documentation that describes the conceptual model in detail, and thorough testing to ensure that the model is performing as intended.

2.3.1. Describing the conceptual model

As shown in Figure 2-1, designing the conceptual model is an early stage in model development. There is a great deal of value in explicitly documenting this conceptual model. Such documentation can be used to assess the conceptual validity of the model (see below), but, at a more basic level, it can provide a standard by which the correctness of a model can be judged (Knepell and Arangno, 1993; Scheller et al., 2010). The purpose of a written model specification is to describe, in clear, accessible language, the purpose, requirements and conceptual details of a model. The intended audience of such a document includes the modelers themselves, as well as any technical personnel who will be involved in implementing the model, among others (see section 2.4.2, below). The model specification can also provide a basis for model testing (*NAADSM* Development Team, 2010a; Scheller et al., 2010).

In the case of *NAADSM*, the model specification document (*NAADSM* Development Team, 2010a) describes every component of the modeling framework in detail: it is the authoritative source that describes how the conceptual model should operate, and is the standard by which the software implementation of the conceptual model is judged. Although the specification may be updated as needed, to correct ambiguities or to incorporate new features, the complete history of the specification is tracked, and every version is available for reference and evaluation by independent researchers (*NAADSM* Development Team, 2008, 2010a).

2.3.2. Model testing

Fairley (1978) and Whitner and Balci (1989) distinguish between two forms of model testing, which they refer to as “static” and “dynamic”. For simple models, static testing may be sufficient. This approach involves a structured examination of the formulas, algorithms and code used to implement a model, preferably by several reviewers who were not directly involved in

writing the implementation themselves. Garner and Beckett (2005) describe the use of this approach in the development of *AusSpread*, a simulation platform designed initially to model the spread and mitigation of FMD.

For more complex models, dynamic testing is often useful. During dynamic testing, a computer program is run repeatedly under different conditions to ensure that the output it produces is correct, according to the conceptual model, and consistent with expectations. Often, such tests are established to be run repeatedly and automatically, to ensure that any changes to the software implementation did not inadvertently introduce errors; this process is referred to as regression testing. Scheller et al. (2010) describe several levels of testing, from simple unit tests that evaluate specific, individual functions; to broader system testing that assesses the interaction of all of the components of a model. We will illustrate these approaches in the following sections, with examples from the development of *NAADSM*.

3.2.1. Automated software testing of the NAADSM *framework*

To ensure that the *NAADSM* application correctly implements the conceptual model specification, *NAADSM* relies upon an automated regression-testing approach. Simple models have been constructed to test every aspect of the *NAADSM* application. There are currently well over 1,000 individual models in this suite of tests, and new tests are continually being developed. When the *NAADSM* application is compiled from program source code, every test is automatically run and results are tracked using a freely available framework for software testing (Savoye, 2004). Prior to the public release of any new version of *NAADSM*, every test in the suite must be passed. Every simple model developed for testing is published, along with the complete source code for the *NAADSM* application.

3.2.2. Manual testing of NAADSM

In addition to the automated use of simple tests, manual testing using more complex situations has been carried out for the *NAADSM* framework. Every aspect of the model framework is examined by analysts working independently of the programmers to confirm that the model conforms to the published specification. Any errors identified during manual testing are noted and must be corrected before public release.

2.3.3. The limitations of model verification

Model verification procedures can be quite objective and thorough. Many techniques developed in the field of software engineering can be rigorously applied to the programming of models (Baxter et al., 2006; Scheller et al., 2010). Model verification offers no answer, however, to the crucial questions: "Is the model useful?" and "Is the model adequate for the purposes for which it was designed?" Questions like these can be addressed by a variety of approaches that fall under the general heading of "model validation".

2.4. Model validation

Validation refers to the process of determining whether a model is an acceptable representation of the system that it is intended to represent, given the purpose of the model or study (Law and McComas, 2001; Sargent, 2009). A more elaborate definition is provided by Schlesinger (Schlesinger, 1979): model validation is the "substantiation that a ... model within its domain of applicability possesses a satisfactory range of accuracy consistent with the intended application of the model". It is important to note that "acceptable representation" in the definition above does not mean an "accurate" or a "true" representation: Oreskes et al. (1994) convincingly argued that it is impossible to establish whether any particular model is an accurate

representation of a natural system, and that the use of the term "validation" in this sense is highly misleading.

2.4.1. The problem of model validation

In contrast to the process of model verification, establishing the validity of models is not clear cut, and can be quite problematic. As McCarl (1984) observed, "there is not, and never will be, a totally objective and accepted approach to model validation". The standards by which a model's validation is judged are partly dependent upon the purpose of the model. The validation of models designed strictly to address research questions (for example, to generate and test hypotheses concerning population or disease dynamics or to identify new areas of research) does not have to be as stringent as the evaluation of models that will be used to inform operational management decisions. When such decisions are made on the basis of the results of modeling studies, it is important to know that these studies are appropriate, accurate and correct. Given the difficulties associated with the study of very complex multifactorial problems, the subjective elements of modeling itself, and philosophical issues like those presented by Oreskes et al. (1994), the threshold for accepting a model cannot be "proof" of its accuracy or validity. Rather, this threshold should be that of reasonable confidence in the results produced by the model. As Holling (1978) stated, "provisional acceptance of any model implies not certainty, but rather a sufficient degree of belief to justify further action". The task of model validation, as described here, is that of evaluating models in order to have a justifiable level of confidence in their results before they influence policy or management decisions.

It is often constructive to think of a model in a similar way to a scientific hypothesis. An epidemiologic model, for example, represents the modelers' hypotheses about the interactions among members of a population, the dynamics of disease in that population, the mechanisms of

disease spread, and the efficacy of different disease control measures. As with any hypothesis, models should be tested and challenged. As models are subjected to and withstand increasing levels of scrutiny in diverse situations, their credibility is increased. Such models can then be applied to problems of management and policy with greater confidence, provided that it is always clearly understood that no model truly represents physical reality, and that the acceptance of any model must be subject to continuing evaluation.

What follows is not a set of methods that will prove that a model represents a real system, but rather a set of activities that might be undertaken to provide evidence which may either support or refute the hypothesis presented by a model. Several authors present descriptions and detailed taxonomies of the methods used to assess model validity (Knepell and Arangno, 1993; Law and Kelton, 2000; Rykiel, 1996; Sargent, 2009). Our intention, in the following sections, is to present and discuss the usefulness of some of these methods, together with examples of their application, both from our own experiences and from other published reports of animal disease modeling. We also refer readers to several excellent discussions of model validation, including those presented by Oreskes et al. (1994), Rykiel (1996), and Taylor (2003).

2.4.2. Conceptual validity

A particularly useful – and a foundational – criterion for the validation of an epidemiologic model is the answer to the question, "Does the structure of the model make logical and biological sense?" This has been referred to as "conceptual validity" (Rykiel, 1996; Sargent, 2009). For a model to have conceptual validity, its theoretical underpinnings should be shown to be based on known and scientifically accepted properties of the system of interest, or at least on reasonable and justifiable assumptions about such properties. Among some of the questions that might be addressed in assessing the conceptual validity of a model are the following:

- does the model fit the purpose or purposes for which it was designed?
- does the structure of the model sufficiently capture the relationships and interactions among components of the system being modeled?
- given the purpose of the model, are key components of the system absent from the model, or oversimplified? Is additional detail necessary for any component?
- based on existing knowledge and experience, are the outcomes produced by the model reasonable?

Review by independent experts on the subject matter concerned – sometimes referred to as establishing "face validity" (Rykiel, 1996) – can be used as a means of assessment. In this case, it is quite helpful to have a detailed document that describes the conceptual model, as noted earlier. Such a document can provide a basis for discussion and evaluation of the details of the model's operation. The publication of model descriptions (Bates et al., 2003b; Harvey et al., 2007; Jalvingh et al., 1999; Stärk et al., 2000) greatly facilitates the assessment of the conceptual validity of models.

Reliance on the peer-reviewed literature provides one avenue for the conceptual assessment of epidemiologic models. The *NAADSM* Development Team has also taken a more direct approach and sponsored a series of meetings of subject-matter experts, including epidemiologists, virologists, economists, policy-makers and other modelers, to review the *NAADSM* modeling framework (Dubé et al., 2008; USDA-APHIS-VS-CEAH (United States Department of Agriculture-Animal and Plant Health Inspection Service-Veterinary Services-Centers for Epidemiology and Animal Health), 2002, 2004). The structure and assumptions of the modeling platform have been described in detail during these workshops, and discussion,

suggestions and advice are solicited from all participants. The results of these expert panel evaluations are then used to guide future research and development.

2.4.3. The use of data in model validation

As noted in section 2.2, it is possible to assess the conceptual framework separately from the data used to inform a model. Empirical data are generally used in two ways during modeling:

- input data are used to develop parameters that will influence model outcomes
- data that represent the outcomes or results of a system (output data) are used to provide a basis for comparison with model-produced outcomes.

In a few cases, particularly for endemic disease situations, large amounts of both types of data may be available for models of disease spread in populations. In many instances, however, we have access to information pertaining to only a single outbreak of disease in a particular set of circumstances. Information collected during the 2001 outbreak of FMD in the United Kingdom (UK), which has been widely used for modeling studies (Ferguson et al., 2001a, 2001b; Keeling et al., 2001, 2003; Savill et al., 2007), represents one such data set. In still other instances, models are developed to explore hypothetical situations (Bates et al., 2003a, 2003b; Garner and Beckett, 2005; Patyk et al., in preparation). In these cases, some information is generally established to inform model inputs, but there can be no data on the (non-existent) system outcomes.

Whatever the form or source of data used to inform models, their correctness and validity should also be considered. As Rykiel (1996) points out, there is no guarantee that available data necessarily provide a better or more accurate depiction of a real system than a conceptual model. The process of ensuring so-called data validity (Rykiel, 1996; Sargent, 2009) can in itself be complex.

Several authors have emphasized the notion that, in order to demonstrate validity, models should be tested against data not used during their construction (Kitching et al., 2007; Spedding, 1988). Green and Medley (2002) indicated that such a step should be a requirement before a model is used to inform policy decisions. This is one of several possible approaches that fall into the general category of "operational validation" (Sargent, 2009).

Although this suggestion seems straightforward, its implementation for incompletely understood biological and epidemiologic systems is problematic. First, it implies that reliable, valid data exist for at least two situations, for both the development of parameters and for comparison to actual system outcomes. Secondly, this approach would require the existence of a suitable means of evaluation by which the similarity of model-produced outcomes to system outputs can be assessed. Thirdly, it implies that these situations are sufficiently dissimilar from one another that they represent unique tests of a model, but are still similar enough that exactly the same approach to modeling developed for one situation can be legitimately applied to the others. We have already mentioned the first difficulty. The remaining two problems are discussed below.

A variety of quantitative, statistical approaches to show the correspondence between model-produced outputs and outcomes generated by biological systems have been devised and applied in a few situations (Fay et al., 2006; Kleijnen, 1999; Loehle, 1997; Mayer and Butler, 1993; Power, 1993; Reynolds Jr. et al., 1981; Robinson and Froese, 2004; Waller et al., 2003). Most of these approaches to what has been called statistical validation rely upon the existence of a large amount of data (i.e. many observations) pertaining to the outcome of the natural system, which limits their applicability to most situations of interest to animal disease modelers.

Waller et al. (2003) proposed the use of Monte Carlo hypothesis tests, which, in essence, compare a single set of outcome data from a real system to multiple model-generated outcome data sets, and seek to answer the question, "Do the observed data appear consistent with the model?" rather than the more typical question, "Does the model appear consistent with the observed data?" Although this approach is not without value, it raises an additional question: how representative is any single outcome? When considering recent outbreaks of FMD in the UK, for example, is the 2001 outbreak, which resulted in the infection of over 2,000 herds (Anderson, 2002), more or less representative than the 2007 outbreak, which produced only eight infected herds (Anderson, 2008)? How "consistent" would each of these two outcomes have to be with model-produced data to conclude affirmatively that the data are consistent with the model? Efforts to compare outcomes from epidemiologic models to data generated by individual outbreaks should be undertaken with care: such comparisons are potentially informative, but an over-reliance on quantitative approaches for evaluation of models may well be misleading.

The disparity between these two recent FMD outbreaks in the UK also illustrates the third potential problem raised above: the dissimilarities among outbreaks of even the same diseases in generally the same types of populations make it difficult to test a model against data not used during its construction. As described in section 2.2, the use of data is integral to model construction. Although the conceptual framework of a model and the data used to inform this model are distinct and can (and should) be evaluated individually, output generated by a model is inseparable from the combination of these two elements. The correspondence of model output to a natural system cannot be evaluated without considering the conceptual model and the source data simultaneously.

2.4.4. Validation of model components

Although it is difficult to demonstrate the validity of an entire model by the means described above, especially in the absence of relevant data, it may be possible to assess the validity of some individual components of a more complex model. This component-based approach to validation is sometimes recommended (Martin et al., 1987). An example is a recently completed validation of the process used in *NAADSM* to simulate animal movements and contacts among farm premises (Dubé, 2009).

Briefly, the objective of this study was to validate the contact component used in *NAADSM* by comparing simulated movements to real-world, farm-to-farm movements that had been recorded for adult milking cows in Ontario, Canada. The study concluded that the approach used in *NAADSM* performed reasonably well in simulating average network characteristics observed in real-world movement data, but did not perform as well in simulating extreme upper percentiles of movement network components, involving rare but observed farms with excessively high shipment frequencies. The results of this study will be used to inform future development, with the objective of providing better representations of actual events and thus leading to greater confidence in the results of modeling studies.

2.4.5. Comparison of models

Comparison of the results from several independently developed models may be used to improve the level of confidence in the models tested. This process has been called "relative validation" (Dubé et al., 2007).

Dubé *et al*. (2007) conducted a comparison of three simulation models using relatively simple disease scenarios. Among the findings of this comparison was that, although statistically significant differences were observed among model outputs, results from all three models

supported the same or very similar conclusions on approaches for disease control. This finding could be used to increase the confidence of end users and decision-makers in modeling results. The results of a follow-up investigation that considered more complex scenarios were subsequently reported (Sanson et al., 2011).

Several similar comparisons of models of the spread and control of animal disease have also been undertaken. Vigre (2008) reported on a comparison of mathematical and simulation-based models. The differences identified were more substantial than those reported by Dubé *et al*. (2007), and may reflect the broader distinctions between the fundamental assumptions made by the individual models. Continued investigations in this vein would be quite helpful. Gloster et al. (2010) also recently reported on the comparison of several models of airborne dispersion of FMD virus. Like Dubé *et al*. (2007), they reported that the results of the models evaluated were broadly similar but, of course, highly dependent on the assumptions made and the data used by different groups of modelers.

Loehle (1997) identified the comparison of models as a component of the larger process of what he called structural analysis, or an evaluation of the inherent assumptions and identification of the deficiencies of various models. Loehle argued that, because of the existence of such structural differences among models, and because comparing multiple models is the most effective way to identify and determine the effects of such differences, it is essential to direct multiple modeling efforts towards any important policy or management problem.

2.4.6. Sensitivity analysis as a form of validation

When data from real systems are limited, sensitivity analysis is sometimes suggested to inform model validation efforts (Bates et al., 2003c; Karsten et al., 2005; Kleijnen, 1999). Sensitivity analysis is used to determine the amount of influence that particular parameters have

on the outcome produced by a model. Sensitivity analysis can also be used to assess the conceptual validity of a model: if certain parameters are expected to be important in a system, based on prior knowledge of that system, then sensitivity analysis should bear out these expectations (Kleijnen, 1999).

Of greater value is the use of sensitivity analysis to determine which parameters in a model are important. If a model includes parameters about which there is a high degree of uncertainty, but which are shown by sensitivity analysis to have a substantial impact on model results, such parameters are good targets for additional research. An example of applying such sensitivity analysis to animal disease modeling was recently published (Owen et al., 2011).

2.5. Suggestions for the construction of useful, credible models of animal disease

As discussed in the preceding sections, the primary objective of model verification and validation is not to demonstrate that a model is a true or even a highly accurate representation of a real system, but rather to provide a set of approaches and criteria by which a model can be evaluated. For models that might be used as a partial basis for policy or management decisions, it is essential that such evaluation establishes a foundation of support and credibility. To that end, we suggest the following practical steps that members of the veterinary epidemiologic community can take to produce credible, useful models of the spread and control of disease in animal populations. These suggestions are drawn from our own experience, as well as from many of the other valuable sources cited throughout this article; in particular, those written by Bart (1995), Rykiel (1996), Law and McComas (2001) and Sargent (2009).

Clearly and precisely state the purpose for which a model was designed

The importance of the first step, illustrated in Figure 2-1: that of determining and then clearly and precisely stating the questions to be asked of a model, may seem self-evident, but this

step is often overlooked (Bart, 1995). Overton (1977) remarked that: “the great majority of criticisms of models relate to a capacity for which the model was not designed in the first place”. A clear understanding of the purpose of a model is a prerequisite for any further evaluation.

Provide a detailed description of the conceptual model, and documentation concerning the assumptions and limitations of the model

Virtually every paper on techniques for the verification and validation of models stresses the importance of documentation for the conceptual model (Bart, 1995; Knepell and Arangno, 1993; Law and McComas, 2001; Sargent, 2009; Scheller et al., 2010). A model description should not be produced solely, or even primarily, for the developers of an individual model. Those who will derive the most benefit from the existence of such documents will be other model users, in the broadest sense of the term: other researchers, analysts and decision-makers, who will be expected to apply or evaluate the model and its results. Such documentation is particularly useful when it includes discussions of the model’s assumptions and limitations, presented in ways that are clear and biologically relevant (Guitian and Pfeiffer, 2006).

Provide details of steps taken for model verification

At its most basic level, the credibility of a model relies upon the demonstration that the model, as implemented in software, does what it is supposed to do. Anyone asked to evaluate a model, particularly if it will be used to influence policy, should have access to a computational implementation of the model and details of the verification procedure employed, as well as to any tests used for verification, so that he or she can reproduce and evaluate the computational correctness of the model.

Describe the data used to develop model parameters, and provide documentation for the approaches and assumptions used to produce model parameters from data

The process of translating raw data into parameters suitable for use in models is seldom straightforward. An understanding of this process, however, is essential if reviewers are to have an adequate basis for judging the model's results. Two recent reports illustrate this suggestion quite nicely: Mardones et al. (Mardones et al., 2010) conducted a meta-analysis based on 21 research papers and documented in detail the procedures that they used to estimate the durations of different disease states for FMD. In a different study, Patyk et al. (in preparation) produced a model of the spread and control of HPAI in South Carolina in the United States. This study included an online supplement that described in detail all the sources of information used for the study, as well as the computational tools that the authors developed and used for parameter development.

Involve independent experts in the evaluation of models and their outcomes

Veterinary epidemiologic modeling is an interdisciplinary undertaking. Modelers can take advantage of a great deal of expertise in different fields by involving experts from these fields. For models to be used for decision-making, it is also essential to involve other stakeholders in this process; for example, those who are responsible for decision-making or for implementing policies in the field. In our own experience with *NAADSM*, we have found that, through its widespread application, they have benefited substantially from the efforts of others to use and evaluate it.

A variety of forums have become available for sharing and discussing veterinary epidemiologic modeling work over the last few years (Dubé et al., 2008; USDA-APHIS-VS-CEAH and OIE, 2008; USDA-APHIS-VS-CEAH, 2002, 2004). We encourage anyone involved

with the construction, use or evaluation of models to seek out and take advantage of such opportunities when they occur.

When possible, use existing information for data-driven validation of models or their components

We have discussed the limitations and advantages of this approach in sections 2.4.3 and 2.4.4 above. Such approaches should be undertaken with care, and with the recognition that the results will not be definitive: a poor conceptual model may still produce a good fit to observed data and *vice versa*. In situations where appropriate information is available, however, the comparison of model-produced outcomes to real data can still be enlightening. Retrospective analysis of past outbreaks is crucial to understanding them, and modeling can be a very useful tool in this pursuit (Garner et al., 2007; Kitching et al., 2006).

Present a range of possible outcomes, including "best case" and "worst case" scenarios

As discussed above, models are not definitive representations of reality. We are often uncertain about the ways in which at least some components of our systems operate, and also about specific parameter values. Presenting a range of results is one way to capture some of this uncertainty.

Use sensitivity analysis to determine the importance of parameters used in a model

In addition to the benefits discussed in section 2.4.6, evaluating the importance of model parameters – especially those for which data are limited – can be used to estimate the potential effects of parameters about which the modelers are uncertain.

Compare the purposes, conceptual bases, and outcomes of different models

During the modeling process, different modelers make different subjective decisions and assumptions. Qualitative agreement among several models may lend credibility to the

conclusions drawn from model-based studies. Areas of disagreement among models should prompt additional research and investigation to improve our level of understanding of the system components in question.

Finally, treat model evaluation as an on-going process, not as settled fact

Every epidemiologic model is a work in progress, informed and updated by existing and new knowledge about the dynamics of disease; changes in agricultural and social practices; and changes in the forms, sources and quality of available data. The validity of any epidemiologic model should be continually reassessed under new conditions or as the state of our knowledge improves.

2.6. Conclusions

The careful evaluation of any model intended to inform management or policy decisions is an essential activity. Two key steps in assessing the quality and usefulness of epidemiologic models are verification and validation. Unfortunately, there are no purely quantitative, strictly objective means by which to evaluate models. Each model, and each situation to which modeling will be applied, is unique, and unique means may be necessary to evaluate a model and its particular applications.

Holling (1978) pointed out that, "provisional acceptance of any model implies not certainty, but rather a sufficient degree of belief to justify further action". We have outlined a set of recommendations that can be used by epidemiologic modelers to cultivate confidence in applying this technique to important problems in animal population health. Individual models will continue to be developed and compared, and will evolve as they are scrutinized. Through these exercises, our collective aim of providing useful tools to assist in decision-making processes can be met.

To achieve a sufficient level of credibility for model outcomes, it is essential not to involve solely modelers in their evaluation. As Rykiel (1996) observed, “to the extent that a model is a scientific experiment and theoretical development, its testing and validation are within the purview of the scientific community”. We agree, and would add that, in the case of models for animal diseases, the evaluation of models is also within the purview of field epidemiologists and veterinary practitioners, policy planners and decision-makers, and animal industry representatives.

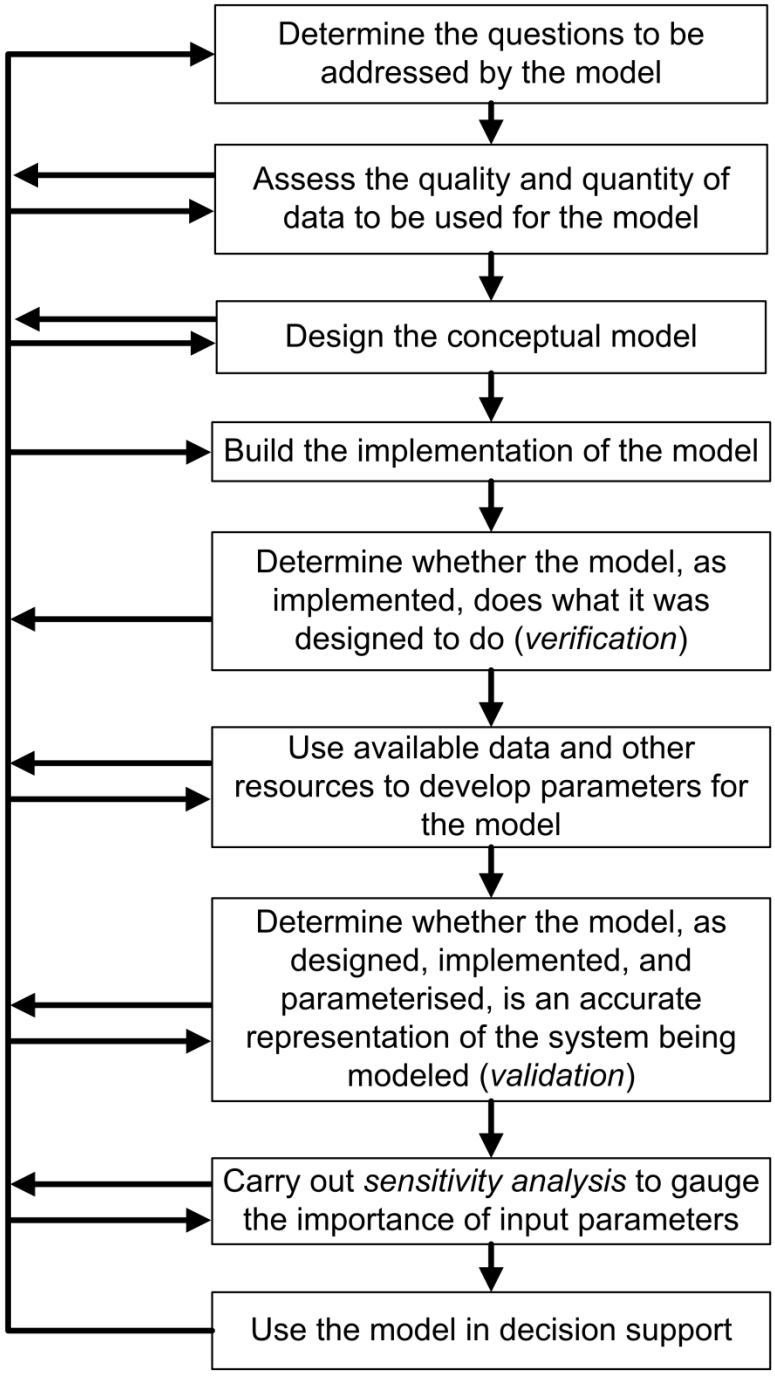

Figure 2-1. Schematic diagram of the stages of model development, evaluation, and application. Adapted from Dent and Blackie (1979), Martin et al. (1987), and Taylor (2003).

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3. Development of a stochastic, individual-based modeling framework for within-unit transmission of highly infectious animal diseases

Summary

The dynamics of spread of disease within individual herds or flocks, which may have different degrees of immunity to disease due to vaccination, can have important implications for disease detection and surveillance, as well as for disease transmission between herds or flocks, especially for highly infectious diseases. We have developed a simulation modeling framework for within-unit disease spread that operates at the level of the individual animal and fully incorporates sources of individual-level variation, such as variability in the durations of incubating and infectious periods, the stochastic nature of disease spread among individuals, and the effects of vaccination. We describe this stochastic modeling framework, along with the processes employed for its verification and validation. We also illustrate the use of the framework to explore within-unit disease dynamics of foot-and-mouth disease and highly pathogenic avian influenza, with a particular emphasis on disease detection.

The incorporation of this approach to modeling of within-unit disease dynamics into models of between-unit disease spread and control should improve the utility of such models for emergency preparedness and response planning by making it possible to assess the value of different approaches to disease detection and surveillance in populations with or without some existing level of vaccine immunity. An implementation of this conceptual model is freely available via the internet at *http://www.naadsm.org/wh*.

3.1. Introduction

Models of disease spread often incorporate information about the transmission of disease at different levels, depending on their purpose. Models of within-unit disease dynamics (*i.e.*, processes that occur within individual flocks or herds) have been used to estimate changes in disease prevalence over time (Evans et al., 2010; Perez et al., 2002), to estimate rates and parameters associated with disease transmission (Bouma et al., 2009; Perez et al., 2002), to assess the utility of within-unit disease interventions such as vaccination (Bouma et al., 2009; Savill et al., 2006b), or to investigate the likelihood and timing of detection of disease under different conditions (Carpenter et al., 2004; Savill et al., 2006b). Models of between-unit spread of disease (*i.e.*, spread of disease from individual flocks or herds to others) have been used to inform policy decisions regarding disease control methods and outbreak response plans, to estimate the possible magnitude of an outbreak, and to estimate resources needed for outbreak response (*e.g.*, Bates et al., 2003a, 2003b; Dorea et al., 2010; Garner and Lack, 1995; Nielen et al., 1999; Schoenbaum and Disney, 2003; Stegeman et al., 2010).

Existing modeling frameworks for simulation of between-unit spread and control of disease represent within-unit disease dynamics in different ways. Some do not consider within-unit dynamics at all, either for the sake of conceptual simplicity or due to lack of available data (Savill et al., 2007; Schoenbaum and Disney, 2003). In others (*e.g.*, Garner and Beckett, 2005; Garner and Lack, 1995; Harvey et al., 2007; *NAADSM* Development Team, 2010), within-unit disease dynamics are not explicitly simulated, and disease states and durations apply to entire units, but allowances may be made so that changes in disease prevalence in infected units over time can be represented.

Some authors have suggested that representations of within-unit disease dynamics should be incorporated into models of between-unit transmission of disease (Carpenter et al., 2004; Kostova-Vassilevska, 2004). Some models explicitly represent these phenomena (*e.g.*, Bates et al., 2003a) albeit in ways that do not fully account for true individual-level variation.

Additionally, in many countries and situations, there is interest in modeling the dynamics of disease in populations characterized by variable levels of vaccine coverage and efficacy (Dubé et al., 2011). Limitations in an existing model of between-unit spread and control (Harvey et al., 2007) were found during attempts to apply this model to situations in countries in South America. The need for a model that more realistically simulates the process and effects of vaccination was identified in a meeting of subject matter experts from North and South America (Dubé et al., 2008, 2011).

Finally, as a practical matter, it is difficult to develop justifiable parameters for models of between-unit spread without considering within-unit disease dynamics. Consider, for example, the notion of the duration of a disease state. The vast majority of data on the durations of disease states are collected at the level of individual infected animals (Bates et al., 2003b; Bouma et al., 2009; Mardones et al., 2010; Perkins and Swayne, 2003; Spickler et al., 2008), rather than at the level of the unit. These individual animal-level durations, together with parameters that describe within-unit disease transmission, determine unit-level disease state durations.

Here we present an approach that can be used to take advantage of this kind of individual-level information in a structured, reproducible fashion to inform models of between-unit disease spread and control. The purpose of this paper is three-fold: 1) to describe a computationally efficient, individual-based, fully stochastic framework for modeling within-unit disease progression, disease spread, and vaccination; 2) to discuss procedures employed to verify

and validate the model; and 3) to briefly illustrate the utility of the framework by constructing simulation models of the dynamics of foot-and-mouth disease (FMD) and highly pathogenic avian influenza (HPAI) infection in representative situations. We also discuss the practicality and potential value of incorporating this conceptual within-unit modeling framework directly into models of between-unit spread, detection, and control of disease.

3.2. Materials and Methods

3.2.1. Description and implementation of the conceptual model

The conceptual model is a stochastic, state transition framework that operates in discrete time steps of fixed duration. The modeler is responsible for selecting the time step (*e.g.*, days, ½ days, or hours) most appropriate to the question of interest. Every individual within a closed population is explicitly simulated. At each time step, every individual is assumed to have one of several disease or immune states, as shown in Table 3-1. Upon infection, individuals progress through each of several infected states. The number of time steps that each individual spends in each of these infected states is stochastically determined from an appropriate, user-defined distribution, provided in the form of a probability density function. Infection may be transmitted among individuals within the population, which is assumed to be randomly mixing, upon adequate exposure to disease. Disease mortality and mortality due to causes unrelated to the disease under consideration may both be simulated, and the effects of vaccination of all or part of the population may also be included. An overview of the model framework is provided in Figure 3-1. Details are presented in section 3.3.1.

The conceptual model framework has been implemented in a computer program, called *WH*, for Microsoft Windows platforms. The program and its source code, written in the Delphi programming language (Borland Software Corporation, 2002), are published under an open

source software license (Free Software Foundation, 2007) and are distributed via the internet at *http://www.naadsm.org/wh*. This program was used to generate all results presented in this paper.

3.2.2. Verification and validation of the model

Verification of the computational correctness of the modeling application and ongoing efforts to validate the conceptual modeling framework (Reeves et al., 2011) are described in section 3.3.2.

3.2.3. Modeling the within-herd spread of foot-and-mouth disease

Three scenarios representing the spread of foot-and-mouth disease (FMD) in a hypothetical dairy herd of 1000 cattle were constructed based on the example of Carpenter et al. (2004), and were simulated using the described modeling framework. Parameters for these scenarios are summarized in Table 3-2. Each scenario used a different distribution for the within-herd transmission parameter (*i.e.*, the number of adequate exposures per infectious individual per time step), also based on Carpenter et al. (2004), to represent low, moderate, and high rates of within-herd disease spread. In each case, the herd was assumed to be entirely susceptible to infection by FMD at the outset of the simulation. Parameters representing the durations of disease states were adapted from the report of Mardones et al. (2010).

Simulated outbreaks of FMD proceeded in daily time steps. For each simulated outbreak, the time to disease detection was determined, again based on the example of Carpenter et al. (2004). Detection of disease was assumed to be visual, and based on a threshold value for prevalence of individuals showing clinical signs of disease: disease was considered to be detected on the day that the specified threshold was met. Two detection thresholds, 1% and 5%,

were considered. The prevalence of all infected individuals within the herd (*i.e.*, individuals in the latent and subclinical states, as well as individuals showing clinical signs of disease) was determined for the day on which the detection thresholds were met.

One thousand iterations were run for each scenario. Summary statistics and figures were generated using the statistical software package R, version 2.14.2, and associated libraries (Maechler et al., 2011; R Development Core Team, 2012). Results were compared to the similar model of Carpenter et al. (2004).

3.2.4. Modeling the within-flock spread of highly pathogenic avian influenza

Three scenarios representing the spread of highly pathogenic avian influenza (HPAI) in broiler chickens were constructed, based on the example of Savill et al. (2006). Parameters are summarized in Table 3-3. Disease spread was simulated in a population of 20,000 birds, a population size typical of commercial broiler houses for the southeastern United States (Dorea et al., 2010; Patyk et al., in preparation). The three scenarios simulated the spread of disease in populations with levels of effective vaccine immunity of 0%, 50%, and 90%. Parameters for disease state durations, disease mortality, and transmission rates representative of the H5N1 strain of HPAI were derived from published reports (Bouma et al., 2009; Easterday et al., 1997; Spickler et al., 2008; Swayne and Halvorson, 2008).

Simulated outbreaks of HPAI proceeded in hourly time steps. Detection of disease was based on incidence of mortality. Two detection thresholds were used: within-flock mortality of 0.2% over a single 24-hour period (Dorea et al., 2010; Vieira et al., 2009); and within-flock mortality of 0.5% on each of two consecutive 24-hour periods (Bos et al., 2007).

The number of days to disease detection was recorded for each simulated outbreak based on each of the two detection criteria. The actual prevalence of infection among living birds in

the flock at the time of detection was also determined. Results generated by 1000 iterations of each scenario were compared to outcomes from similar investigations (Dorea et al., 2010; Savill et al., 2006).

3.3. Results

3.3.1. The conceptual model

An overview of the model framework, which is composed of four distinct but interrelated subcomponents, is provided in Figure 3-1. The four major subcomponents of the model framework simulate the following events: disease spread among individuals (Section 3.3.1.1); disease progression in infected individuals, disease mortality, and progression of immunity (Section 3.3.1.2); background mortality *(i.e.*, death unrelated to disease) (Section 3.3.1.3); and the process of vaccination itself (Section 3.3.1.4).

3.3.1.1. Subcomponent for spread of disease among individuals

The model simulates spread of disease from infectious to susceptible individuals by contact or exposure. A transmission parameter (the number of secondary infections per infectious individual per time step) is specified as a distribution by the user. This distribution represents the variability in the number of secondary cases that arise per infectious case per time step. The number of adequate exposures that occur in each time step for each infectious individual is determined stochastically by the model from this distribution. Other individuals in the population are selected at random as the targets of these adequate exposures. Susceptible targets will subsequently become infected.

For large populations, in cases where there are potentially many infected individuals and many exposures, it is not practical, simply as a result of the large number of calculations that would be required, to simulate every single exposure as a random occurrence between two

individuals. Computational efficiency can be substantially increased, however, by using an approximation illustrated in Figure 3-2. The algorithm used in the model framework first determines how many total adequate exposures occur during a single time step and then makes use of a distribution described by Gani (2002, 2004) and an approach to calculation using Stirling numbers of the second kind (Abramowitz and Stegun, 1972) to determine how many individuals are exposed at least once.

Once the number of individuals which will receive at least one adequate exposure has been determined, the number of these individuals which are susceptible and will become infected is modeled as a hypergeometric process (Vose, 1996): the total (finite) population (designated M) consists of all living individuals, and the subpopulation of interest includes all susceptible individuals (D). From the total population, the number of individuals who receive at least one adequate contact will be selected (n). A hypergeometric distribution defined by these three parameters [Hypergeometric(n, D, M)] is then used to stochastically determine how many susceptible individuals were selected. These individuals will become infected during this time step. A similar calculation is made to determine how many vaccinated but not yet immune individuals will become infected in each time step (Figure 3-2). In our tests, use of the approximation described above reduces required computational time for the model, in some cases from hours to seconds, without having a substantial effect on the model outcome (data not shown).

3.3.1.2. Subcomponent for disease progression, disease mortality, and progression of immunity

At each time step, disease transitions may be made from one state to the next (latent to subclinical, subclinical to clinical, *etc*.) as shown in Table 3-1 and Figure 3-3. The number of time steps that an infected individual will spend in the latent, subclinical, or clinical disease

states is determined stochastically from user-provided distributions that represent the durations of these individual-level states. Similarly, the number of time steps that a naturally or vaccine immune individual will remain immune is determined from appropriate, user-specified distributions. It is possible to represent states with durations of zero time steps. This capability allows the modeler to exclude or skip disease states that are not of interest: individuals with a subclinical state duration of zero time steps, for example, will progress from the latent state directly to the clinical state.

When an individual's clinical disease period ends, death from disease is modeled as a Bernoulli trial (Law and Kelton, 2000): whether this individual will die from disease or recover is determined by the probability that disease will result in death.

3.3.1.3. Subcomponent for mortality unrelated to disease

All individuals regardless of their disease or immune state are equally likely to die of non-disease-related causes. Death unrelated to disease is modeled as a binomial process (Vose, 1996): at each time step, the number of individuals who will die from causes unrelated to disease is determined using a binomial distribution based on the number of living individuals in the population and the time-step-specific probability that an individual will die of causes unrelated to disease.

3.3.1.4. Subcomponent for vaccination

When vaccination occurs, a user-specified model parameter determines the proportion of the population to be vaccinated (Figure 3-4). Living individuals are selected at random from the population to be vaccinated, regardless of their disease or immune state. A second user-specified proportion represents vaccine efficacy, *i.e.*, the proportion of vaccinated individuals which will develop effective immunity. The time required for onset of immunity after vaccination and the

duration of immunity for each effectively vaccinated individual are determined from user-provided distributions.

Vaccination may precede or follow the introduction of disease, as shown in Figure 3-1. The model may be applied to investigate the effects of different levels of vaccine coverage (*i.e.*, the proportion of a population vaccinated) and vaccine efficacy.

3.3.1.5. Model outputs

Among the outputs generated by the model are the following: time-step-specific and cumulative incidence of infection; time-step-specific prevalence of each of the disease and immune states listed in Table 3-1 (*e.g.*, prevalence of latent, subclinical, clinical, or all infected individuals, or prevalence of vaccine immunity); and time-step-specific and cumulative mortality, due either to the disease of interest or to causes unrelated to the disease of interest.

3.3.2. Verification and validation of the model

Reeves et al. (2011) presented a set of suggestions intended to aid in the process of model evaluation. Here, we describe our efforts to follow these suggestions.

3.3.2.1. The purpose of and motivation for the conceptual model

The need for a model that realistically represents within-unit dynamics of disease and effects of vaccination arose during an effort to apply an existing between-unit model of disease spread and control (Harvey et al., 2007) in countries in South America (Dubé et al., 2008, 2011). In consultation with subject matter experts representing nine countries in North and South America, it was determined that existing models did not adequately represent such characteristics, nor did they fully take advantage of within-unit dynamics to inform approaches for disease detection (Dubé et al., 2008). The model described here is intended to more realistically, and more

credibly, represent these characteristics, in a computationally efficient way, such that it would be practical to incorporate a model of within-unit disease dynamics into a larger model of between-unit disease spread and control.

3.3.2.2. Verification of the computational implementation of the model

Static and dynamic testing of the computational implementation (Fairley, 1978; Whitner and Balci, 1989) of the model described here have been conducted. Static testing involved the examination by software engineers not directly involved in the initial development of the model of algorithms and code originally developed by the authors. Dynamic testing involving the development and detailed analysis of test cases run with the modeling application has also been carried out by the authors.

3.3.2.3. Assessing the conceptual validity of the model

The conceptual model and its computational implementation were presented at a follow-up workshop involving many of the subject matter experts involved in its initial conception. This expert review constituted one effort to assess the face validity of the model (Rykiel, 1996). Subsequent application of the model (Patyk et al., in preparation; Sanderson et al., 2009; USDA-APHIS-VS-CEAH, 2009; USDHS-STD, 2012) and evaluation of results generated constituted a second, and ongoing, effort to establish the conceptual validity of the model.

3.3.2.4. Other considerations for model evaluation

In addition to the steps described above, this report represents an effort to follow several additional recommendations for the construction and evaluation of models of animal disease, namely, by providing a description of the conceptual model and its assumptions; by describing

the data used to generate results; and by comparing model outcomes to those of other models (Reeves et al., 2011).

3.3.3. Detection of FMD based on prevalence of clinical disease

Results of the scenarios of FMD spread in a herd of dairy cattle are presented in Figure 3-5 and Table 3-4. The rate of disease spread (whether low, moderate, or high as shown in Table 3-2) had little effect on the overall duration of simulated outbreaks in these scenarios: median outbreak duration ranged from 31 to 34 days in all cases. The use of a threshold of 1% prevalence of clinical disease versus 5% similarly had little effect on time to detection: the median time to detection varied by only 1 to 2 days for all scenarios. The 1 to 2 day delay did, however have a considerable impact on the prevalence of infection (*i.e.*, the total proportion of infected animals, whether they showed clinical signs or not) present in herds at the time of detection. When the lower threshold for disease detection was used, the median prevalence of infection at the time of detection ranged from 37% to 67%. By marked contrast, when the higher detection threshold was used, median prevalence of infection at the time of detection ranged from 91% to 98%.

3.3.4. Detection of HPAI based on mortality in broiler chickens

Outcomes of scenarios for HPAI for three levels of vaccine coverage and two detection thresholds (described in Table 3-3) are shown in Figure 3-6 and Table 3-5. Results are similar to those described above for scenarios of FMD: the use of the higher threshold for detection had little impact on the time to detection, adding only 1.1 to 1.5 days to the median time to detection based on the lower threshold, but the effect of the delay can again be observed in the prevalence of infection at the time of detection. In the case where vaccination was not employed, the higher

detection threshold (and the corresponding delay) resulted in disease detection on average only after the peak of the epidemic had passed: by the time disease was detected using the higher threshold in this case, the median prevalence of infection in the flock was already declining.

The use of vaccination also delayed time to detection in these scenarios: median time to detection roughly doubled in flocks with 90% vaccine coverage versus those without vaccination, regardless of the detection threshold. This effect was accompanied, however, by a 15-fold reduction in prevalence of infection at the time of detection in the case of the lower detection threshold (from 99.8% to 6.5%), and a 10-fold reduction in the case of the more stringent detection threshold (from 72% to 6.9%).

3.4. Discussion

3.4.1. The conceptual model

The conceptual model of within-unit disease spread described here is an elaboration of concepts and approaches used previously (*e.g.*, Abbey, 1952; Bates et al., 2003a; Carpenter et al., 2004; Perez et al., 2002; Savill et al., 2006). This framework is distinct, however, in that the durations of each disease state and the number of adequate exposures generated by each infectious individual are truly applied to individuals: earlier models either are deterministic or draw a single value from each of the individual-level distributions and apply those values to every individual within an iteration of the model (Bates et al., 2003b; Carpenter et al., 2004; Perez et al., 2002). In other words, these other models draw new values from the individual-level distributions only once per iteration, and treat all individuals as though they are equivalent. This approach has the advantages of simplicity and computational efficiency but is not a realistic representation of variability among individuals. By utilizing improved computer power as well

as the algorithm described in Section 2.1.1, the current model is able to more realistically simulate truly individual-level variation.

As demonstrated by investigations that have used the modeling framework described here (Patyk et al., in preparation; Sanderson et al., 2009; USDA-APHIS-VS-CEAH, 2009; USDHS-STD, 2012), results generated by models of within-unit disease dynamics can be used to inform and to reduce some of the subjectivity associated with the development of parameters for representations of the spread and control of disease among farms or premises. The incorporation of the approach to modeling of within-unit disease dynamics should improve the utility of models for emergency preparedness and response planning by making it possible to assess the value of different approaches to disease detection and surveillance.

3.4.2. Results of FMD and HPAI modeling

The results of the FMD modeling illustration reported above are consistent with earlier work done by Carpenter et al. (2004). Using similar models and contact rates, they concluded that detection of disease would occur on average between 10 and 13.5 days. The corresponding range from this study (which used different data to represent disease state durations and individual-level stochastic contact rates, unlike the earlier report) is 8 to 10 days. Carpenter et al. reported that the range in the average within-herd prevalence of infection at the time of detection in their study was between 65% and 97%. Here we showed an analogous range of 37% to 98%, depending on the contact rate and detection threshold used.

Using a deterministic model of within-flock disease spread of HPAI, Dorea et al. (2010) reported that the average (mean) time to detection based on a detection threshold of 0.2% mortality over a 24-hour period was 5 days. The corresponding outcome from this study ranged from 1.8 to 3.1 days, with a median time to detection of 2.1 days. Dorea et al. assumed that

infected birds were latent for 2 days and infectious for 6 days, and modeled disease transmission in daily time steps. The shorter corresponding values (mean durations of 0.24 and 2.1 days for the latent and clinical periods, respectively) and the less coarse choice of time step likely account for this difference. Given the influence that just a few days can have in this setting, a more detailed evaluation would be helpful.

Savill et al. (2006) discussed the implications of the use of vaccination for HPAI on the so-called "silent spread" of disease in vaccinated flocks. We likewise show that HPAI can spread in flocks even with relatively high levels of vaccine efficacy and coverage, and that detection of disease will be delayed in vaccinated flocks. Given the very dramatic decreases in prevalence of disease in vaccinated flocks, however, the use of vaccination on balance might be beneficial to reduce the potential between-flock spread of disease.

3.5. Conclusions

The processes by which within-unit disease transmission occurs have immediate implications for detection and subsequent control of disease in a population, and likely for spread of disease between farms or premises as well. The simulation framework presented here provides model users with a straight-forward, computationally efficient tool with which to explore these processes. The simple role of chance can have a considerable impact on the initiation and progression of a disease outbreak, particularly in small populations or in early phases of epidemics when stochastic events influence whether a major outbreak will develop or if disease will die out relatively quickly. The stochastic, truly individual-based design of this framework provides the analyst with practical information about the range of outcomes that might be produced under the specified initial conditions. The data requirements of this model are modest and easily described to policy makers, response planners, and other stakeholders.

Table 3-1. Disease and immune transition states included in the conceptual framework for the stochastic simulation model of within-unit spread of disease.

Transition state	*Description and comments*
Susceptible	Susceptible individuals will become infected upon effective exposure to disease. Upon infection, susceptible individuals will make a transition to the latent state.
Latent	Latent individuals are infected, but not yet infectious or showing clinical signs of disease. At the end of its latent period, an individual will make the transition to the sublinical state.
Subclinical	Infected and infectious (i.e., capable of transmitting disease), but not yet showing clinical signs of disease. At the end of its subclinical period, an individual will make the transition to the clinical state.
Clinical	Infected, infectious and showing clinical signs of disease. Upon the end of its clinical state, an individual will transition either to the recovered or to the dead-from-disease state.
Naturally immune/recovered	An infected individual that completes its disease cycle and recovers from disease will have this state. Recovered individuals are no longer infected or infectious, and cannot become infected upon exposure to disease. This state may be permanent, or may last for a specified length of time, after which a recovered individual will become susceptible to infection.
Dead from disease	An infected individual that completes its disease cycle and dies as a result of infection will have this state. This state is permanent.
Dead from causes unrelated to disease	Individuals in any state may die from causes unrelated to disease. The probability of death unrelated to disease is equal for individuals in all disease states. This state is permanent.
Vaccinated but not yet immune to disease	Individuals have been vaccinated but have not yet mounted an immune response. These individuals are susceptible to disease.
Vaccinated and immune to disease	Adequate time to develop an immune response has passed in these vaccinated individuals. These individuals will be immune to infection. This state may be permanent, or may last for a specified length of time, after which a vaccine immune individual will become susceptible to infection.
Not effectively vaccinated	These individuals will not develop an immune response after vaccination, and will remain susceptible to infection.

Table 3-2. Parameters used for models of foot-and-mouth disease.

Parameter description	*Distribution/Value*[1]	*Notes and references*
Population size (number of cattle)	1000	Based on Carpenter et al. (2004).
Latent period (days)	Weibull(1.782, 3.974)	Mardones et al. (2010).
Subclinical infectious period (days)	Gamma(1.222, 1.672)	Mardones et al. (2010).
Clinical infectious period (days)	Weibull(1.453, 3.544)	Derived from Mardones et al. (2010)., based on reported durations of the subclinical infectious period and the overall infectious period.
Number of adequate exposures per day	High: Poisson(54.1) Moderate: Poisson(21.8) Low: Poisson(13.7)	Means from Carpenter et al. (2004); within-herd contact was assumed to follow a Poisson process (Vose, 1996).
Detection threshold based on prevalence of clinical cattle	1%, 5%	Based on Carpenter et al. (2004).

[1] Probability density function parameters and calculations follow Hill and Reeves (2006) and Vose (1996).

Table 3-3. Parameters used for models of highly pathogenic avian influenza.

Parameter description	*Distribution/Value*[1]	*Notes and references*
Population size (number of birds)	88,000	Median size of a broiler chicken flock in South Carolina (Patyk et al., in preparation).
Latent period (hours)	Gamma(1.34, 4.3)	Derived from Bouma et al., 2009.
Subclinical infectious period (hours)	0	Because detection is based on mortality, and because subclinically and clinically infectious individuals are equally infectious in the conceptual framework, there is no practical distinction between the subclinical and clinical infectious stages for the purposes of the models of HPAI used here. Consequently, all infectious individuals are assumed to be clinical.
Clinical infectious period (hours)	Gamma(13.36, 3.77)	Derived from Bouma et al., 2009.
Number of adequate exposures per hour	Poisson(1.375)	Mean derived from Bouma et al., 2009; within-flock contact was assumed to follow a Poisson process (Vose, 1996).
Probability that an infected bird will die from disease	0.90	Easterday et al. (1997); Spickler et al. (2008); Swayne and Halvorson (2008).
Vaccination coverage	0%, 50%, 90%	Based on Savill et al. (2006b).
Vaccine efficacy	100%	Based on Savill et al. (2006b).
Detection threshold based on total mortality	0.2% during one 24-hour period	Dorea et al. (2010).
	0.5% during each of two consecutive 24-hour periods	Bos et al., 2007

[1] Probability density function parameters and calculations follow Hill and Reeves (2006) and Vose (1996).

Table 3-4. Outcomes produced by models of foot-and-mouth disease for three levels of disease spread and two detection thresholds based on prevalence of clinical disease.

All results are based on 1000 iterations of each stochastic model.

Model outcome	***Rate of disease spread***		
	Low	*Moderate*	*High*
Outbreak duration (days)[1]	34 (0 - 49)	33 (1 - 45)	31 (1 - 49)
Detection based on threshold of 1% prevalence of clinical disease			
Percent of outbreaks detected	98.4%	98.8%	98.8%
Time to detection (days) [1]	8 (4 - 18)	8 (3 - 17)	7 (3 - 18)
Prevalence of infection at time of detection[1]	0.37 (0.12 - 0.696)	0.4605 (0.172 - 0.873)	0.673 (0.309 - 0.988)
Detection based on threshold of 5% prevalence of clinical disease			
Percent of outbreaks detected	98.4%	98.8%	98.8%
Time to detection (days) [1]	10 (6 - 19)	9 (5 - 18)	8 (4 - 19)
Prevalence of infection at time of detection[1]	0.907 (0.658 - 0.968)	0.959 (0.816 - 0.985)	0.983 (0.955 - 0.994)

[1] Values shown indicate the median and range from 1000 stochastic iterations of each model.

Table 3-5. Outcomes produced by models of highly pathogenic avian influenza for three levels of vaccine coverage and two detection thresholds based on mortality.

All results are based on 1000 iterations of each stochastic model.

Model outcome	***Vaccine coverage***		
	0%	*50%*	*90%*
Outbreak duration (days)[1]	7 (6.2 - 9.2)	7.2 (6.4 - 8.9)	10.1 (1 - 14.2)
Detection based on threshold of 0.2% mortality over a 24-hour period			
Percent of outbreaks detected	100%	100%	100%
Time to detection (days) [1]	2.1 (1.8 - 3.1)	2.5 (2 - 3.6)	4.2 (3.1 - 6.9)
Prevalence of infection at time of detection[1]	0.998 (0.998 - 0.999)	0.498 (0.497 - 0.498)	0.065 (0.049 - 0.076)
Detection based on threshold of 0.5% mortality observed during each of two consecutive 24-hour periods			
Percent of outbreaks detected	100%	100%	100%
Time to detection (days) [1]	3.2 (2.9 - 4.2)	3.7 (3.2 - 4.8)	5.7 (4.6 - 8.3)
Prevalence of infection at time of detection[1]	0.717 (0.68 - 0.75)	0.352 (0.331 - 0.377)	0.069 (0.063 - 0.075)

[1] Values shown indicate the median and range from 1000 stochastic iterations of each model.

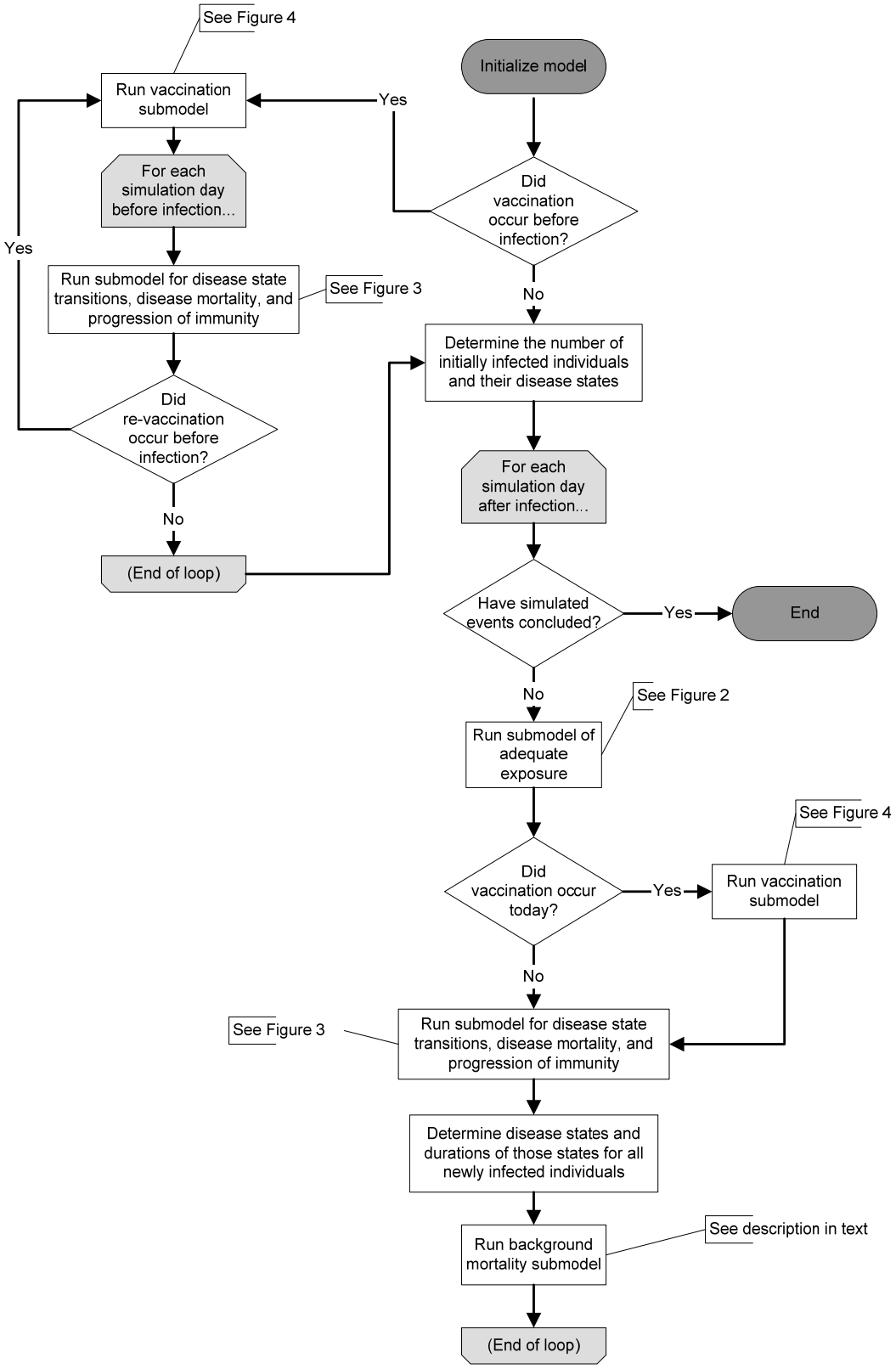

Figure 3-1. Schematic representation of the processes included in the model of within-unit spread of disease, as described in section 3.3.1.

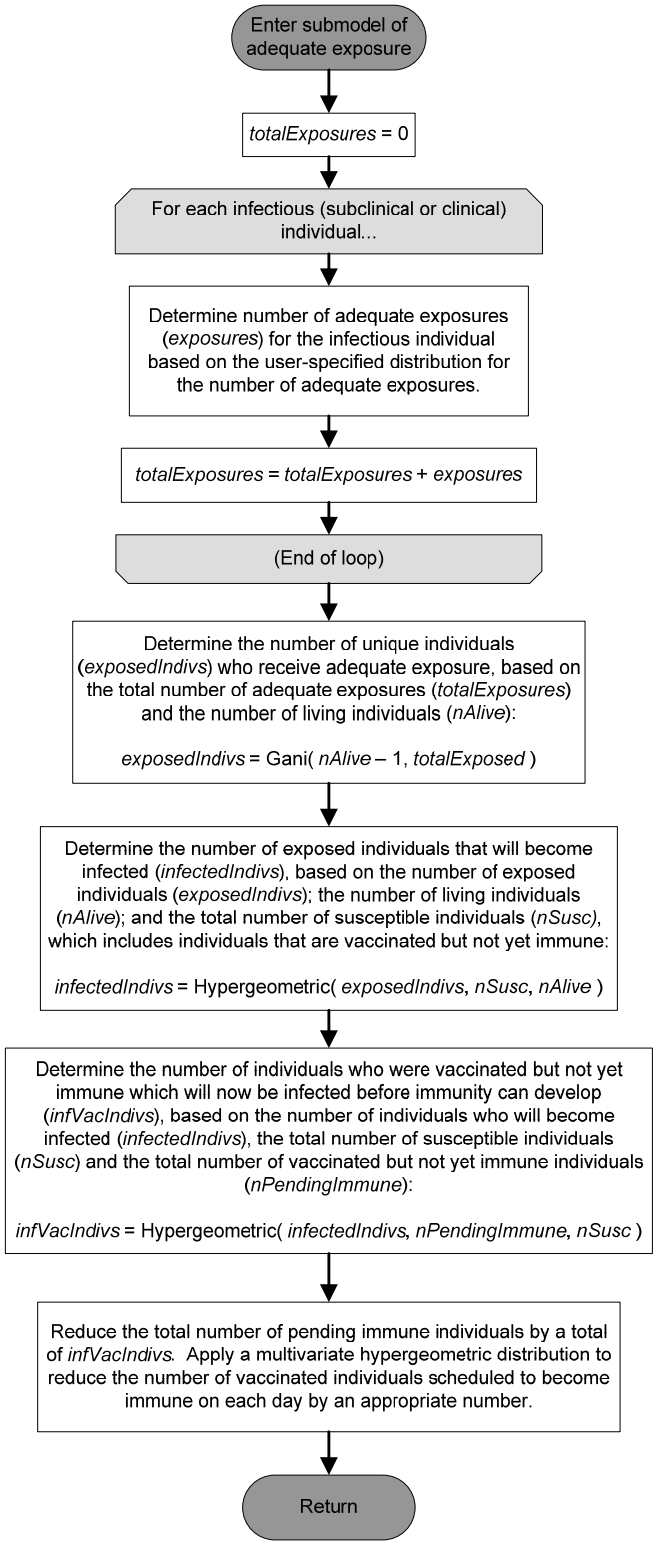

Figure 3-2. Schematic representation of the approximation algorithm employed by the model to improve computational efficiency associated with the determination of the number of new cases in each time step of the model, as described in section 3.3.1.1.

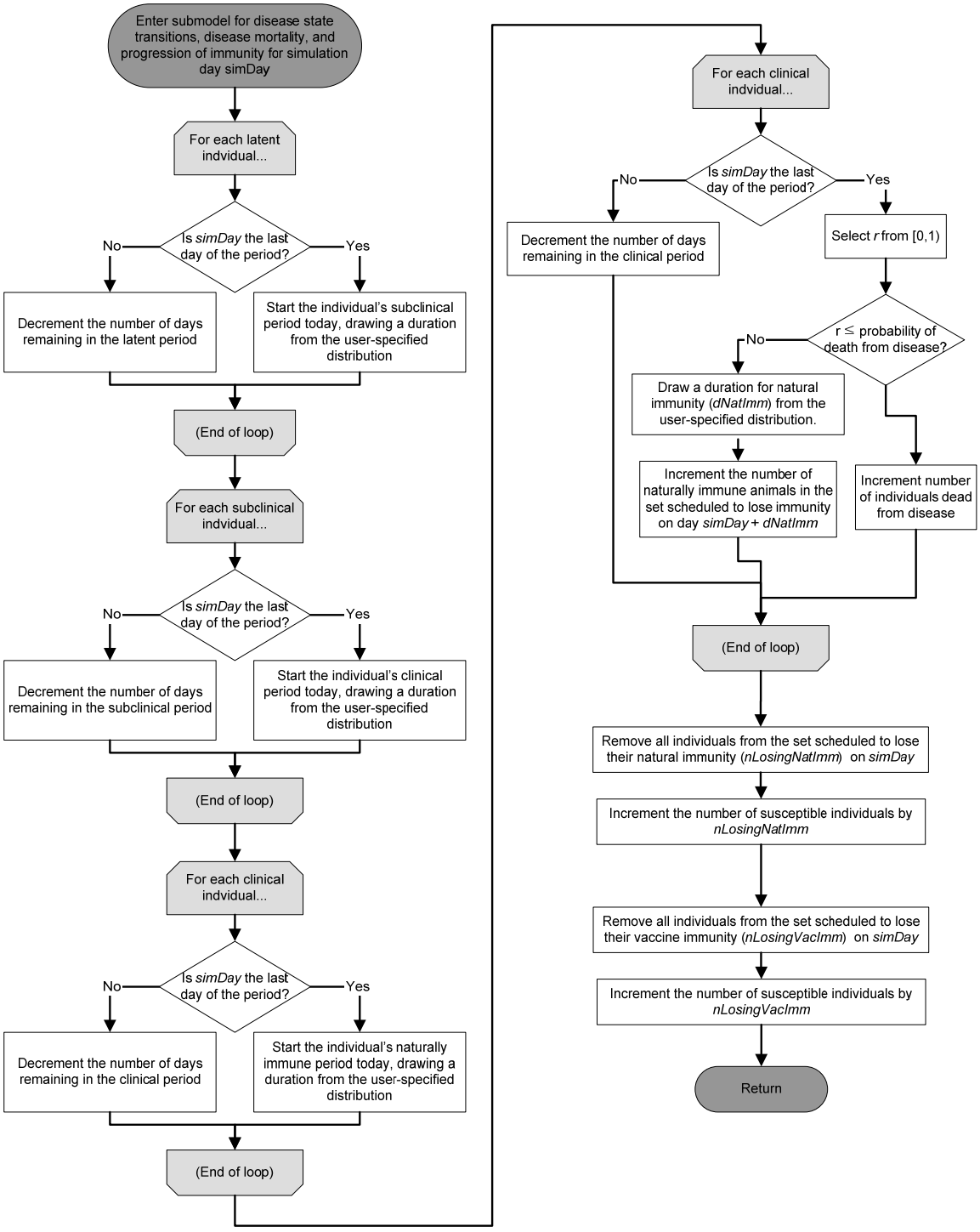

Figure 3-3. Schematic representation of disease progression (*i.e.*, disease state transitions), mortality, and immunity in the model, as described in section 3.3.1.2.

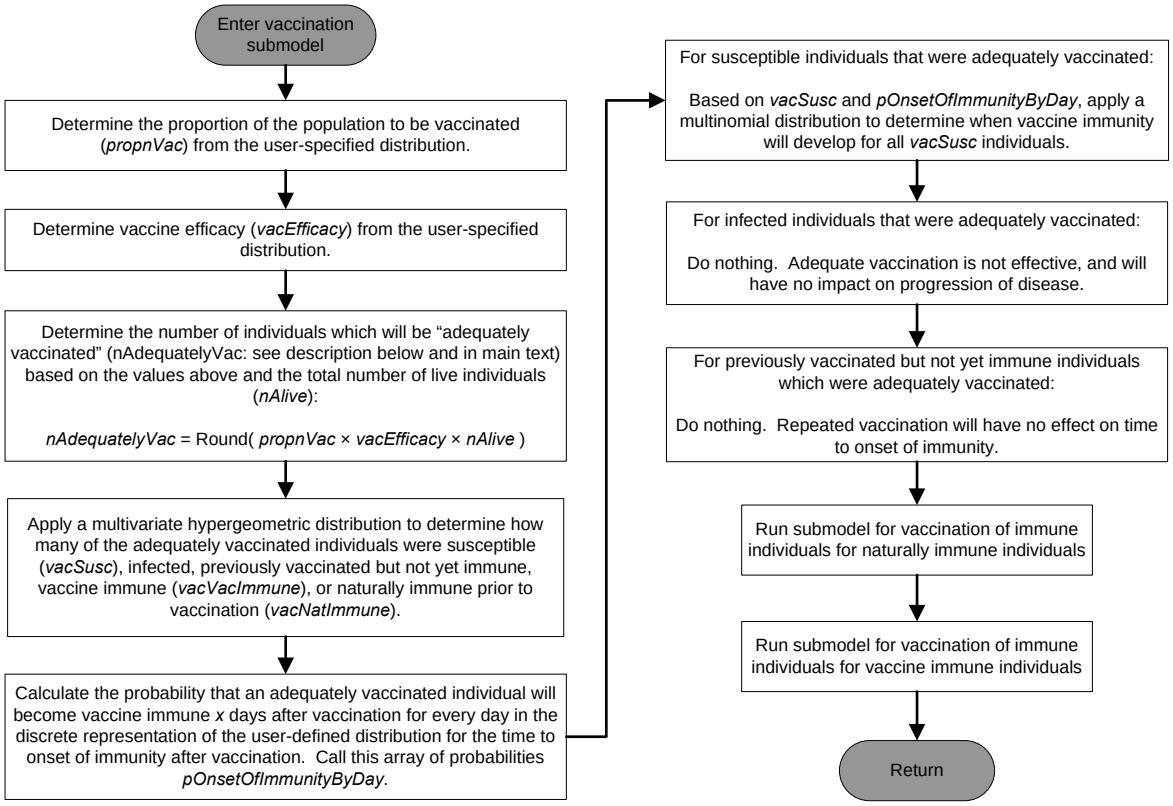

Figure 3-4. Schematic representation of the vaccination subcomponent used in the model, as described in section 3.3.1.4.

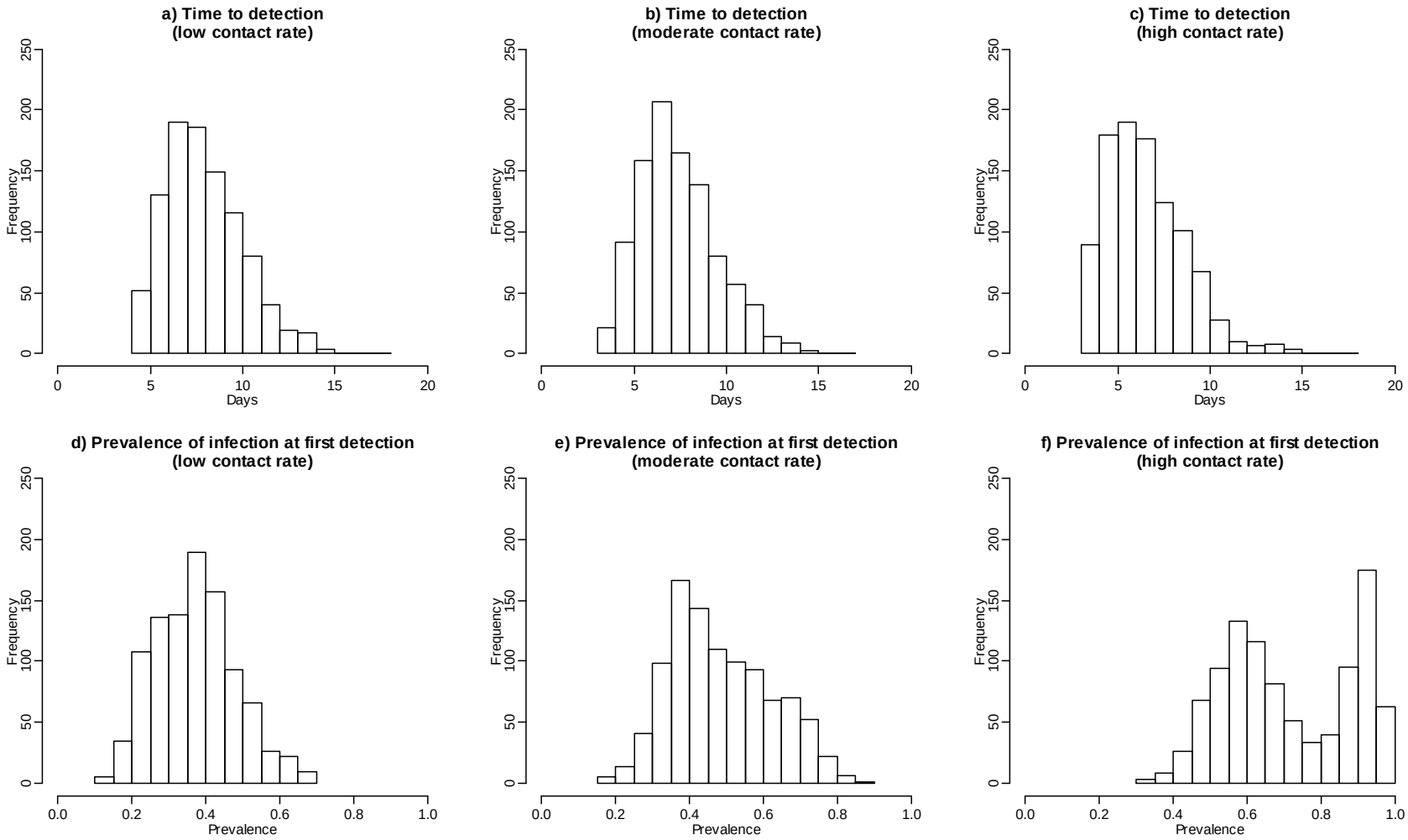

Figure 3-5. Results of models of within-herd spread of foot-and-mouth disease, using detection threshold of 1% prevalence of clinical disease. Columns show the effects of different contact rates. Top row: time to detection. Bottom row: total prevalence of infection at time of first detection.

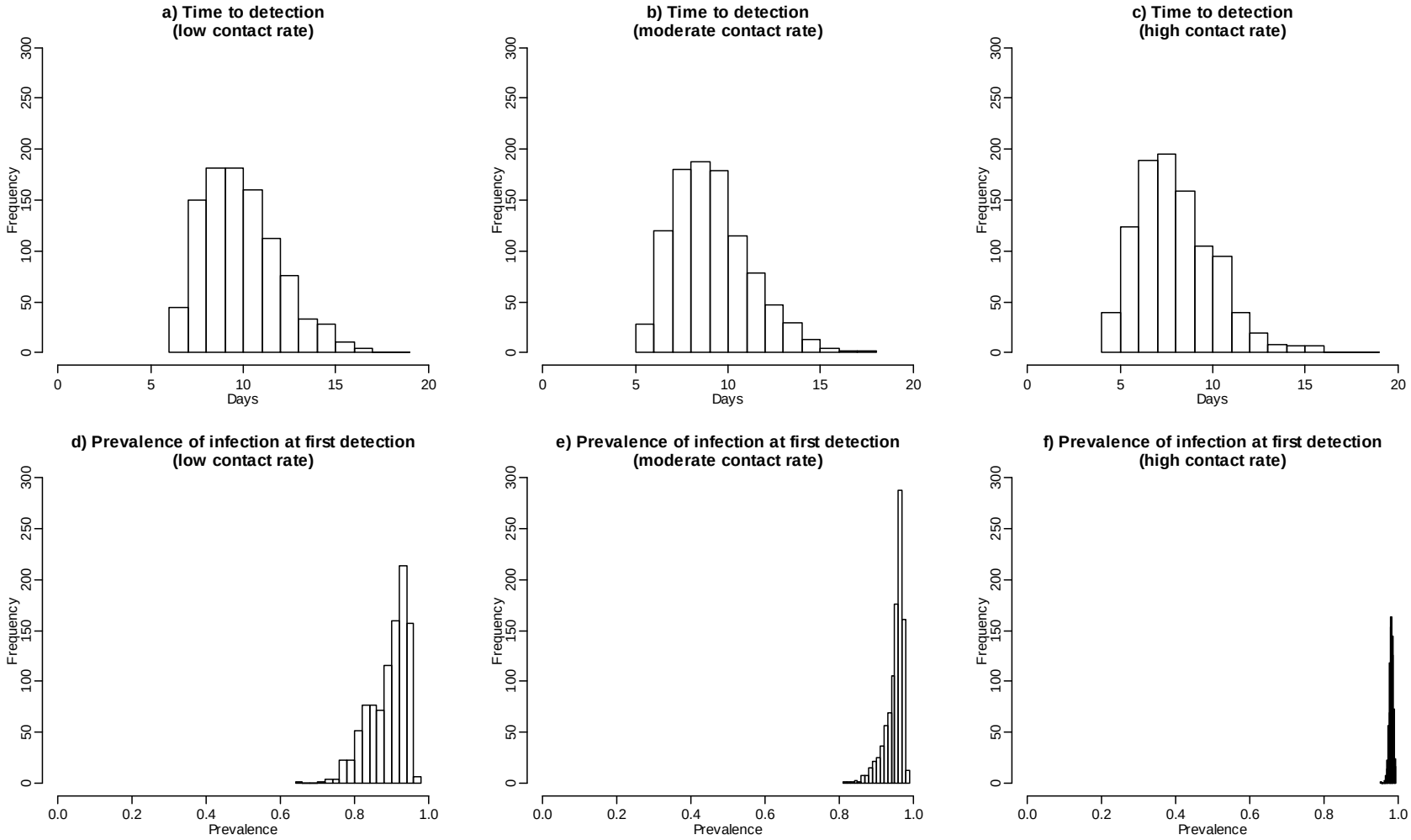

Figure 3-6. Results of models of within-flock spread of avian influenza, using detection threshold of 5% prevalence of clinical disease. Columns show the effects of different contact rates. Top row: time to detection. Bottom row: total prevalence of infection at time of first detection.

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4. A comparison of actual versus synthetic population datasets for simulation modeling of the spread and control of highly pathogenic avian influenza (H5N1) among commercial poultry flocks in South Carolina, United States

Summary

Spatially explicit models of the spread and control of disease in populations of livestock and poultry rely heavily upon valid representations of the populations of interest, including such characteristics as the geographic locations of farms and their proximity to other farms in the population. Unfortunately, in the United States, little information regarding the locations of actual farm premises is available, and modeling work often makes use of artificially generated population datasets. In order to evaluate the accuracy and validity of the use of such artificially generated datasets, we compared the outcomes of mechanistic epidemiologic simulation models that were run using an accurate population dataset to those of models that made use of several readily available synthetic population datasets for animal populations. We chose to simulate the spread and control of the H5N1 strain of highly pathogenic influenza among commercial poultry in the state of South Carolina, a system that was recently well characterized for the purposes of epidemiologic simulation modeling. Although there was generally good qualitative agreement regarding the relative efficacies of potential disease control measures among models run using various population datasets, the quantitative differences in model outcomes could be substantial. When quantitative outcomes from epidemiologic models are desired or required, such as in the case of estimation of resources needed for disease response, care should be taken to adequately capture or describe the uncertainty in model-based outcomes due to the use of synthetic population datasets.

4.1. Introduction

Mathematical and simulation-based models are often used to estimate the potential impact and consequences of disease outbreaks in livestock and poultry populations. Such models are used to inform policy decisions regarding disease control methods and outbreak response plans (Bates et al., 2003a, 2003c; Keeling et al., 2001; Tildesley et al., 2006) and to estimate the resources needed for outbreak response (USDA-APHIS-VS-CEAH, 2009). These assessments may be primarily qualitative in nature, with an emphasis, for example, on comparing the relative efficacies of different strategies for disease control (*e.g.*, Premashthira, 2012; Schoenbaum and Disney, 2003); they may be intended to provide quantitative information to guide estimates of specific resource needs (*e.g.*, USDA-APHIS-VS-CEAH, 2009); or they may include elements of both.

Several epidemiologic models are spatially explicit: they consider the number and locations of the epidemiologic units of interest (often herds, flocks, or farms) in the population under consideration. These characteristics of the population then influence factors as the rate or probability of spread of disease among units in the population. In most cases, these models require at a minimum a point coordinate to represent the geo-location of each unit in the study population (Bates et al., 2003b; Garner and Beckett, 2005; Harvey et al., 2007; Stevenson et al., 2012).

In the United States, limited information regarding the locations of farm premises is available. Such detailed data either does not exist (with certain exceptions) or is not accessible by the public. Spatially explicit veterinary epidemiologic modeling in the United States, then, often relies on artificially generated population datasets. Some of the datasets used have been purely artificial, with characteristics thought to be broadly representative of different regions of

the US (*e.g.*, Schoenbaum and Disney, 2003). More recently, considerable attention has been devoted to the construction of population datasets from county- or state-level farm demographic data (USDA-NASS, 2004, 2009), with varying degrees of effort expended to ensure that the resulting spatial distributions of farms are realistic (Bruhn et al., 2012; Geter, 2006; Melius, 2007; Melius et al., 2006). Such datasets have been called "synthetic" (Bruhn et al., 2012; Rorres et al., 2011a, 2011b; Tildesley et al., 2012). In at least once case, it has been possible to generate a synthetic population dataset directly from actual farm-level location information (Martin, 2009; Patyk et al., in preparation).

In this study, we sought to compare the outcomes of epidemiologic models run with an accurate population dataset to those of models that made use of several available synthetic population datasets produced specifically for use in veterinary epidemiologic simulation modeling. For this purpose, we chose to simulate the spread and control of the H5N1 strain of highly pathogenic avian influenza (HPAI) in commercial poultry flocks in the state of South Carolina. This setting was attractive for several reasons: 1) an accurate dataset for commercial poultry in the state, which includes premises locations, exists at the South Carolina animal health authority at the Clemson University Livestock Poultry Health Division; 2) several synthetic datasets representing the poultry population in the state are available; and 3) a detailed set of input parameters for an epidemiologic model of HPAI in South Carolina was recently developed (Patyk et al., in preparation). Within this context, this study is intended to address the following questions:

1. How similar (or dissimilar) are the sizes, spatial distributions, and densities of several synthetic population datasets relative to one another, as well as to a reliable reference dataset that contains information on actual premises?

2. Does the use of synthetic datasets lead to different qualitative conclusions from modeling work regarding the efficacies of various strategies for disease control, relative to conclusions made based on the reference population dataset?
3. Does the use of synthetic datasets affect quantitative conclusions regarding outcomes of epidemiologic interest (such as outbreak duration, cumulative incidence of disease, and other model-produced outputs) relative to conclusions made based on the reference dataset?

4.2. Materials and Methods

The conceptual modeling framework provided by the *North American Animal Disease Spread Model* (*NAADSM*) version 3.2 (Harvey et al., 2007; *NAADSM* Development Team, 2010b) was used to develop the simulation models presented in this study. *NAADSM* is a spatially explicit, stochastic state transition model for simulating the spread and control of highly infectious diseases of animals. Disease spread in *NAADSM* is simulated at the unit (*i.e.*, flock or premises) level. Each unit in *NAADSM* is characterized by its production type, its size (the number of animals in the unit), and its location (specified by latitude/longitude coordinates). The population datasets used in this study are described in section 4.2.1.

A comprehensive set of input parameters suitable for simulating the spread and control of HPAI in the state of South Carolina was previously developed and described (Patyk et al., in preparation). These parameters were used as a basis for the disease control scenarios for this study, described in section 4.2.2.

We utilized the publicly available source code for *NAADSM* version 3.2.18 (*http://www.naadsm.org*) and introduced modifications into the application so that, in each iteration of the stochastic model (that is, in each simulated outbreak), one flock from the

population is selected at random to be the initially infected unit for that particular simulated outbreak, from which disease might spread. This change was made to ensure that subsequent conclusions were not unduly influenced by the location of any single flock in each dataset. The modified version, called "Wheatland", is available via the *NAADSM* website (*NAADSM* Development Team, 2012).

4.2.1. Population datasets

A total of five population datasets were used for this study, as described in Table 4-1 and illustrated in Figure 4-1. Throughout the remainder of this paper, names used for the population datasets are based on their original data sources as shown in the table.

4.2.1.1. The reference population dataset

The reference population dataset, provided by the Clemson University Livestock Poultry Health Division, contained information on the actual distribution and demographics of over 95% of all commercial poultry premises in the state of South Carolina as of March 2012. Geographic coordinates (latitude and longitude) are recorded for each of these commercial premises. This information was collected in cooperation with the poultry industry in the state of South Carolina, under an agreement that confidentiality of the data would be maintained, and that it could be used for disease control efforts. All work carried out with this reference dataset was performed at the Clemson University Livestock Poultry Health Division in Columbia, South Carolina, and no information that could be used to identify individual poultry operations was further distributed.

4.2.1.2. Synthetic population datasets

One of the synthetic datasets was generated directly from the reference dataset according to methods described by Martin (2009) and used previously by Patyk et al. (in preparation). This method is intended to produce an artificial population dataset based on actual data in such a way that prevents the identification of specific farms and protects producer privacy while maintaining realistic demographic and spatial distributions of premises in the population.

Three additional synthetic population datasets representing poultry in the state of South Carolina were also used. These population datasets were produced by the Lawrence Livermore National Laboratory (LLNL) (Melius, 2007), Research Triangle Institute (RTI) (Bruhn et al., 2007; Bruhn et al., 2012), and the United States Department of Agriculture (USDA) – Animal and Plant Health Inspection Service – Veterinary Services – Centers for Epidemiology and Animal Health (Geter, 2006). All three of these synthetic datasets were based on data from the 2002 US Census of Agriculture, published by the USDA – National Agricultural Statistics Service (NASS) (USDA-NASS, 2004), but different methodologies were used to produce locations of premises, production types, and flock sizes for these three datasets.

4.2.1.3. Modifications to LLNL, RTI, and USDA synthetic datasets

The three synthetic datasets described by LLNL, RTI, and USDA were modified so that a standard set of commercial poultry production types developed for use with the dataset from Clemson University (Patyk et al., in preparation) could be consistently applied, as described in sections 4.2.1.3.1 and 4.2.1.3.2.

4.2.1.3.1. Distinguishing between commercial and noncommercial poultry operations

Although the reference (CLPHD) dataset includes data on some small noncommercial flocks, this information is thought to represent only about one sixth of all such in the state.

Rather than rely on limited information or on artificially generated data to represent these small noncommercial flocks, we chose to focus solely on disease spread and control among commercial operations.

To ensure that only commercial flocks were included in each synthetic population dataset, we removed all flocks that were explicitly identified as noncommercial or backyard flocks. Not all of the synthetic datasets used for this study, however, distinguish between commercial and noncommercial poultry operations. To account for this, we made further assumptions about differences in size between commercial and noncommercial flocks. After a visual examination of the distributions of flock sizes in synthetic population datasets, a minimum threshold of either 1000 birds (LLNL and USDA) or 500 birds (RTI) was established to distinguish between commercial and noncommercial poultry operations (*i.e.*, smaller flocks were assumed not to be commercial operations). These thresholds are generally compatible with those used in US monitoring studies and in other modeling studies (Garber et al., 2007, 2009; Smith and Dunipace, 2011; USDA-APHIS-VS-CEAH-NAHMS, 2005, 2008). Poultry operations with fewer than the specified number of birds were then removed from datasets used for disease modeling.

4.2.1.3.2. Standardization and assignment of production types

Patyk et al. (in preparation) developed modeling parameters consistent with the *NAADSM* conceptual modeling framework for the following commercial poultry production types, which are identified in the reference (CLPHD) dataset: broilers, broiler breeders, broiler breeder pullets, egg layers, layer pullets, turkey brooders, turkey grow-out operations, quail, and quail breeders.

The original RTI and USDA datasets include the following production types: broilers, turkeys, pullets, and layers. In both cases, "broilers" were assumed to include broiler flocks and

broiler breeder flocks. In both the RTI and USDA datasets, flocks identified as "broilers" were reassigned at random to either the broiler or the broiler breeder types. Random assignment was based on the proportion of each type of flock present in the reference dataset. Similar operations were performed to divide turkey flocks into turkey brooder and turkey grow-out flocks, pullet flocks into layer pullets and broiler breeder pullets, and in the case of the RTI dataset, "other" flocks into quail and quail breeder flocks.

The population dataset obtained from LLNL contained several more production types, distinguished on the basis of flock size [*e.g.*, "broilers (small)" and "broilers (large)"]. Because model parameters described by Patyk et al. (in preparation) do not distinguish between flocks on the basis of size, these categories were combined in such instances to give production types as defined in the reference dataset. Turkeys and quail in the LLNL dataset were divided as described above to give turkey brooders and turkey grow-out operations, and quail and quail breeders, respectively. Hatcheries and commercial pigeon flocks were removed from the LLNL dataset, because these production types do not appear in the reference dataset and were not included in the models of Patyk et al. (in preparation).

4.2.2. Model input parameters for disease spread and control

Parameters used to represent disease manifestation, transmission, and detection were all used directly as reported by Patyk et al. (in preparation), with one exception. The *NAADSM* framework allows modelers to account for the influence of within-unit prevalence of disease on the spread of disease between units by direct contact (the introduction of infected birds into a previously uninfected flock) and by local-area spread. Patyk et al. (in preparation) utilized this capability in their models. The decision to not utilize this capability in the current study was made for two reasons: 1) the results from Patyk et al. (in preparation) illustrated that indirect

contact among units (which is not affected by within-unit prevalence of disease in *NAADSM*) is likely to be far more important than either disease spread by direct contact or by local-area spread; and 2) deficiencies in current versions of *NAADSM* with regard to modeling of within-unit prevalence of disease and local-area spread have been recognized (Dunipace et al., 2009; Reeves and Harvey, 2011).

Seven strategies for disease control were devised based on the baseline strategy described by Patyk et al. (in preparation), as shown in Table 4-2. These strategies employed combinations of various measures for disease control including restriction of movements among premises after detection of disease, depopulation of detected infected flocks, tracing of direct and indirect contacts among flocks, and preemptive culling.

4.2.3. Model outcomes

Thirty five scenarios (5 population datasets × 7 disease control strategies) were developed, and 1000 iterations of each scenario were run. Each iteration ran until no infected units remained in the population. Distributions generated by each scenario for the following simulation outputs of epidemiological interest were compared: the duration of the outbreak, the total number of units infected, the proportion of units in the population that were infected, the total number and proportion of units in the population that were depopulated for purposes of disease control, and the total number and proportion of birds in the population that were depopulated for purposes of disease control.

4.2.3.1. Statistical analyses of model outcomes

As a stochastic modeling framework, *NAADSM* produces distributions for each output. Because outputs produced by *NAADSM* tend not to be normally distributed, we employed nonparametric statistical methods as described below. We used the medians as the measures of

location or central tendency for these distributions. A 95% confidence interval was estimated for each median using a bias-corrected accelerated (BC_a) bootstrap method (Canty and Ripley, 2012; Davison and Hinkley, 1997; Diciccio and Efron, 1996; Efron and Tibshirani, 1994; Haukoos and Lewis, 2005). In addition to the median and its confidence interval, we also calculated two measures of the range of each distribution: the total range (the minimum value to the maximum value produced by the scenario) and the 80% probability interval (the range encompassing the central 80% of scenario results for each outcome, *i.e.*, the range between the 10^{th} and the 90^{th} percentiles).

The design employed for this study utilized two factors (population dataset and disease control strategy) with multiple replications for each combination of factors. We used a nonparametric method devised by Mack and Skillings for testing main effects in a two-factor design (Hollander and Wolfe, 1999; Mack and Skillings, 1980). This test addresses the null hypothesis that, after accounting for the effects of one factor, the treatment effects of the other factor are equal. When the presence of a statistically significant difference ($p < 0.05$) was detected, a set of pairwise tests also described by Mack and Skillings was used to assess which factor values produced outcomes that differed from one another.

For purposes of comparison, outcomes were also analyzed as though they had been generated from a one-factor experimental design. In this case, five separate one-factor analyses (one for the reference population dataset and four more for each of the synthetic population datasets) were carried out to compare the treatment effects of the seven disease control strategies. This enabled us to determine whether the use of any of the synthetic population datasets alone would have produced conclusions regarding the efficacies of the different disease control

strategies that were qualitatively different from conclusions based on scenarios that used the reference population dataset.

When analysis was performed for one-factor designs, the Kruskal-Wallis test (Conover, 1999; Kruskal and Wallis, 1952) was used to evaluate the null hypothesis that the median outcome produced by all control strategies were identical. In cases where the Kruskal-Wallis test indicated support for the alternative hypothesis that median outcome produced by at least one control strategy differed from that produced by at least one other strategy, a series of Bonferroni-adjusted Wilcoxon rank sum tests were conducted to identify unequal medians (Sheskin, 2007; Wilcoxon, 1945).

For all statistical tests, differences were deemed to be statistically significant for α less than 0.05. Implementations of the Mack-Skillings test and the associated pairwise comparison test, the Kruskal-Wallis test, and the Wilcoxon rank sum test in R version 2.14.2 (R Development Core Team, 2012) were used. In addition to those mentioned above, several other R packages were used to carry out the various analyses presented here (Dragulescu, 2012; Keitt et al., 2012; Lewin-Koh et al., 2012; Maechler et al., 2011; Neuwirth, 2011; Ripley and Lapsley, 2012; Urbanek, 2011).

4.2.4. Sensitivity analysis

Of the disease spread mechanisms simulated by *NAADSM*, local-area spread is the most sensitive to spatial proximities among premises. For all of the scenarios described above, we assumed that the daily probability of local-area spread from an infected to a susceptible flock, both of average size and located 1 km apart from one another, was 0.01 (Patyk et al., in preparation), and declined exponentially with greater distances (Harvey et al., 2007; *NAADSM* Development Team, 2010b).

In order to evaluate the robustness of the conclusions drawn from these scenarios, we ran an additional 70 scenarios in order to repeat all analyses for two additional levels of local-area spread: a "low" level (in which the daily probability of spread of disease as described above was 0.005) and a "high" level (with a daily probability of spread of 0.02).

4.3. Results

4.3.1. Characterizing the populations represented by the different datasets

Among the characteristics of each population dataset that might influence simulation outcomes are the number of flocks in the population, the overall density of those flocks (*i.e.*, number of flocks per unit area), the size distribution (number of birds) within flocks in each population, and the level of spatial aggregation or clustering of flocks in the dataset. These characteristics are summarized for each of the five population datasets in Table 4-3, Figure 4-1, and Figure 4-2.

4.3.1.1. Flocks in the reference population dataset

According to the reference (CLPHD) dataset, there are 832 commercial flocks in the state, with an average density of roughly 0.010 flocks per square kilometer. Flock sizes in the CLPHD dataset range from 2500 to 1.07 million birds per flock, with a median of 73,800 birds per flock and a mean of 82,617 birds per flock. Because the number of flocks and distributions of flock sizes in the CLPHD(A) synthetic dataset were derived directly from the reference dataset, there are no differences between these two datasets with respect to these characteristics.

4.3.1.2. Flocks in the synthetic population datasets

Of the synthetic population datasets, the USDA dataset shows the least correspondence to reference (CLPHD) population dataset: relative to the reference population, it overestimates by

roughly a factor of 2 the number (and overall density) of flocks, and underestimates by a factor of 10 the median size and a factor of 2.5 the mean size of commercial flocks. Relative to the reference population dataset, the synthetic population datasets from LLNL and RTI underestimate the number of flocks by 20% to 40%, respectively, and give estimates of median and mean flock size that are more consistent with those of the reference population dataset.

The LLNL, RTI, and USDA synthetic population datasets all underestimate the range of flock sizes relative to the reference population (Figure 4-2). The USDA dataset again gives the poorest estimate of the range of flock sizes when compared to the range from the reference (CLPHD) dataset: the difference from smallest to largest flocks in this dataset is approximately 170,000. For the reference (CLPHD), LLNL, and RTI datasets, this range is approximately 1.07 million, 460,000, and 855,000, respectively.

4.3.1.3. Spatial distributions of the reference and synthetic populations

At least three of the four synthetic datasets considered in this study [CLPHD (A), RTI, and USDA] were produced by means that were explicitly intended to reproduce realistic spatial distributions (Bruhn et al., 2012; Geter, 2006; Martin, 2009; Patyk et al., in preparation). The degree to which these efforts succeeded can be evaluated by comparing the degree of clustering among premises in the reference dataset (CLPHD) to those in the synthetic datasets. Table 4-3 and Figure 4-1 present information regarding the spatial distributions of commercial poultry premises in the datasets used for this study.

The nearest neighbor index (Clark and Evans, 1954) provides a simple measure of spatial aggregation. Values of this index can range from 0 (indicating perfect clustering) to 1 (indicating complete spatial randomness). The nearest neighbor index calculated for the CLPHD dataset is 0.46, indicating considerable spatial clustering. Processes used to generate all other

datasets produce populations with considerably less clustering of premises, with the exception of the approach described by Martin (2009), used to generate the CLPHD (A) dataset, which has a nearest neighbor index of 0.48 (Table 4-3).

4.3.2. Assessing the efficacies of disease control strategies using different population datasets

In most simulation modeling studies designed to evaluate disease control strategies, several model scenarios, each of which represents a different strategy, are run using the same population dataset (*e.g.*, Rorres et al., 2011a; Schoenbaum and Disney, 2003; Tildesley et al., 2012). These scenarios are then compared to rate or rank the efficacies of those strategies. In this section, we address the question of whether differences among population datasets affect qualitative conclusions about the relative efficacies of different disease control strategies, drawn from simulation modeling of HPAI in South Carolina. For each population dataset, seven disease control scenarios (described in Table 4-2) were run. Strategies were ranked on the basis of the epidemiologic outcomes described in section 4.2.3 using statistical techniques appropriate for one-factor experimental designs (the disease control strategy used is the factor of interest). Ranks of the various strategies were then compared across all population datasets, in order to determine whether conclusions concerning the relative efficacies of the different strategies would differ depending on the population dataset used.

4.3.2.1. Results for the reference (CLPHD) dataset

When the CLPHD dataset was used, three statistically distinguishable groups can be discerned among the seven disease control strategies when outbreak duration is considered (Table 4-4a). Among all disease control strategies, the use of enhanced movement restrictions

(strategy *mr*) most effectively minimized outbreak duration. Strategies that made use of preemptive destruction after tracing of exposed flocks (with or without the addition of ring culling within 1 km: strategies *trcDestr* and *trcDestrRing1km*) constituted the second-highest rated group. The remaining strategies had the least effect on outbreak duration. The use of enhanced movement restrictions also most effectively minimized the number and proportion of all flocks infected (Table 4-4b-c: both the number and proportion of infected flocks are considered for reasons discussed below).

When the total number or proportion of units or birds depopulated was considered, the strategies considered here were ranked in essentially four statistically distinguishable groups (with some overlap in the case of number of flocks depopulated: Table 4-4d-g). The use of enhanced movement restrictions most effectively minimized the numbers of units and of birds depopulated. Strategies that incorporated no preemptive culling (*trc* and *baseline*) made up the group with the second lowest number of depopulated flocks and birds, followed by a third group composed of strategies that use preemptive culling (*trcDestr*, *trcDestr1km*, and *ring1km*). Finally, the use of 3 km culling rings (*ring3km*) resulted in the largest numbers of units and birds depopulated.

4.3.2.2. Results for synthetic population datasets

When any one of the four synthetic datasets [CLPHD (A), LLNL, RTI, or USDA] was used, the general patterns described in the previous section can be discerned. In all four cases, just as in the reference population, use of enhanced movement restrictions most effectively minimized outbreak duration, followed by strategies that used preemptive culling of exposed units identified by tracing. As when the reference population is used, the remaining strategies are generally not distinguishable from one another (Table 4-4a).

With regard to the number or proportion of flocks infected, similar patterns could be discerned when the synthetic population datasets were used compared to when the reference population dataset was used: the use of enhanced movement restrictions always resulted in the smallest number of cases, followed by remaining strategies (Table 4-4b-c).

For numbers or proportions of flocks or birds depopulated, the same trends observed in the case scenarios run with the CLPHD dataset were seen in scenarios run with three of the four synthetic datasets [CLPHD (A), LLNL, and RTI: Table 4-4d-g]. In these cases, the use of enhanced movement restrictions resulted in the fewest depopulated flocks and birds. Strategies that do not use preemptive culling resulted in the second-fewest depopulated flocks, followed by strategies that made use of preemptive culling. The use of 3 km culling rings resulted in the largest number of birds depopulated, either in the last-rated group by itself or with one other control strategy. In the case of the USDA population dataset, unlike the others, it was not possible to discern differences among strategies other than the use of enhanced movement restrictions.

4.3.2.3. Ranking disease control strategies regardless of the population dataset used

The analyses presented in sections 4.3.2.1 and 4.3.2.2 were conducted as though the outcomes were produced by experiments with one-factor, in which the only effects of interest were those of the disease control strategies being simulated. Although this is typically the case for investigations that make use of only one population dataset, the use of a two-factor analysis is a more appropriate technique for ranking control strategies in the current study. We ranked the seven disease control strategies after accounting for the effects of all 5 population datasets using the Mack-Skillings test, as described in section 4.2.3.1. Results are presented in Table 4-5

(column 1). The patterns described in the preceding two sections were still evident after this analysis.

4.3.3. Assessing quantitative differences in model outcomes when different population datasets are used

Table 4-4 and Figures 4– 3 through 4–6 show quantitative results for each outcome of interest generated by each population dataset/disease control strategy scenario. A simple visual assessment suggested that there were marked differences in the distributions of these outcomes due to the use of different population datasets. Table 4-6 summarizes the results of a statistical comparison of the effects of the different population datasets (after accounting for the effects of disease control strategies) on several epidemiologic outcomes. For each outcome considered, results generated with the CLPHD (A) population dataset were statistically indistinguishable from those generated with the CLPHD population dataset.

By contrast, use of the LLNL and RTI datasets were significantly more likely to produce smaller values for all outcomes than those from scenarios that used the CLPHD dataset, thus underestimating the consequences of epidemics when compared to this baseline. The median numbers of flocks infected were 38% and 39% lower on average for LLNL scenarios and RTI scenarios, respectively, than the corresponding values from scenarios based on the CLPHD dataset (Table 4-6b).

Finally, for every outcome considered, the set of scenarios that used the USDA dataset had the lowest rank (Table 4-6): use of the USDA population dataset is statistically significantly more likely to produce larger values than use of any of the other population datasets. Relative to scenarios based on the CLPHD dataset, scenarios that made use of the USDA dataset showed a significant tendency to overestimate the consequences of an epidemic, regardless of the disease

control strategy employed. For example, the median number of flocks infected in scenarios based on the USDA dataset was on average more than 2500% higher than the median number of flocks infected in scenarios based on the CLPHD dataset (Table 4-6b).

Among the scenarios that use different population datasets, the quantitative outcomes described above are not simply proportional to the number of units in the population. As shown in Table 4-6c, scenarios from outcomes based on different population datasets differed significantly in not only the number of units infected, but also in the proportion of units in the population infected. Significant differences were also present in the proportion of units in the population depopulated, and in the proportion of birds in the population depopulated (Table 4-6e,g).

4.3.4. Sensitivity of model outcomes to different levels of local-area spread

4.3.4.1. Ranking disease control strategies for all levels of local-area spread

The ranks of disease control strategies based on model outcomes for all three levels of local-area spread (moderate, low, and high) after adjusting for the effects of the population datasets are shown in Table 4-5. Although the statistical grouping of control strategies varied slightly for the different levels of local-area spread, the same general ranks and trends described in section 4.3.2 can be observed.

4.3.4.2. Assessing differences in model outcomes with different population datasets and different levels of local-area spread

The ranks of model outcomes from scenarios based on different population datasets for all three levels of local-area spread after adjusting for the effects of the disease control strategies simulated are shown in Table 4-7. Again, although there is some overlap among statistically

distinguishable groups, the ranks and patterns are generally the same for all levels of local-area spread.

4.4. Discussion

It is generally acknowledged that the number and spatial distribution of premises are critical factors in simulation modeling of infectious diseases of animals (*e.g.*, Bruhn et al., 2012; Carpenter, 2011). Earlier work has shown that the spatial scales and distributions used to represent animal populations can affect outcomes of simulated epidemics in livestock, poultry, and wildlife (Carpenter, 2011; Highfield et al., 2008; Rorres et al., 2011b). Our aim in this study was to assess the impact on simulation modeling outcomes of several available synthetic population datasets, and to compare the conclusions drawn from scenarios that make use of such synthetic datasets to those drawn from scenarios that use a reliable reference population. A summary of our findings, within the context of the current study, is as follows:

1. *Substantial differences exist among synthetic population datasets with regard to the number of flocks, the number of birds per flock, and spatial distribution of premises.*

Although three of the four synthetic population datasets considered here (LLNL, RTI, and USDA) are based on the same underlying information, different methods were used to produce premises locations, production types, and flock sizes for these three datasets. These differences resulted in considerable variation among population datasets.

Data available from NASS does not specify the number of individual premises within a county or state. Due to the way in which individual operations are defined for the purposes of NASS, poultry operations with multiple production types present at the same location will be recorded multiple times in the agricultural census. The total number of poultry operations recorded by NASS, then, can exceed the number of actual premises. This situation is known to

occur, particularly among smaller poultry operations (USDA-APHIS-VS-CEAH-NAHMS, 2008). There is no single, reliable, publicly available estimate of the number of unique farm locations represented in data from NASS. The problem was acknowledged and addressed in the production of the original RTI dataset (Bruhn et al., 2012), acknowledged but unaddressed in the production of the original LLNL dataset (Melius, 2007), and apparently neither acknowledged nor addressed in the production of the USDA dataset (Geter, 2006). This handling of NASS premises definitions may be partly responsible for the substantial discrepancies in the number of flocks among these population datasets, but other factors must also affect estimates of the number of farms: the RTI and LLNL datasets are in relatively close agreement on the number of commercial flocks, in spite of the fact that the NASS premises definition is accounted for in one but not in the other.

The discrepancies in the number of flocks are even more substantial when the small operations (excluded from the current study) are included. According to estimates from the Clemson Livestock Poultry Health Division, there are approximately 6200 flocks (commercial and noncommercial) in the state of South Carolina (Patyk et al., in preparation). In the original synthetic datasets from LLNL, RTI, and USDA, there are 9668, 1959, and 2900 total poultry operations, respectively.

2. *Use of any of the synthetic population datasets included in this study generally does not affect qualitative conclusions regarding strategies for disease control of HPAI in South Carolina.*

We have demonstrated that there is general agreement among models of HPAI in South Carolina that utilize different population datasets (actual or synthetic) when the scope of the investigation is limited to performing a qualitative assessment of the efficacies of various disease

control measures. This conclusion was shown to hold for several levels of local-area spread, which is expected to be the model parameter most strongly affected by differences in spatial distributions among farms.

An exception to this general conclusion is evident when the numbers of flocks and birds depopulated are considered. When the USDA dataset is used, it is not possible to distinguish among most disease control strategies simulated here from one another. If only this population dataset had been used, very different conclusions would have been drawn regarding the benefits and costs of implementing preemptive ring culling than if the reference population dataset or any of the other synthetic population datasets had been used.

3. *The choice of the synthetic population dataset to use for modeling can have a considerable impact on quantitative outcomes.*

Pronounced differences among model outcomes are observed when the attempt is made to draw conclusions regarding the quantitative consequences of simulated outbreaks. These consequences may be substantially under- or overestimated relative to outcomes generated with the reference population, depending on properties of the population dataset used. These differences in model outcomes are not simply proportional to the number of premises in each population.

4. *The (qualitative) conclusions drawn from this study are not sensitive to the values used to represent local-area spread.*

Of the parameters used in the *NAADSM* framework, those that represent local-area spread (that is, the non-directional spread of disease among premises in close proximity to one another) are the most difficult to quantitatively characterize. Efforts to characterize similar phenomena

have been developed for spatial kernel-based mathematical models of disease spread (*e.g.*, Rorres et al., 2010, 2011a).

Here, we represented local-area spread as a range of values, informed by the opinions and experience of the authors, in order to determine whether any value of local-area spread within a reasonable range would lead to different conclusions. Regardless of the values for local-area spread used, we found no differences in the ranks of disease control strategies with regard to their relative efficacies, nor in the ranks of population datasets with regard to their quantitative outcomes. Quantitative values for outcomes such as number of infected flocks and outbreak duration did vary with different levels of local-area spread (data not shown), but these differences are not germane to the objectives or conclusions of this particular study.

4.4.1. Additional caveats

4.4.1.1. Backyard flocks

Backyard flocks were excluded from the present study for two reasons. First, the purpose of this study was to investigate potential differences among model outcomes when population datasets containing coordinates of actual poultry operations are used, versus model outcomes produced when artificially generated locations of premises are used. This would not have been possible for backyard flocks, for the vast majority of which the actual locations are not known. Second, preliminary modeling investigations demonstrated that, in the scenarios presented, backyard flocks made very small contributions to the outcomes described above (data not shown). This finding is consistent with previous modeling work conducted on the impact of backyard flocks on the spread of avian influenza in commercial flocks (Bavinck et al., 2009; Smith and Dunipace, 2011).

4.4.1.2. Production type determinations

As described in section 4.2.1.3.2, the original population datasets produced by Lawrence Livermore National Laboratory, RTI International, and USDA-APHIS-VS-CEAH were modified to allow the use of poultry production types as defined in the study by Patyk et al. (in preparation). These modifications were made to allow as fair a comparison as possible among results generated with the different population datasets: an attempt to parameterize each model separately based on the production types included in the original population datasets would have obscured the effects of the factors of primary interest, namely, the differences in number, size, and spatial distribution of flocks in the population datasets. The process that we used, although somewhat subjective, was not unlike the process used in the construction of most other simulation models. Given the aims of the current study, it is our opinion that these modifications did not meaningfully affect our conclusions.

4.4.2. Implications for the control of HPAI in populations of commercial flocks

Although comparing the efficacies of strategies for disease control for highly pathogenic avian influenza was not a primary purpose of this study, some useful conclusions can still be drawn. It is clear from the results presented above, and not unexpected, that reducing the frequency of effective contact (for example, by reducing the number of movements of birds, personnel, or equipment between farms) has a much greater impact on the control of disease than other efforts to control disease: the imposition of enhanced movement restrictions resulted in simulated outbreaks of the shortest durations, and with the smallest numbers of infected and depopulated flocks, compared to all other control strategies. Of greater interest is the question of what additional steps should be taken once contacts have been restricted to the lowest practical level. Results from this study suggest that tracing of potentially dangerous contacts, coupled

with quarantine or preemptive destruction of flocks identified by such tracing activities, will be more effective in this setting than preemptive culling strategies based on proximity to detected infected flocks.

The enhanced movement restrictions simulated in this study were applied statewide, which likely would not be practical in the event of an actual outbreak. It would be useful in future studies to assess the effects of more localized application of such restrictions. This study also assumed near-perfect capabilities to detect disease in infected flocks: detection based on diagnostic testing was assumed for the sake of simplicity to be perfect, and the probability of detection based on observation of clinical disease was assumed to be high as well. The effects of more realistic capabilities to detect highly pathogenic avian influenza in commercial settings should also be explored further.

4.5. Conclusions

The results of this study suggest that quantitative outcomes from epidemiologic modeling are highly sensitive to the number of farms included. Continuing efforts to use data from the US Census of Agriculture to generate synthetic population datasets for epidemiologic modeling should critically consider how to more accurately represent the actual number of farms in the population. In situations when a reliable reference dataset is available, as is the case for poultry in South Carolina, opportunities exist for validation of methods used to produce synthetic population datasets.

Although this study indicates that there are differences among the synthetic population datasets with respect to how well they reflect the spatial distribution of farm premises (*i.e.*, the degree of clustering in the population), this study does not address the sensitivity of simulation

modeling outcomes to the spatial distributions of farms. It would be helpful to further explore this characteristic, as it likely also has an effect on quantitative simulation outcomes.

For results of simulation models to be credible, the population datasets on which they are based should represent reality to as great an extent as possible. In situations where actual data exists but cannot be shared due to concerns about privacy or confidentiality, an approach to generating artificial populations such as that described by Martin (2009), which preserves spatial context as well as population demographics, is clearly useful. When actual data is simply not available and when credible quantitative outcomes are either desired or required, it may be reasonable to base conclusions on models derived, not from a single population dataset, but from several such datasets. The ability to incorporate parameter uncertainty and estimate a range of possible outcome values that account for such uncertainty is a key advantage of the stochastic modeling framework. When a source of uncertainty is the population dataset itself, this factor should be accounted for. At a minimum, studies that rely on synthetic population datasets to generate quantitative estimates should explicitly acknowledge the potentially high degree of uncertainty surrounding those estimates.

Table 4-1. Population datasets used in this study.

Population dataset	*Description*	*Relevant sources*
CLPHD	The reference population dataset. Actual premises locations provided by the Clemson University Livestock Poultry Health Division (CLPHD). This dataset represents over 95% of all commercial poultry operations in the state of South Carolina as of March 2012.	
CLPHD (A)	Data from the CLHPD dataset, modified in order to prevent identification of individual premises while preserving realistic spatial relationships among premises.	Martin, 2009; Patyk et al., in preparation
LLNL	Population dataset derived from original work conducted at Lawrence Livermore National Laboratory (LLNL) as described in the text.	Melius, 2007
RTI	Population dataset derived from original work conducted at the Research Triangle Institute (RTI) as described in the text.	Bruhn et al., 2007, 2012
USDA	Population dataset derived from original work conducted at the US Department of Agriculture – Animal and Plant Health Inspection Service – Veterinary Services – Centers for Epidemiology and Animal Health (USDA-APHIS-VS-CEAH) as described in the text.	Geter, 2006

Table 4-2. Control strategies used in this study.

Strategy name	***Summary of control measures***
Baseline (*baseline*)	The following control measures are used in the baseline disease control strategy: • Immediate cessation of direct contact involving detected, infected units • Reduction in the rate of direct contact among all flocks to 0% of the normal level by day 7 after detection of disease in any flock • Reduction in the rate of indirect contact among all flocks to 50% of the normal level by day 7 after detection of disease in any flock • Depopulation of all detected infected units • Increase in capacity to carry out depopulation from an initial level of 2 units per day to a level of 5 units per day by day 7 after detection of disease in any flock
Enhanced movement restrictions (*mr*)	All measures employed in the baseline strategy, ***except***: • Rate of direct contact among all flocks is reduced to 0% of the normal level by day 5 after detection of disease in any flock • Rate of indirect contact among all flocks is reduced to 30% of the normal level by day 5 after detection of disease in any flock
1 km ring culling (*ring1km*)	All measures employed in the baseline strategy, ***plus***: • All flocks within 1 km of a detected infected flock will be preemptively depopulated
3 km ring culling (*ring3km*)	All measures employed in the baseline strategy, ***plus***: • All flocks within 3 km of a detected infected flock will be preemptively depopulated
Tracing without preemptive destruction (*trc*)	All measures employed in the baseline strategy, ***plus***: • Tracing forward and tracing back (tracing out and tracing in) of direct and indirect contacts involving an infected detected flock that occurred within 21 days prior to disease detection o 99% probability of successfully identifying other units involved in direct contact o 80% probability of successfully identifying other units involved in indirect contact • Immediate cessation of direct contact involving units identified by tracing • Diagnostic testing for infection in all units identified by tracing. Units detected by diagnostic testing will trigger additional control measures (further tracing, ***etc.***) o Unit-level tests were assumed to be perfect (***i.e.***, 100% sensitivity and 100% specificity) o Delay of 0 to 3 days to obtain diagnostic test results
Tracing with preemptive destruction (*trcDestr*)	All measures employed in *trc*, ***plus***: • Preemptive depopulation of units identified by trace-forward (trace-out) investigations of direct or indirect contact
Tracing with preemptive destruction and 1 km ring culling (*trcDestrRing1km*)	All measures employed in *trcDestr*, ***plus***: • All flocks within 1 km of a detected infected flock will be preemptively depopulated

Table 4-3. Characteristics of commercial poultry population datasets used in this study.

Population dataset[1]	***Number of commercial flocks***[2]		***Number of birds per commercial flock***				***Nearest neighbor index***[4]
	Total count	*Average density (flocks per km²)*	*Median*	*Mean*	*Standard deviation*	*Range*	
CLPHD	832	0.010	73,800	82,617	81,931	2500 – 1,070,000	0.4554
CLPHD (A)[3]							0.4759
LLNL	670	0.008	65,233	65,233	6,9306	1008 – 461,725	0.7556
RTI	506	0.006	64,822	89,514	101,948	720 – 856,076	0.6063
USDA	1740	0.022	6331	33,131	43,530	1384 – 170,916	0.6934

[1] Population datasets are described in Table 4-1.

[2] Overall density was calculated based on an estimate of the area of the state of South Carolina of 80,700 square kilometers.

[3] Number of flocks in this population dataset and the distribution of the number of birds per flock are identical to the primary CLPHD dataset.

[4] Higher values of the Clark-Evans nearest neighbor index indicate lower levels spatial aggregation (Baddeley and Turner, 2005; Clark and Evans, 1954).

Table 4-4. Summaries of model outcomes generated by 1000 stochastic iterations of each population dataset/control strategy scenario.
a) Outbreak duration (days) Outbreaks were considered to have ended when no infected premises remained.

Population dataset		Disease control strategy[4]						
		mr	***trcDestr***	***trcDestrRing1km***	***ring3km***	***trc***	***ring1km***	***baseline***
CLPHD	*Rank*[1]	1[a]	2[bc]	3[bc]	4[bcd]	5[bcd]	6[cd]	7[cd]
	Median (95% CI)[2]	22 (21-22)	30 (28-31)	30 (27-32)	36 (34-39)	36 (33-38)	38 (34-39)	41 (36-44)
	Range (80% PI)[3]	2-113 (13-41)	2-160 (14-113)	2-146 (15-114)	2-151 (15-112)	2-147 (14-113)	2-153 (15-113)	2-150 (16-111)
CLPHD (A)	*Rank*[1]	1[a]	2[bc]	3[bcd]	7[de]	4[cde]	5[cde]	6[cde]
	Median (95% CI)[2]	22 (20-22)	28 (25-29)	31 (29-32)	39 (35-41)	36 (32-37)	38 (33-39)	38 (35-41)
	Range (80% PI)[3]	2-109 (13-41)	2-149 (14-115)	2-150 (14-113)	2-145 (15-111)	2-159 (15-113)	2-153 (15-111)	2-154 (14-111)
LLNL	*Rank*[1]	1[a]	2[b]	3[b]	6[cde]	4[cd]	7[de]	5[cde]
	Median (95% CI)[2]	20 (19-20)	23 (22-22)	24 (23-24)	30 (28-31)	27 (26-26)	31 (29-32)	29 (27-30)
	Range (80% PI)[3]	2-61 (12-31)	2-124 (14-67)	2-127 (13-73)	2-129 (14-68)	2-119 (14-66)	2-128 (14-74)	2-126 (14-63)
RTI	*Rank*[1]	1[a]	2[b]	3[b]	7[c]	4[c]	6[c]	5[c]
	Median (95% CI)[2]	20 (19-20)	22 (21-22)	24 (22-24)	30 (28-30)	28 (26-29)	29 (27-30)	29 (27-29)
	Range (80% PI)[3]	2-70 (12-31)	2-90 (13-51)	2-104 (13-55)	2-96 (15-61)	2-93 (14-62)	2-95 (15-59)	2-95 (14-59)
USDA	*Rank*[1]	1[a]	2[bc]	3[bcd]	5[bcd]	4[bcd]	6[bcd]	7[cd]
	Median (95% CI)[2]	25 (23-25)	96 (94-97)	96 (93-96)	96 (94-96)	96 (93-96)	97 (95-97)	97 (95-98)
	Range (80% PI)[3]	2-189 (13-133)	2-168 (18-116)	2-179 (17-117)	2-183 (19-117)	2-172 (18-116)	2-209 (19-118)	2-180 (21-120)

[1] Ranks for each control strategy are based on the rank sum score calculated for the Kruskal-Wallis test (Conover, 1999).
[2] Bootstrap confidence intervals for medians were generated as described in the text.
[3] The 80% probability interval includes the central 80% of values from each simulation, *i.e.*, the range between the 10th and 90th percentiles.
[4] Disease control strategies are described in Table 4-2.
[a-g] Within each set of disease control strategies run for a particular population dataset, outcomes indicated with the same letter do not differ significantly from one another, as determined by post-hoc pairwise comparisons made after application of the Kruskal-Wallis test (Sheskin, 2007) as described in the text.

Table 4-4 (continued).

Note: Disease control strategies are listed in rank order for each individual outcome of interest, based on the reference (CLPHD) population dataset. This order is not necessarily the same for all outcomes.

b) Total number of infected flocks

Population dataset		Disease control strategy[4]						
		mr	***trcDestr***	***ring3km***	***trcDestrRing1km***	***trc***	***ring1km***	***baseline***
CLPHD	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]
	Median (95% CI)[2]	18 (16-19)	48 (42-56)	52 (43-60)	50 (41-59)	60 (51-70)	65 (55-75)	66 (56-77)
	Range (80% PI)[3]	0-527 (2-97)	0-780 (4-752)	0-787 (4-747)	0-775 (5-748)	0-782 (4-751)	0-783 (5-748)	0-783 (5-747)
CLPHD (A)	*Rank[1]*	1[a]	2[b]	6[b]	3[b]	4[b]	7[b]	5[b]
	Median (95% CI)[2]	19 (16-20)	41 (34-45)	66 (55-72)	52 (46-62)	56 (47-68)	64 (54-72)	60 (53-73)
	Range (80% PI)[3]	0-505 (2-85)	0-787 (3-750)	0-785 (5-744)	0-783 (4-750)	0-789 (4-748)	0-788 (5-748)	0-785 (4-749)
LLNL	*Rank[1]*	1[a]	2[bc]	6[bcd]	3[bcd]	4[bcd]	7[cd]	5[bcd]
	Median (95% CI)[2]	14 (12-14)	29 (25-31)	37 (31-40)	30 (26-33)	31 (28-34)	38 (34-44)	35 (31-38)
	Range (80% PI)[3]	0-223 (2-48)	0-641 (4-263)	0-644 (2-260)	0-643 (3-277)	0-651 (3-253)	0-642 (3-302)	0-637 (3-211)
RTI	*Rank[1]*	1[a]	2[bc]	7[de]	3[bcd]	4[cde]	6[cde]	5[cde]
	Median (95% CI)[2]	14 (12-14)	24 (21-26)	40 (33-44)	29 (26-32)	34 (30-36)	35 (31-39)	35 (31-40)
	Range (80% PI)[3]	0-302 (2-49)	0-414 (2-172)	0-456 (4-224)	0-445 (3-197)	0-457 (3-236)	0-445 (4-193)	0-445 (3-182)
USDA	*Rank[1]*	1[a]	3[b]	4[b]	2[b]	5[b]	6[b]	7[b]
	Median (95% CI)[2]	29 (24-30)	1689 (1686-1690)	1688 (1685-1690)	1688 (1685-1689)	1689 (1685-1690)	1688 (1686-1689)	1689 (1686-1689)
	Range (80% PI)[3]	0-1566 (3-1398)	0-1721 (10-1703)	0-1717 (9-1704)	0-1717 (9-1703)	0-1717 (8-1704)	0-1719 (10-1704)	0-1718 (13-1702)

Table 4-4 (continued).

c) Proportion of all flocks in the population infected

Population dataset		Disease control strategy[4]						
		mr	***trcDestr***	***ring3km***	***trcDestrRing1km***	***trc***	***ring1km***	***baseline***
CLPHD	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[b]	7[b]
	Median (95% CI)[2]	0.022 (0.019-0.023)	0.058 (0.05-0.069)	0.062 (0.052-0.072)	0.06 (0.049-0.071)	0.072 (0.061-0.084)	0.078 (0.066-0.091)	0.079 (0.067-0.093)
	Range (80% PI)[3]	0-0.633 (0.002-0.117)	0-0.938 (0.005-0.904)	0-0.946 (0.005-0.898)	0-0.931 (0.006-0.899)	0-0.94 (0.005-0.903)	0-0.941 (0.006-0.899)	0-0.941 (0.006-0.898)
CLPHD (A)	*Rank[1]*	1[a]	2[b]	6[b]	3[b]	4[b]	7[b]	5[b]
	Median (95% CI)[2]	0.023 (0.019-0.024)	0.049 (0.041-0.054)	0.079 (0.066-0.086)	0.063 (0.054-0.074)	0.067 (0.056-0.081)	0.077 (0.064-0.087)	0.073 (0.064-0.088)
	Range (80% PI)[3]	0-0.607 (0.002-0.102)	0-0.946 (0.004-0.901)	0-0.944 (0.006-0.894)	0-0.941 (0.005-0.902)	0-0.948 (0.005-0.899)	0-0.947 (0.006-0.899)	0-0.944 (0.005-0.9)
LLNL	*Rank[1]*	1[a]	2[bc]	6[bcd]	3[bcd]	4[bcd]	7[cd]	5[bcd]
	Median (95% CI)[2]	0.021 (0.018-0.022)	0.043 (0.037-0.046)	0.055 (0.046-0.06)	0.044 (0.039-0.049)	0.046 (0.042-0.051)	0.057 (0.052-0.066)	0.052 (0.046-0.056)
	Range (80% PI)[3]	0-0.333 (0.003-0.072)	0-0.957 (0.006-0.393)	0-0.961 (0.003-0.388)	0-0.96 (0.004-0.413)	0-0.972 (0.004-0.378)	0-0.958 (0.004-0.451)	0-0.951 (0.004-0.315)
RTI	*Rank[1]*	1[a]	2[bc]	7[de]	3[bcd]	4[cde]	6[cde]	5[cde]
	Median (95% CI)[2]	0.028 (0.024-0.028)	0.047 (0.042-0.051)	0.079 (0.065-0.086)	0.057 (0.049-0.062)	0.067 (0.059-0.071)	0.069 (0.06-0.077)	0.069 (0.061-0.078)
	Range (80% PI)[3]	0-0.597 (0.004-0.097)	0-0.818 (0.004-0.34)	0-0.901 (0.008-0.443)	0-0.879 (0.006-0.39)	0-0.903 (0.006-0.467)	0-0.879 (0.008-0.382)	0-0.879 (0.006-0.36)
USDA	*Rank[1]*	1[a]	3[b]	4[b]	2[b]	5[b]	6[b]	7[b]
	Median (95% CI)[2]	0.017 (0.014-0.017)	0.971 (0.969-0.971)	0.97 (0.969-0.971)	0.97 (0.968-0.971)	0.971 (0.968-0.971)	0.97 (0.968-0.971)	0.971 (0.969-0.971)
	Range (80% PI)[3]	0-0.9 (0.002-0.804)	0-0.989 (0.006-0.979)	0-0.987 (0.005-0.979)	0-0.987 (0.005-0.979)	0-0.987 (0.005-0.979)	0-0.988 (0.006-0.979)	0-0.987 (0.007-0.978)

Table 4-4 (continued).

d) Total number of flocks depopulated

Note: Simulated outbreaks ended when no infected flocks remained in the population, not when all disease control activities had been completed: it is possible that, due to limited capacity to carry out depopulation, not all scheduled depopulation had been carried out at the time of the end of each simulated outbreak. Consequently, the numbers and proportions of depopulated flocks and birds do not necessarily represent the total required depopulation effort.

Population dataset		***Disease control strategy[4]***						
		mr	***trc***	***baseline***	***ring1km***	***trcDestr***	***trcDestrRing1km***	***ring3km***
CLPHD	*Rank[1]*	1[a]	2[bcd]	3[bcde]	4[bcdef]	5[cdefg]	6[defg]	7[efg]
	Median (95% CI)[2]	18 (15-19)	60 (51-70)	65 (57-77)	76 (66-86)	78 (68-91)	85 (68-94)	110 (95-125)
	Range (80% PI)[3]	0-505 (3-95)	0-680 (5-505)	0-690 (6-500)	0-705 (6-510)	0-740 (10-505)	0-665 (11-510)	0-700 (11-505)
CLPHD (A)	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[bcd]	6[cde]	7[de]
	Median (95% CI)[2]	19 (17-20)	57 (48-69)	60 (52-70)	74 (63-84)	70 (58-79)	90 (79-99)	130 (113-141)
	Range (80% PI)[3]	0-480 (3-85)	0-740 (5-510)	0-710 (5-500)	0-705 (6-500)	0-690 (9-515)	0-690 (11-505)	0-670 (12-495)
LLNL	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[cde]	6[de]	7[de]
	Median (95% CI)[2]	15 (13-16)	32 (29-35)	36 (32-38)	39 (34-46)	47 (40-50)	50 (44-54)	56 (50-63)
	Range (80% PI)[3]	0-217 (3-48)	0-540 (4-252)	0-565 (4-207)	0-590 (4-295)	0-560 (9-275)	0-575 (7-301)	0-565 (4-280)
RTI	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[c]	7[d]
	Median (95% CI)[2]	14 (12-14)	34 (29-36)	36 (31-40)	39 (34-44)	41 (36-44)	50 (44-51)	68 (60-74)
	Range (80% PI)[3]	0-280 (3-49)	0-405 (3-230)	0-410 (4-179)	0-410 (5-198)	0-380 (6-195)	0-455 (8-220)	0-410 (8-235)
USDA	*Rank[1]*	1[a]	2[b]	6[b]	5[b]	3[b]	4[b]	7[b]
	Median (95% CI)[2]	30 (26-32)	425 (410-430)	425 (410-425)	430 (420-435)	420 (410-420)	425 (410-425)	425 (415-430)
	Range (80% PI)[3]	0-885 (4-605)	0-780 (9-530)	0-776 (14-543)	0-833 (13-535)	0-790 (20-525)	0-820 (20-530)	0-865 (23-535)

Table 4-4 (continued).

e) Proportion of all flocks in the population depopulated

Note: Simulated outbreaks ended when no infected flocks remained in the population, not when all disease control activities had been completed: it is possible that, due to limited capacity to carry out depopulation, not all scheduled depopulation had been carried out at the time of the end of each simulated outbreak. Consequently, the numbers and proportions of depopulated flocks and birds do not necessarily represent the total required depopulation effort.

Population dataset		***Disease control strategy[4]***						
		mr	***trc***	***baseline***	***ring1km***	***trcDestr***	***trcDestrRing1km***	***ring3km***
CLPHD	*Rank[1]*	1[a]	2[bcd]	3[bcde]	4[bcdef]	5[cdefg]	6[defg]	7[efg]
	Median (95% CI)[2]	0.022 (0.019-0.023)	0.072 (0.061-0.084)	0.078 (0.068-0.093)	0.091 (0.079-0.103)	0.094 (0.083-0.11)	0.102 (0.082-0.114)	0.133 (0.115-0.15)
	Range (80% PI)[3]	0-0.607 (0.004-0.114)	0-0.817 (0.006-0.607)	0-0.829 (0.007-0.601)	0-0.847 (0.007-0.613)	0-0.889 (0.012-0.607)	0-0.799 (0.013-0.613)	0-0.841 (0.013-0.607)
CLPHD (A)	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[bcd]	6[cde]	7[de]
	Median (95% CI)[2]	0.023 (0.019-0.024)	0.069 (0.058-0.083)	0.072 (0.062-0.085)	0.089 (0.076-0.101)	0.084 (0.07-0.095)	0.108 (0.094-0.119)	0.156 (0.136-0.169)
	Range (80% PI)[3]	0-0.577 (0.004-0.102)	0-0.889 (0.006-0.613)	0-0.853 (0.006-0.601)	0-0.847 (0.007-0.601)	0-0.829 (0.011-0.619)	0-0.829 (0.013-0.607)	0-0.805 (0.014-0.595)
LLNL	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[cde]	6[de]	7[de]
	Median (95% CI)[2]	0.022 (0.019-0.024)	0.048 (0.042-0.052)	0.054 (0.048-0.058)	0.058 (0.052-0.069)	0.07 (0.06-0.075)	0.075 (0.066-0.082)	0.084 (0.075-0.093)
	Range (80% PI)[3]	0-0.324 (0.004-0.072)	0-0.806 (0.006-0.376)	0-0.843 (0.006-0.309)	0-0.881 (0.006-0.44)	0-0.836 (0.013-0.41)	0-0.858 (0.01-0.449)	0-0.843 (0.006-0.418)
RTI	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[c]	7[d]
	Median (95% CI)[2]	0.028 (0.024-0.028)	0.067 (0.056-0.07)	0.071 (0.061-0.079)	0.077 (0.067-0.087)	0.081 (0.071-0.087)	0.099 (0.087-0.101)	0.133 (0.119-0.147)
	Range (80% PI)[3]	0-0.553 (0.006-0.097)	0-0.8 (0.006-0.455)	0-0.81 (0.008-0.354)	0-0.81 (0.01-0.392)	0-0.751 (0.012-0.385)	0-0.899 (0.016-0.435)	0-0.81 (0.016-0.464)
USDA	*Rank[1]*	1[a]	2[b]	6[b]	5[b]	3[b]	4[b]	7[b]
	Median (95% CI)[2]	0.017 (0.015-0.018)	0.244 (0.236-0.247)	0.244 (0.236-0.244)	0.247 (0.241-0.25)	0.241 (0.233-0.241)	0.244 (0.236-0.244)	0.244 (0.239-0.247)
	Range (80% PI)[3]	0-0.509 (0.002-0.348)	0-0.448 (0.005-0.305)	0-0.446 (0.008-0.312)	0-0.479 (0.007-0.307)	0-0.454 (0.011-0.302)	0-0.471 (0.011-0.305)	0-0.497 (0.013-0.307)

Table 4-4 (continued).

f) Total number of birds depopulated (millions)

Note: Simulated outbreaks ended when no infected flocks remained in the population, not when all disease control activities had been completed: it is possible that, due to limited capacity to carry out depopulation, not all scheduled depopulation had been carried out at the time of the end of each simulated outbreak. Consequently, the numbers and proportions of depopulated flocks and birds do not necessarily represent the total required depopulation effort.

Population dataset		***Disease control strategy[4]***						
		mr	***trc***	***baseline***	***ring1km***	***trcDestr***	***trcDestrRing1km***	***ring3km***
CLPHD	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[cd]	6[cd]	7[cd]
	Median (95% CI)[2]	1.4 (1.3-1.6)	4.6 (4-5.5)	5.4 (4.5-6.1)	5.6 (5.1-6.7)	6.3 (5.6-7.1)	6.9 (5.7-7.9)	8.7 (7.8-10.4)
	Range (80% PI)[3]	0-43.5 (0.1-7.7)	0-59.4 (0.2-49.8)	0-60.4 (0.3-48.8)	0-60 (0.3-49.3)	0-61.5 (0.6-49.8)	0-59 (0.6-49.7)	0-59.8 (0.5-49)
CLPHD (A)	*Rank[1]*	1[a]	3[bc]	2[bc]	4[bcd]	5[bcd]	6[cde]	7[de]
	Median (95% CI)[2]	1.5 (1.3-1.6)	4.6 (4-5.3)	4.8 (4-5.3)	6.2 (5.1-6.8)	5.3 (4.6-6.1)	7.1 (6-8.1)	10.1 (9.1-11.7)
	Range (80% PI)[3]	0-40.4 (0.1-6.8)	0-62.2 (0.2-49.5)	0-60 (0.2-48.7)	0-60.7 (0.3-48.6)	0-60.8 (0.5-49.9)	0-59.5 (0.5-49.3)	0-59.2 (0.7-48.5)
LLNL	*Rank[1]*	1[a]	2[b]	3[b]	4[cd]	5[cde]	6[de]	7[de]
	Median (95% CI)[2]	1 (0.9-1.1)	2.4 (2.1-2.6)	2.7 (2.3-2.9)	3 (2.7-3.3)	3.6 (3.3-3.9)	3.8 (3.4-4.1)	4.5 (4.2-4.9)
	Range (80% PI)[3]	0-17.1 (0.1-3.2)	0-49 (0.2-18.6)	0-51.7 (0.2-15.6)	0-53.5 (0.2-22.5)	0-48.3 (0.5-20.5)	0-52.8 (0.4-22.8)	0-51.7 (0.3-21.3)
RTI	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[c]	7[d]
	Median (95% CI)[2]	1.1 (1-1.3)	3 (2.5-3.4)	3.1 (2.7-3.5)	3.3 (2.8-3.7)	3.2 (2.8-3.7)	4.3 (3.8-4.7)	6.6 (6-7.4)
	Range (80% PI)[3]	0-25.2 (0.1-4.7)	0-38.9 (0.2-18.6)	0-38.9 (0.2-15.5)	0-38.8 (0.2-17.4)	0-35.5 (0.3-17.9)	0-39.7 (0.3-19.3)	0-37.6 (0.5-21)
USDA	*Rank[1]*	1[a]	2[b]	5[b]	4[b]	3[b]	6[b]	7[b]
	Median (95% CI)[2]	0.8 (0.7-0.9)	37.4 (36.8-37.9)	37.6 (36.8-38.3)	37.4 (36.8-38.1)	37 (36.3-37.5)	37.4 (36.6-38.1)	37 (36.3-37.8)
	Range (80% PI)[3]	0-41.2 (0.1-29.3)	0-47.8 (0.2-44.8)	0-47 (0.3-44.4)	0-47.2 (0.3-44.3)	0-47.8 (0.4-44.8)	0-48.1 (0.5-44.7)	0-47.3 (0.7-44.2)

Table 4-4 (continued).

g) Proportion of all birds in the population depopulated

Population dataset		Disease control strategy[4]						
		mr	***trc***	***baseline***	***ring1km***	***trcDestr***	***trcDestrRing1km***	***ring3km***
CLPHD	*Rank[1]*	1[a]	2[bc]	3[bc]	4[bcd]	5[cd]	6[cd]	7[cd]
	Median (95% CI)[2]	0.021 (0.019-0.023)	0.066 (0.058-0.08)	0.079 (0.066-0.089)	0.082 (0.074-0.097)	0.091 (0.082-0.103)	0.101 (0.084-0.115)	0.127 (0.114-0.151)
	Range (80% PI)[3]	0-0.634 (0.002-0.113)	0-0.865 (0.003-0.725)	0-0.879 (0.004-0.71)	0-0.874 (0.004-0.718)	0-0.896 (0.008-0.726)	0-0.86 (0.009-0.724)	0-0.871 (0.007-0.713)
CLPHD (A)	*Rank[1]*	1[a]	3[bc]	2[bc]	4[bcd]	5[bcd]	6[cde]	7[de]
	Median (95% CI)[2]	0.021 (0.019-0.024)	0.067 (0.058-0.077)	0.069 (0.059-0.079)	0.09 (0.074-0.099)	0.078 (0.067-0.09)	0.103 (0.088-0.118)	0.148 (0.133-0.17)
	Range (80% PI)[3]	0-0.588 (0.002-0.099)	0-0.905 (0.004-0.721)	0-0.874 (0.003-0.71)	0-0.884 (0.005-0.708)	0-0.885 (0.007-0.727)	0-0.867 (0.007-0.718)	0-0.862 (0.01-0.706)
LLNL	*Rank[1]*	1[a]	2[b]	3[b]	4[cd]	5[cde]	6[de]	7[de]
	Median (95% CI)[2]	0.018 (0.016-0.02)	0.042 (0.037-0.046)	0.047 (0.041-0.051)	0.053 (0.047-0.059)	0.063 (0.057-0.068)	0.066 (0.061-0.072)	0.079 (0.073-0.086)
	Range (80% PI)[3]	0-0.3 (0.002-0.057)	0-0.86 (0.003-0.326)	0-0.907 (0.003-0.273)	0-0.939 (0.004-0.394)	0-0.848 (0.009-0.36)	0-0.927 (0.006-0.4)	0-0.906 (0.005-0.374)
RTI	*Rank[1]*	1[a]	2[b]	3[b]	4[b]	5[b]	6[c]	7[d]
	Median (95% CI)[2]	0.025 (0.022-0.029)	0.067 (0.055-0.076)	0.068 (0.059-0.078)	0.072 (0.063-0.082)	0.071 (0.063-0.081)	0.095 (0.085-0.104)	0.146 (0.131-0.164)
	Range (80% PI)[3]	0-0.557 (0.003-0.104)	0-0.858 (0.003-0.411)	0-0.859 (0.004-0.341)	0-0.857 (0.005-0.384)	0-0.785 (0.007-0.396)	0-0.875 (0.007-0.427)	0-0.831 (0.011-0.463)
USDA	*Rank[1]*	1[a]	2[b]	5[b]	4[b]	3[b]	6[b]	7[b]
	Median (95% CI)[2]	0.013 (0.011-0.015)	0.649 (0.637-0.658)	0.653 (0.637-0.665)	0.649 (0.639-0.66)	0.642 (0.631-0.651)	0.649 (0.634-0.662)	0.641 (0.629-0.656)
	Range (80% PI)[3]	0-0.714 (0.001-0.508)	0-0.829 (0.003-0.777)	0-0.814 (0.005-0.77)	0-0.818 (0.006-0.768)	0-0.829 (0.007-0.778)	0-0.834 (0.008-0.775)	0-0.821 (0.012-0.767)

Table 4-5. Disease control strategies ranked based on indicated model outcomes after adjusting for the effects of all population datasets for several levels of local-area spread.

Disease control strategies are described in Table 4-2. Results are presented for three levels of local-area spread, as described in section 4.3.4.

a) Outbreak duration

Disease control strategy	Level of local-area spread		
	1) Moderate	2) Low	3) High
mr	1[a]	1[a]	1[a]
trcDestr	2[b]	3[b]	2[b]
trcDestrRing1km	3[b]	2[b]	3[b]
trc	4[cd]	4[cd]	4[c]
ring3km	5[cde]	7[de]	6[d]
baseline	6[cde]	5[cde]	5[d]
ring1km	7[de]	6[cde]	7[d]

b) Number of infected flocks[1]

Disease control strategy	Level of local-area spread		
	1) Moderate	2) Low	3) High
mr	1[a]	1[a]	1[a]
trcDestr	2[bc]	3[bcd]	3[c]
trcDestrRing1km	3[bcd]	2[bc]	4[c]
trc	4[cde]	4[cde]	2[b]
baseline	5[cde]	7[de]	5[d]
ring3km	6[de]	6[de]	6[d]
ring1km	7[de]	5[cde]	7[d]

c) Number of depopulated flocks[1]

Disease control strategy	Level of local-area spread		
	1) Moderate	2) Low	3) High
mr	1[a]	1[a]	1[a]
trc	2[bc]	2[bc]	2[b]
baseline	3[bcd]	3[bcd]	3[c]
ring1km	4[cde]	4[cde]	4[c]
trcDestr	5[def]	5[def]	5[d]
trcDestrRing1km	6[ef]	6[ef]	6[d]
ring3km	7[g]	7[g]	7[e]

d) Number of depopulated birds[1]

Disease control strategy	Level of local-area spread		
	1) Moderate	2) Low	3) High
mr	1[a]	1[a]	1[a]
trc	2[bc]	2[bc]	2[b]
baseline	3[bcd]	3[bcd]	4[b]
ring1km	4[cde]	4[cde]	3[b]
trcDestr	5[def]	5[def]	5[c]
trcDestrRing1km	6[ef]	6[ef]	6[c]
ring3km	7[g]	7[g]	7[d]

[a-g] Strategies indicated with the same letter [within the same section of the table (a-d) and the same column (1-3)] do not differ significantly from one another, based on post-hoc pairwise comparisons made after application of the Mack-Skillings test (Hollander and Wolfe, 1999; Mack and Skillings, 1980) as described in the text.

[1] The ranks of control strategies and results of further statistical analyses are identical for outcomes that considered the proportion of all flocks/birds affected.

Table 4-6. Scenarios based on different population datasets ranked by indicated model outcomes after adjusting for the effects of disease control strategies, and quantitative differences relative to the CLPHD dataset.

Simulation modeling outcome	*Population dataset*				
	CLPHD	***CLPHD (A)***	***LLNL***	***RTI***	***USDA***
a) Outbreak duration (days)					
Rank[1]	3[b]	4[b]	2[a]	1[a]	5[c]
Difference in median, relative to CLPHD[2]	-	0% (-7%, 7%)	-21% (-29%, -9%)	-21% (-29%, -9%)	154% (14%, 220%)
Difference in 90th percentile, relative to CLPHD[3]	-	0% (-2%, 2%)	-37% (-43%, -24%)	-45% (-55%, -24%)	36% (3%, 224%)
b) Total number of infected flocks					
Rank[1]	3[b]	4[b]	2[a]	1[a]	5[c]
Difference in median, relative to CLPHD[2]	-	1% (-15%, 26%)	-38% (-48%, -22%)	-39% (-50%, -22%)	2514% (61%, 3419%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-12%, 0%)	-63% (-72%, -51%)	-70% (-77%, -49%)	301% (126%, 1341%)
c) Proportion of all flocks in the population infected					
Rank[1]	3[c]	4[c]	1[a]	2[b]	5[d]
Difference in median, relative to CLPHD[2]	-	1% (-15%, 26%)	-23% (-35%, -3%)	0% (-18%, 28%)	1150% (-23%, 1583%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-12%, 0%)	-54% (-65%, -39%)	-50% (-62%, -17%)	92% (8%, 589%)
d) Total number of flocks depopulated					
Rank[1]	3[b]	4[b]	2[a]	1[a]	5[c]
Difference in median, relative to CLPHD[2]	-	1% (-11%, 18%)	-41% (-49%, -17%)	-41% (-48%, -22%)	403% (67%, 608%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-11%, 2%)	-47% (-59%, -41%)	-57% (-64%, -48%)	81% (4%, 537%)
e) Proportion of all flocks in the population depopulated					
Rank[1]	3[c]	4[c]	1[a]	2[b]	5[d]
Difference in median, relative to CLPHD[2]	-	1% (-11%, 18%)	-27% (-37%, 3%)	-3% (-15%, 28%)	140% (-20%, 239%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-11%, 2%)	-35% (-49%, -27%)	-30% (-41%, -15%)	-13% (-50%, 205%)
f) Total number of birds depopulated					
Rank[1]	3[b]	4[b]	1[a]	2[a]	5[c]
Difference in median, relative to CLPHD[2]	-	1% (-15%, 16%)	-44% (-51%, -27%)	-35% (-48%, -19%)	442% (-47%, 721%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-12%, 0%)	-59% (-68%, -54%)	-60% (-68%, -39%)	31% (-10%, 279%)
g) Proportion of all birds in the population depopulated					
Rank[1]	3[c]	4[c]	1[a]	2[b]	5[d]
Difference in median, relative to CLPHD[2]	-	1% (-15%, 16%)	-33% (-41%, -12%)	-2% (-22%, 23%)	546% (-36%, 878%)
Difference in 90th percentile, relative to CLPHD[3]	-	-2% (-12%, 0%)	-51% (-62%, -45%)	-39% (-52%, -8%)	56% (7%, 351%)

Table 4-6 (continued).

[1] Ranks are based on the average rank sum score calculated for the Mack-Skillings test (Hollander and Wolfe, 1999; Mack and Skillings, 1980).

[2] For each population dataset, the difference between the median outcome value from each control strategy scenario and the median from the corresponding scenario that used the reference population dataset was calculated. The average (mean) difference in medians and the range of differences in medians (in parentheses) are shown.

[3] Similar to (2) above, but for the 90^{th} percentiles.

[a-d] Values indicated with the same letter do not differ significantly from one another, as determined by post-hoc pairwise comparisons made after application of the Mack-Skillings test.

Table 4-7. Scenarios based on different population datasets ranked by indicated model outcomes after accounting for the effects of disease control strategies for several levels of local-area spread.

a) Outbreak duration

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
RTI	1[a]	1[a]	2[a]
LLNL	2[a]	2[a]	1[a]
CLPHD	3[b]	3[b]	3[b]
CLPHD(A)	4[b]	4[b]	4[b]
USDA	5[c]	5[c]	5[c]

b) Total number of infected flocks

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
RTI	1[a]	1[a]	2[a]
LLNL	2[a]	2[a]	1[a]
CLPHD	3[b]	3[b]	3[b]
CLPHD(A)	4[b]	4[b]	4[b]
USDA	5[c]	5[c]	5[c]

c) Proportion of all flocks in the population infected

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
LLNL	1[a]	1[a]	1[a]
RTI	2[b]	2[bc]	2[b]
CLPHD	3[c]	3[bcd]	3[c]
CLPHD(A)	4[c]	4[cd]	4[c]
USDA	5[d]	5[e]	5[d]

d) Total number of flocks depopulated

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
RTI	1[a]	1[a]	2[a]
LLNL	2[a]	2[a]	1[a]
CLPHD	3[b]	3[b]	3[b]
CLPHD(A)	4[b]	4[b]	4[b]
USDA	5[c]	5[c]	5[c]

e) Proportion of all flocks in the population depopulated

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
LLNL	1[a]	1[a]	1[a]
RTI	2[b]	2[b]	2[b]
CLPHD	3[c]	3[c]	3[c]
CLPHD(A)	4[c]	4[c]	4[c]
USDA	5[d]	5[d]	5[c]

f) Total number of birds depopulated

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
LLNL	1[a]	1[a]	1[a]
RTI	2[a]	2[b]	2[b]
CLPHD	3[b]	3[c]	3[c]
CLPHD(A)	4[b]	4[c]	4[c]
USDA	5[c]	5[d]	5[d]

g) Proportion of all birds in the population depopulated

Population dataset	***Level of local-area spread***		
	1) Mod.	*2) Low*	*3) High*
LLNL	1[a]	1[a]	1[a]
RTI	2[b]	2[b]	2[b]
CLPHD	3[c]	3[c]	3[c]
CLPHD(A)	4[c]	4[c]	4[c]
USDA	5[d]	5[d]	5[d]

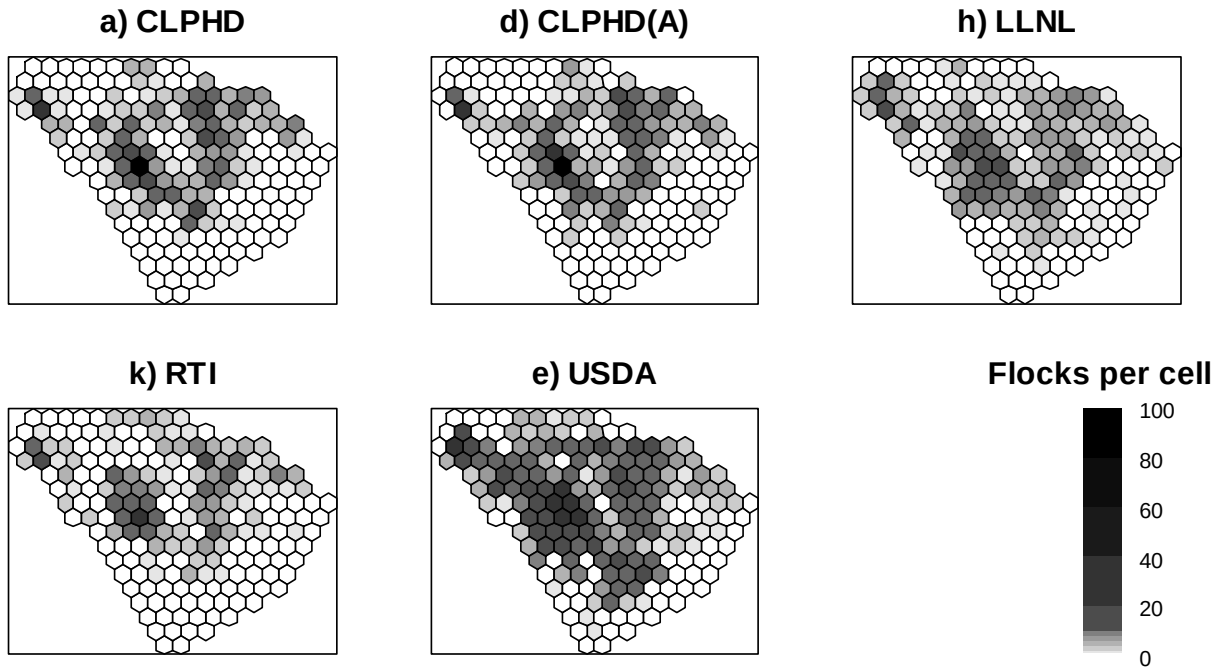

Figure 4-1. Spatial distributions and densities of poultry flocks in each population dataset described in Table 4-1.

Each grid cell represents approximately 465 km^2.

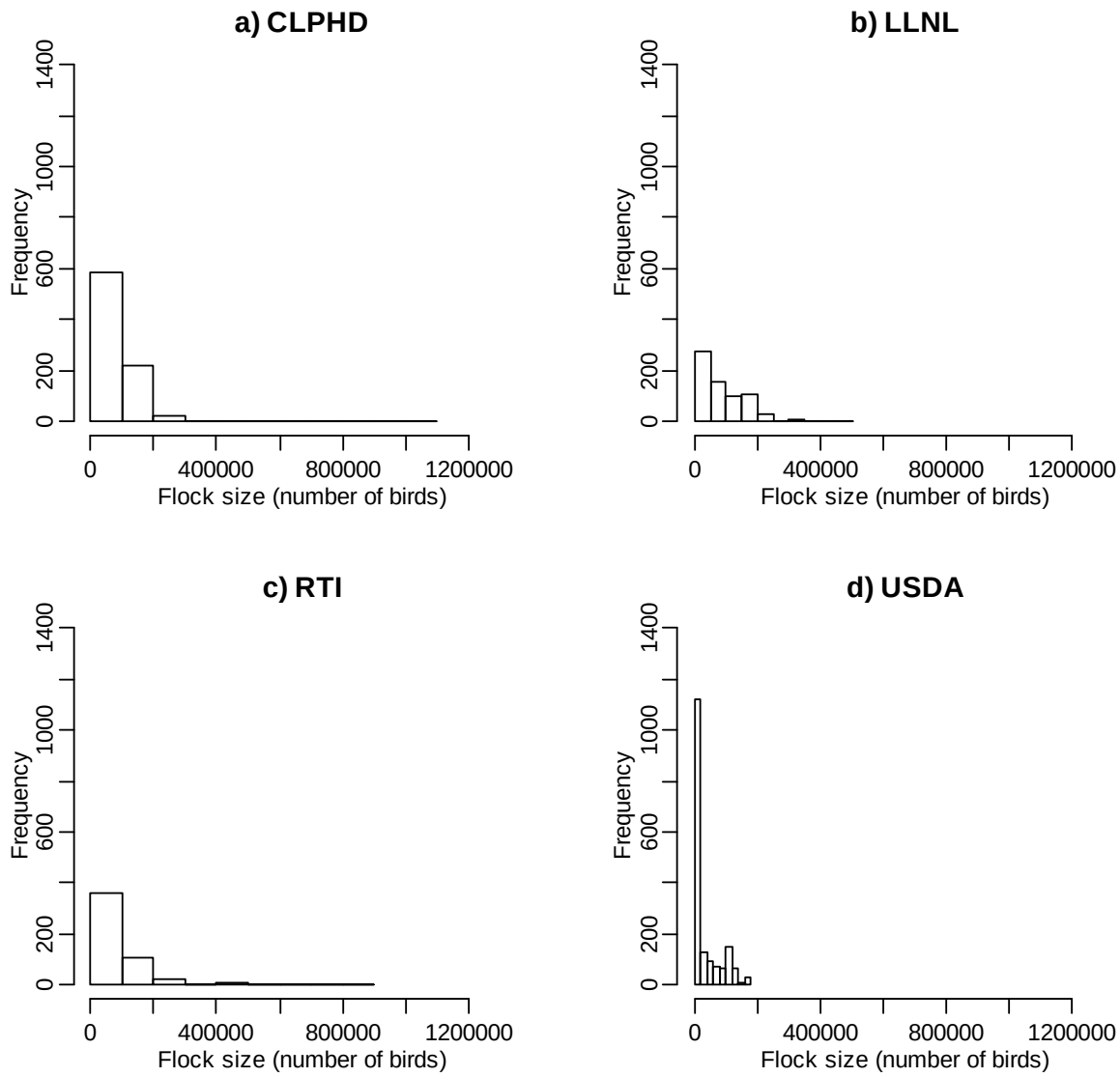

Figure 4-2. Distributions of commercial poultry flock sizes in the four primary population datasets described in Table 4-1.

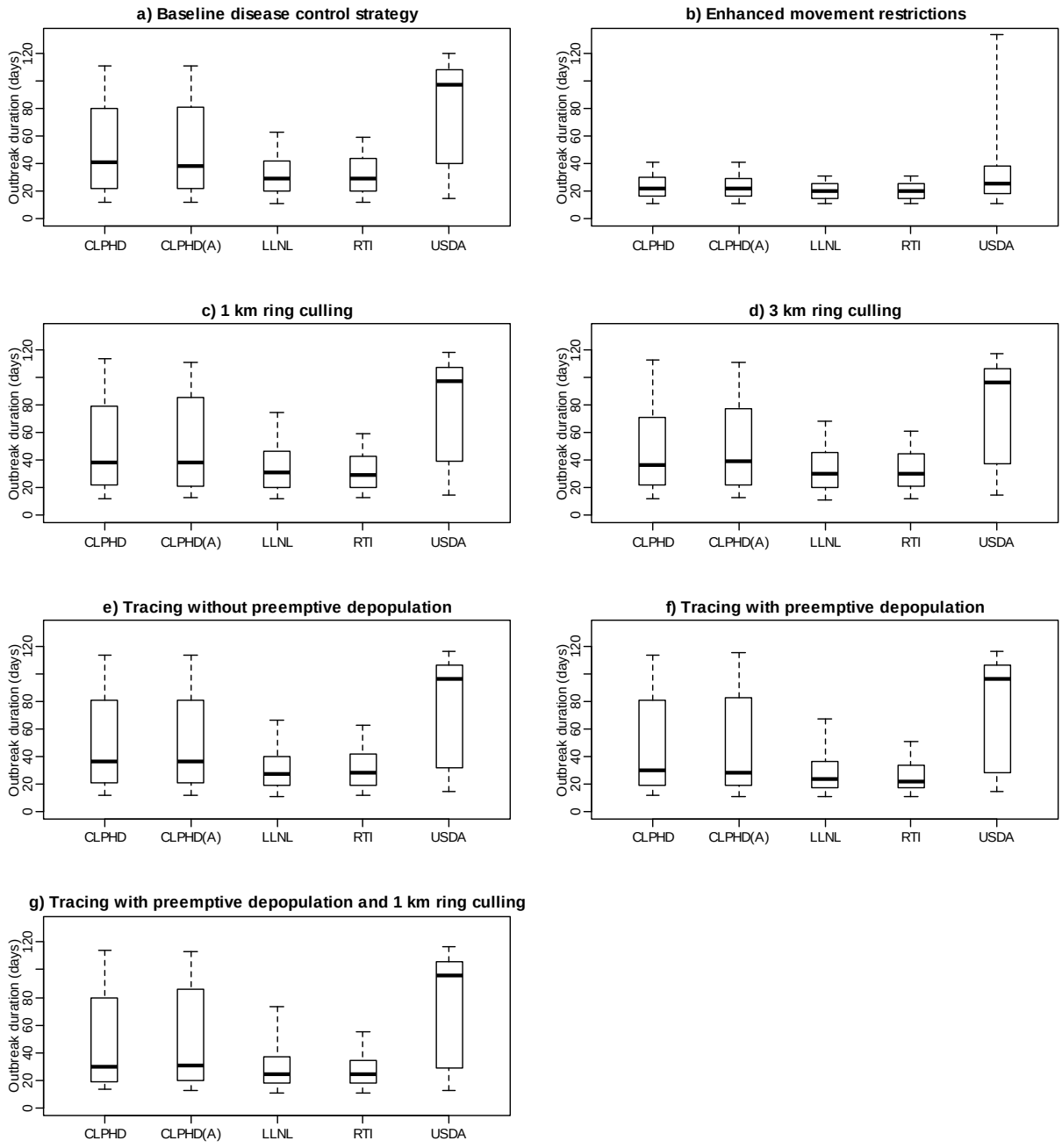

Figure 4-3. Distributions of outbreak durations (in days) produced by each simulated disease control strategy for each population dataset.

Population datasets, indicated for each column in each plot, are described in Table 4-1. Disease control strategies (a-g) are described in Table 4-2.

Thick horizontal lines indicate the median for each scenario. Boxes indicate the interquartile range, *i.e.*, the range between the 25th and 75th percentiles. Dashed lines indicate the 80% probability interval, *i.e.*, the range between the 10th and 90th percentiles.

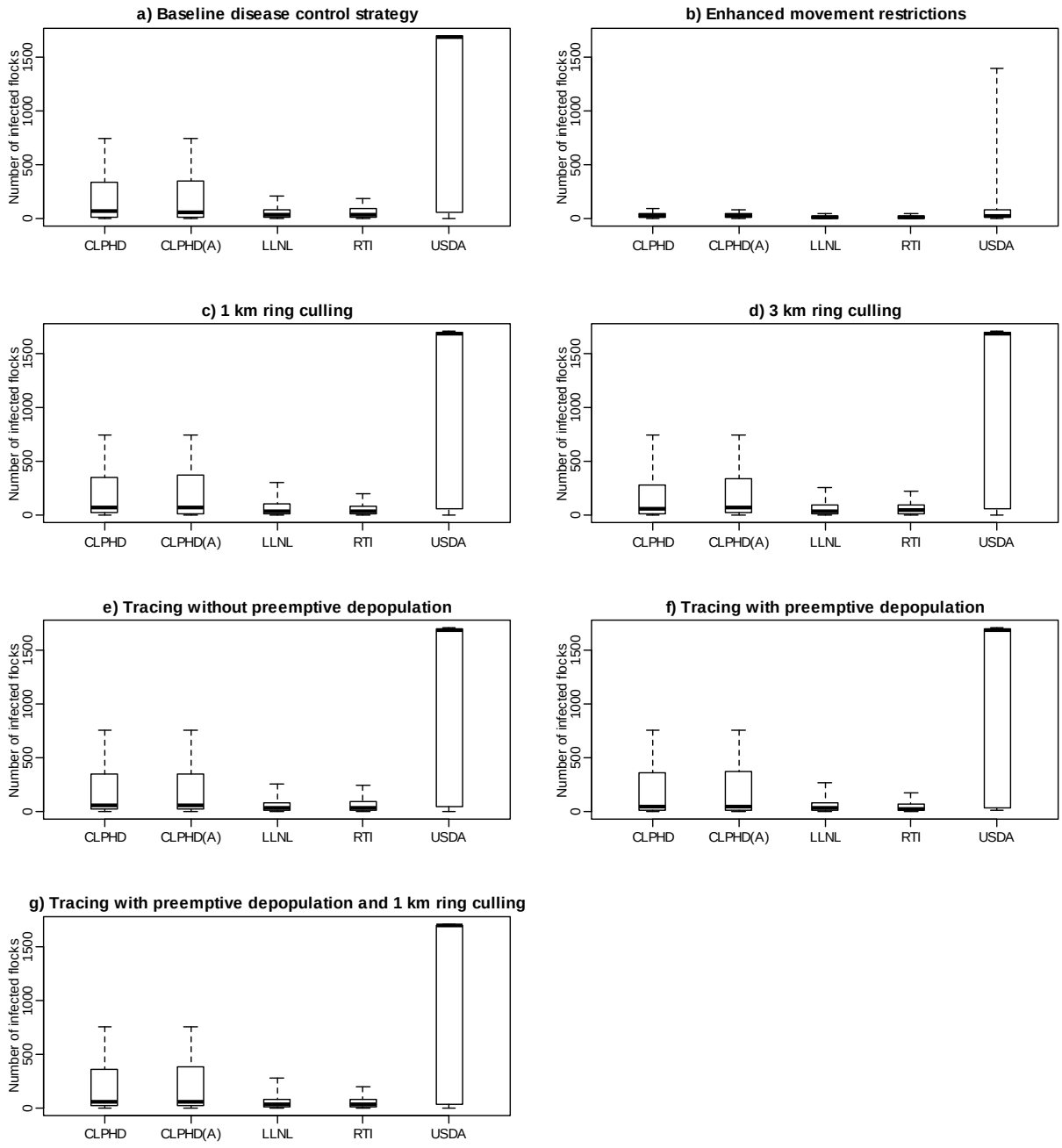

Figure 4-4. Distributions of total number of infected flocks produced by each simulated disease control strategy for each population dataset.

Population datasets, indicated for each column in each plot, are described in Table 4-1. Disease control strategies (a-g) are described in Table 4-2.

Thick horizontal lines indicate the median for each scenario. Boxes indicate the interquartile range, *i.e.*, the range between the 25th and 75th percentiles. Dashed lines indicate the 80% probability interval, *i.e.*, the range between the 10th and 90th percentiles.

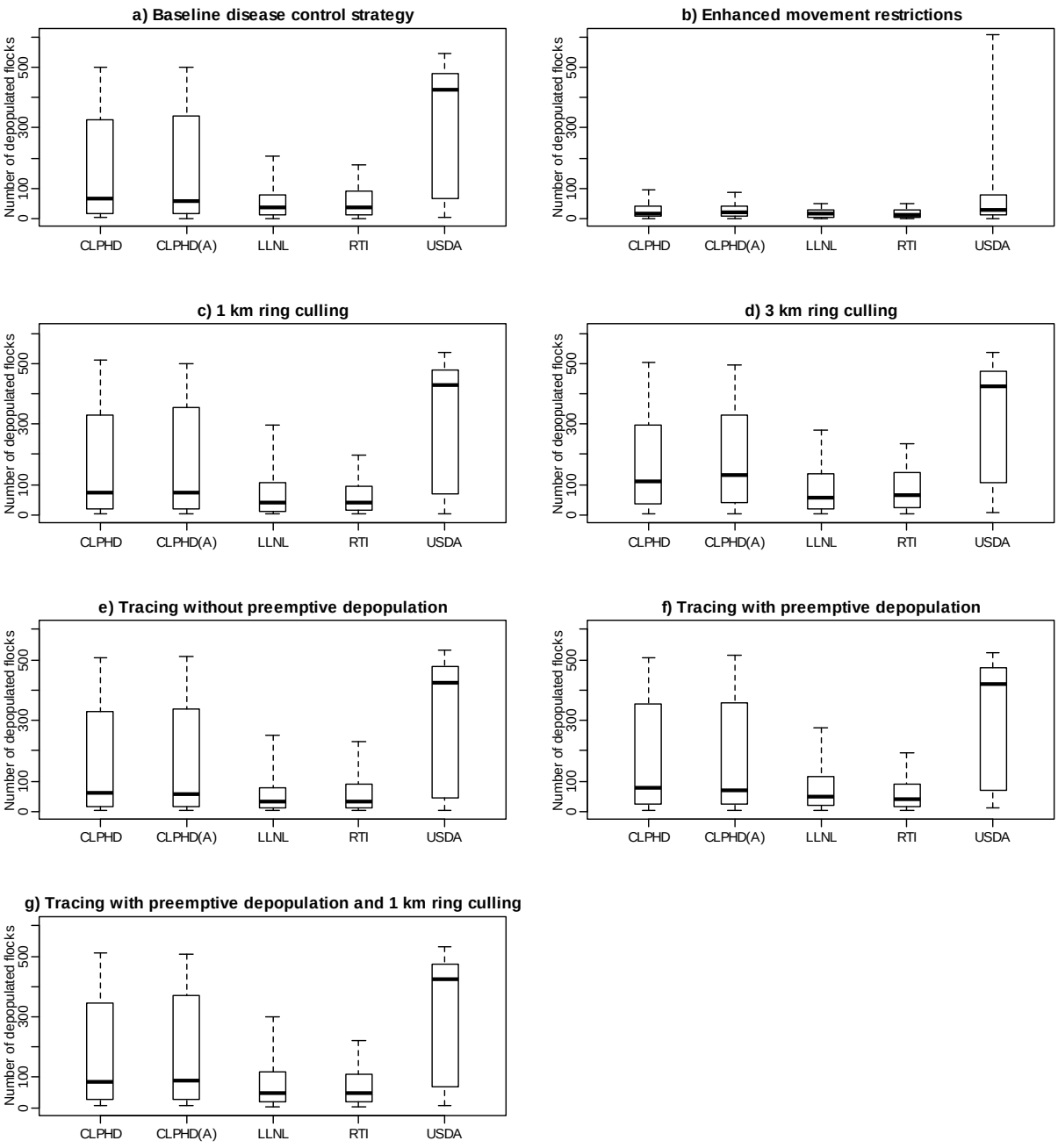

Figure 4-5. Distributions of total number of depopulated flocks produced by each simulated disease control strategy for each population dataset.

Population datasets, indicated for each column in each plot, are described in Table 4-1. Disease control strategies (a-g) are described in Table 4-2.

Thick horizontal lines indicate the median for each scenario. Boxes indicate the interquartile range, *i.e.*, the range between the 25th and 75th percentiles. Dashed lines indicate the 80% probability interval, *i.e.*, the range between the 10th and 90th percentiles.

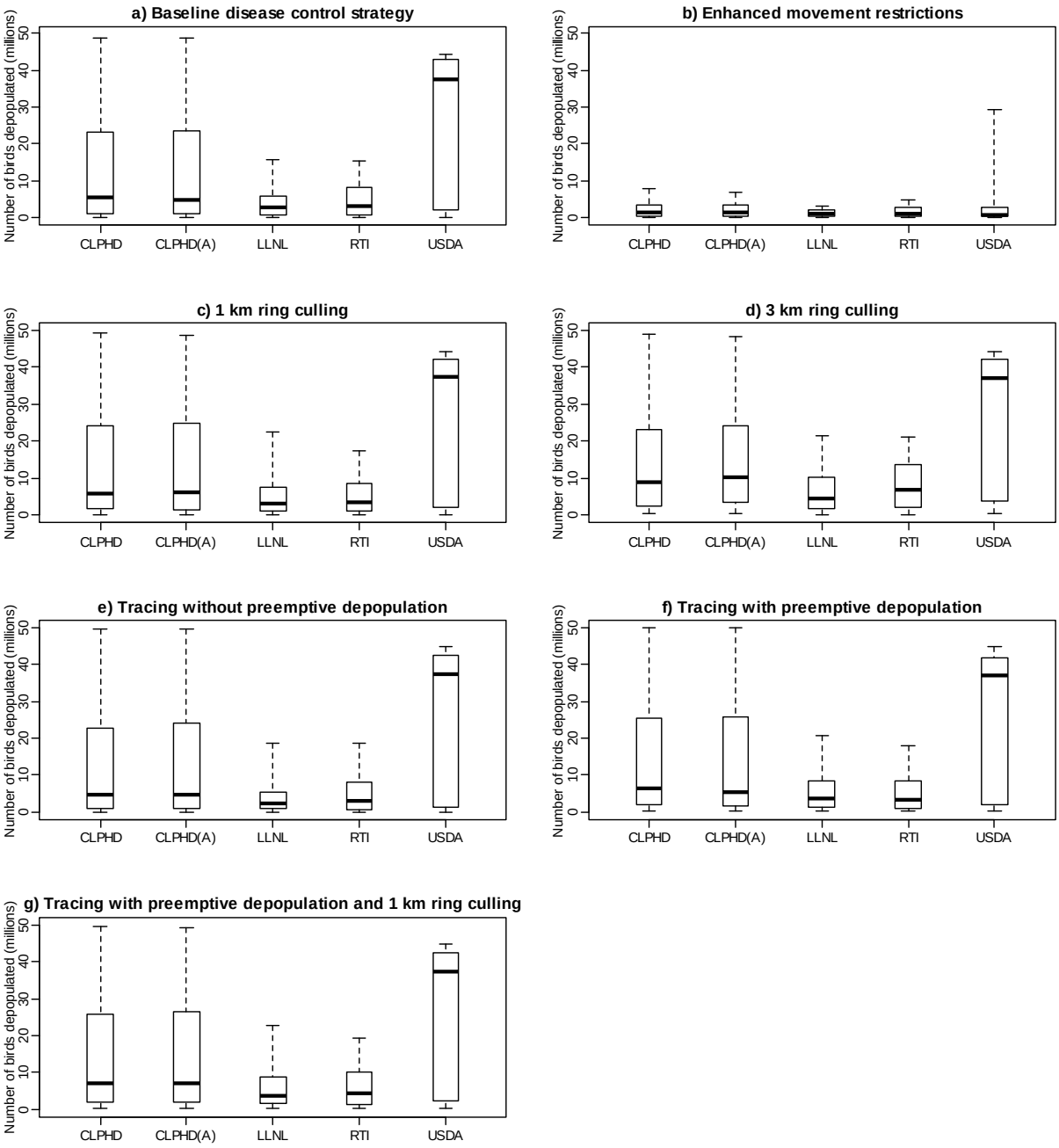

Figure 4-6. Distributions of total number of depopulated birds (shown in millions) produced by each simulated disease control strategy for each population dataset.

Population datasets, indicated for each column in each plot, are described in Table 4-1. Disease control strategies (a-g) are described in Table 4-2.

Thick horizontal lines indicate the median for each scenario. Boxes indicate the interquartile range, *i.e.*, the range between the 25th and 75th percentiles. Dashed lines indicate the 80% probability interval, *i.e.*, the range between the 10th and 90th percentiles.

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5. Summary and conclusions

"The validation of a model is not that it is 'true' but that it generates good testable hypotheses relevant to important problems" (Levins, 1966). As noted in chapter 2, there is no quantitative, objective mechanism that can be relied upon to determine whether a model is useful. Any assessment of a model's utility must be based on practical and subjective evaluations.

In a recent discussion of stochastic modeling, Rorres et al. (2011) quote John von Neumann: "the justification of a mathematical model is 'solely and precisely that it is expected to work.'" The authors then elaborate on this definition and suggest that a "working" model is one that fits available outcome data and can be successfully applied to fit data from future events. This definition is attractive but limited. First, it is only with the advantage of hindsight after an event that we can determine whether a model has "worked" It should be noted that even hindsight is not sufficient to determine whether a model has "worked", as evidenced by the continuing debate about the application of disease models during the effort to eradicate FMD from the UK in 2001 (Keeling, 2005; Kitching, 2004; Kitching et al., 2006; Mansley et al., 2011; Savill et al., 2006a, 2007). Second, the application of models is limited to situations in which outcome data exists, a drawback discussed in chapter 2.

An alternative criterion for determining whether a model "works" is whether the model is helpful in providing direction for action before an outbreak occurs. Without the benefit of hindsight and predictive, fitted epidemiologic models, we might instead attempt to determine if a model is useful, credible, and realistic. The models discussed in chapters 2 and 3 are intended to be used in advance of an outbreak to provide useful insight and information to response planners and policy makers and to be useful, realistic representations of epidemiologic phenomena.

The decision whether to include a realistic representation of within-unit disease dynamics in a model (chapter 3) is partly dependent upon the purpose for which the model is constructed. The decision can have practical effects: in a mathematical model of between-unit spread of disease, for example, Ferguson et al. (2001) showed that assumptions regarding the level of infectiousness of an infected premises could alter model-supported decisions regarding the use of disease control measures, such as the use of pre-emptive culling in addition to rapid depopulation of known infected premises. Savill et al. (2007) pointed out, however, that factors other than within-unit prevalence of infectious individuals, such as the level of farm biosecurity, affect the ability of infected premises to contribute to spread of disease. Both reports indicate that data pertaining to the actual infectiousness of infected premises is difficult to obtain. As a result of their work, Savill et al. (2007) concluded that there is insufficient evidence to support the inclusion of a dynamically changing level of infectiousness of infected premises in their models. By contrast, Kostova-Vassilevska (2004) asserted that "[i]t is generally accepted that the infectiousness of an infected farm increases with time as more animals become infectious" and suggested that models of within-unit disease dynamics should be included in larger models of between-unit spread and control of disease. Carpenter et al. (2004) similarly suggested that intra-unit disease dynamics are a critical component of a model of between-unit transmission of disease.

Although the value and utility of models of within-unit disease dynamics for simulating differences in the levels of unit infectiousness over time remain to be definitively addressed, the use of such models to simulate the effects of different disease surveillance and detection activities is better supported. The ability to detect disease in an infected unit is dependent upon the prevalence of disease or incidence of mortality (Dorea et al., 2010; Savill et al., 2006). As

the application of all disease control measures is contingent upon detection of disease, the use of a model of within-unit disease dynamics does have a place in larger models of between-unit spread and control of disease. The conceptual model of within-unit disease dynamics described in chapter 3 is sufficiently computationally efficient that it should be feasible to incorporate it directly into models of between-unit disease spread and control.

For a model to be credible, it must also be based on reliable, valid data, or alternatively, should explicitly incorporate and account for potential sources of uncertainty when existing data sources are known not to be entirely accurate. In chapter 4, we demonstrated that, for purposes of qualitative-decision making, models can, at least in some instances, rely on artificially generated (but not wildly unrealistic) data. As models are increasingly used to address questions that are more quantitative than qualitative in nature (USDA-APHIS-VS-CEAH, 2009), it is important to be circumspect about the capabilities and limitations of such models.

The development and application of epidemiologic simulation models allows us to address problems in veterinary epidemiology that would otherwise be intractable to experimental investigation. The concluding statement of chapter 2 is worth reiterating in closing: "To the extent that a model is a scientific experiment and theoretical development, its testing and validation are within the purview of the scientific community" (Rykiel, 1996) and all of its associates.

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