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

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Abstract

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.

Keywords: stochastic model, disease transmission, within-flock, within-herd, modeling, poultry, livestock
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., 2006), or to investigate the likelihood and timing of detection of disease under different conditions (Carpenter et al., 2004; Savill et al., 2006). 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., 2003a; 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.

2. Materials and Methods

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 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 1. Details are presented in section 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.

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 3.2.

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 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).

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, 2003).

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. Results

3.1. The conceptual model

An overview of the model framework, which is composed of four distinct but interrelated subcomponents, is provided in Figure 1. The four major subcomponents of the model framework simulate the following events: disease spread among individuals (Section 3.1.1); disease progression in infected individuals, disease mortality, and progression of immunity (Section 3.1.2); background mortality (i.e., death unrelated to disease) (Section 3.1.3); and the process of vaccination itself (Section 3.1.4).

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 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 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).
3.1.2. 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 1 and Figure 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.

3.1.3. 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.
3.1.4. Subcomponent for vaccination

When vaccination occurs, a user-specified model parameter determines the proportion of the population to be vaccinated (Figure 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 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.

3.1.5. 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 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.

3.2. 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.
3.2.1. 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.

3.2.2. 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.

3.2.3. 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.

3.2.4. *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. *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 5 and Table 4. The rate of disease spread (whether low, moderate, or high as shown in Table 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%.
3.4. 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 6 and Table 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%).

4. Discussion

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., 2003a; 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.

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.

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.

6. References cited


USDHS (United States Department of Homeland Security)-STD (Science and Technology Directorate), 2012. Updated Site-Specific Biosafety and Biosecurity Mitigation Risk Assessment, Vol. II. Washington, DC, USA.


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

<table>
<thead>
<tr>
<th>Transition state</th>
<th>Description and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>Susceptible individuals will become infected upon effective exposure to disease. Upon infection, susceptible individuals will make a transition to the latent state.</td>
</tr>
<tr>
<td>Latent</td>
<td>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 subclinical state.</td>
</tr>
<tr>
<td>Subclinical</td>
<td>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.</td>
</tr>
<tr>
<td>Clinical</td>
<td>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.</td>
</tr>
<tr>
<td>Naturally immune/recovered</td>
<td>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.</td>
</tr>
<tr>
<td>Dead from disease</td>
<td>An infected individual that completes its disease cycle and dies as a result of infection will have this state. This state is permanent.</td>
</tr>
<tr>
<td>Dead from causes unrelated to disease</td>
<td>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.</td>
</tr>
<tr>
<td>Vaccinated but not yet immune to disease</td>
<td>Individuals have been vaccinated but have not yet mounted an immune response. These individuals are susceptible to disease.</td>
</tr>
<tr>
<td>Vaccinated and immune to disease</td>
<td>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.</td>
</tr>
<tr>
<td>Not effectively vaccinated</td>
<td>These individuals will not develop an immune response after vaccination, and will remain susceptible to infection.</td>
</tr>
</tbody>
</table>
Table 2. Parameters used for models of foot-and-mouth disease.

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Distribution/Value¹</th>
<th>Notes and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size (number of cattle)</td>
<td>1000</td>
<td>Based on Carpenter et al. (2004).</td>
</tr>
<tr>
<td>Latent period (days)</td>
<td>Weibull( 1.782, 3.974 )</td>
<td>Mardones et al. (2010).</td>
</tr>
<tr>
<td>Subclinical infectious period (days)</td>
<td>Gamma( 1.222, 1.672 )</td>
<td>Mardones et al. (2010).</td>
</tr>
<tr>
<td>Clinical infectious period (days)</td>
<td>Weibull( 1.453, 3.544 )</td>
<td>Derived from Mardones et al. (2010). Based on reported durations of the subclinical infectious period and the overall infectious period.</td>
</tr>
<tr>
<td>Number of adequate exposures per day</td>
<td>High: Poisson( 54.1 )</td>
<td>Means from Carpenter et al. (2004); within-herd contact was assumed to follow a Poisson process (Vose, 1996).</td>
</tr>
<tr>
<td></td>
<td>Moderate: Poisson( 21.8 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low: Poisson( 13.7 )</td>
<td></td>
</tr>
<tr>
<td>Detection threshold based on prevalence of clinical cattle</td>
<td>1%, 5%</td>
<td>Based on Carpenter, Thurmond, &amp; Bates, 2004.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Distribution/Value</th>
<th>Notes and references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size (number of birds)</td>
<td>88,000</td>
<td>Median size of a broiler chicken flock in South Carolina (Patyk et al., in preparation).</td>
</tr>
<tr>
<td>Latent period (hours)</td>
<td>Gamma( 1.34, 4.3 )</td>
<td>Derived from Bouma et al., 2009.</td>
</tr>
<tr>
<td>Subclinical infectious period (hours)</td>
<td>0</td>
<td>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.</td>
</tr>
<tr>
<td>Clinical infectious period (hours)</td>
<td>Gamma( 13.36, 3.77 )</td>
<td>Derived from Bouma et al., 2009.</td>
</tr>
<tr>
<td>Number of adequate exposures per hour</td>
<td>Poisson( 1.375 )</td>
<td>Mean derived from Bouma et al., 2009; within-flock contact was assumed to follow a Poisson process (Vose, 1996).</td>
</tr>
<tr>
<td>Probability that an infected bird will die from disease</td>
<td>0.90</td>
<td>Easterday et al. (1997); Spickler et al. (2008); Swayne and Halvorson (2003).</td>
</tr>
<tr>
<td>Vaccination coverage</td>
<td>0%, 50%, 90%</td>
<td>Based on Savill et al. (2006).</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>100%</td>
<td>Based on Savill et al. (2006).</td>
</tr>
<tr>
<td>Detection threshold based on total mortality</td>
<td>0.2% during one 24-hour period</td>
<td>Dorea et al. (2010).</td>
</tr>
<tr>
<td></td>
<td>0.5% during each of two consecutive 24-hour periods</td>
<td>Bos et al., 2007</td>
</tr>
</tbody>
</table>

Table 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.

<table>
<thead>
<tr>
<th>Model outcome</th>
<th>Rate of disease spread</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Outbreak duration (days)**</td>
<td>34 (0 - 49)</td>
<td>33 (1 - 45)</td>
<td>31 (1 - 49)</td>
</tr>
</tbody>
</table>

Detection based on threshold of 1% prevalence of clinical disease

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Percent of outbreaks detected</td>
<td>98.4%</td>
<td>98.8%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Time to detection (days)**</td>
<td>8 (4 - 18)</td>
<td>8 (3 - 17)</td>
<td>7 (3 - 18)</td>
</tr>
<tr>
<td>Prevalence of infection at time of detection**</td>
<td>0.37 (0.12 - 0.696)</td>
<td>0.4605 (0.172 - 0.873)</td>
<td>0.673 (0.309 - 0.988)</td>
</tr>
</tbody>
</table>

Detection based on threshold of 5% prevalence of clinical disease

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of outbreaks detected</td>
<td>98.4%</td>
<td>98.8%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Time to detection (days)**</td>
<td>10 (6 - 19)</td>
<td>9 (5 - 18)</td>
<td>8 (4 - 19)</td>
</tr>
<tr>
<td>Prevalence of infection at time of detection**</td>
<td>0.907 (0.658 - 0.968)</td>
<td>0.959 (0.816 - 0.985)</td>
<td>0.983 (0.955 - 0.994)</td>
</tr>
</tbody>
</table>

** Values shown indicate the median and range from 1000 stochastic iterations of each model.

Table 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.

<table>
<thead>
<tr>
<th>Model outcome</th>
<th>Vaccine coverage</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>Outbreak duration (days)**</td>
<td>7 (6.2 - 9.2)</td>
<td>7.2 (6.4 - 8.9)</td>
<td>10.1 (1 - 14.2)</td>
</tr>
</tbody>
</table>

Detection based on threshold of 0.2% mortality over a 24-hour period

<table>
<thead>
<tr>
<th></th>
<th>0%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of outbreaks detected</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Time to detection (days)**</td>
<td>2.1 (1.8 - 3.1)</td>
<td>2.5 (2 - 3.6)</td>
<td>4.2 (3.1 - 6.9)</td>
</tr>
<tr>
<td>Prevalence of infection at time of detection**</td>
<td>0.998 (0.998 - 0.999)</td>
<td>0.498 (0.497 - 0.498)</td>
<td>0.065 (0.049 - 0.076)</td>
</tr>
</tbody>
</table>

Detection based on threshold of 0.5% mortality observed during each of two consecutive 24-hour periods

<table>
<thead>
<tr>
<th></th>
<th>0%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of outbreaks detected</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Time to detection (days)**</td>
<td>3.2 (2.9 - 4.2)</td>
<td>3.7 (3.2 - 4.8)</td>
<td>5.7 (4.6 - 8.3)</td>
</tr>
<tr>
<td>Prevalence of infection at time of detection**</td>
<td>0.717 (0.68 - 0.75)</td>
<td>0.352 (0.331 - 0.377)</td>
<td>0.069 (0.063 - 0.075)</td>
</tr>
</tbody>
</table>

** Values shown indicate the median and range from 1000 stochastic iterations of each model.
Figure 1. Schematic representation of the processes included in the model of within-unit spread of disease, as described in section 3.1.
Figure 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 3.1.1.

Enter submodel of adequate exposure

\[ totalExposures = 0 \]

For each infectious (subclinical or clinical) individual...

Determine number of adequate exposures (exposures) for the infectious individual based on the user-specified distribution for the number of adequate exposures.

\[ totalExposures = totalExposures + exposures \]

(End of loop)

Determine the number of unique individuals (exposedIndivs) who receive adequate exposure, based on the total number of adequate exposures (totalExposures) and the number of living individuals (nAlive):

\[ exposedIndivs = \text{Gan}(nAlive - 1, totalExposed) \]

Determine the number of exposed individuals that will become infected (infectedIndivs), based on the number of exposed individuals (exposedIndivs), the number of living individuals (nAlive), and the total number of susceptible individuals (nSusc), which includes individuals that are vaccinated but not yet immune:

\[ infectedIndivs = \text{Hypergeometric}(exposedIndivs, nSusc, nAlive) \]

Determine the number of individuals who were vaccinated but not yet immune which will now be infected before immunity can develop (infVacciIndivs), based on the number of individuals who will become infected (infectedIndivs), the total number of susceptible individuals (nSusc) and the total number of vaccinated but not yet immune individuals (nPendingImmune):

\[ infVacciIndivs = \text{Hypergeometric}(infectedIndivs, nPendingImmune, nSusc) \]

Reduce the total number of pending immune individuals by a total of infVacciIndivs. Apply a multivariate hypergeometric distribution to reduce the number of vaccinated individuals scheduled to become immune on each day by an appropriate number.

Return
Figure 3. Schematic representation of disease progression (i.e., disease state transitions), mortality, and immunity in the model, as described in section 3.1.2.
Figure 4. Schematic representation of the vaccination subcomponent used in the model, as described in section 3.1.4.

Enter vaccination submodel

Determine the proportion of the population to be vaccinated (propnVac) from the user-specified distribution.

Determine vaccine efficacy (vacEfficacy) from the user-specified distribution.

Determine the number of individuals which will be "adequately vaccinated" (nAdequatelyVac: see description below and in main text) based on the values above and the total number of live individuals (nAlive):

\[ n_{\text{Adequately Vac}} = \text{Round}(\text{propnVac} \times \text{vacEfficacy} \times n_{\text{Alive}}) \]

Apply a multivariate hypergeometric distribution to determine how many of the adequately vaccinated individuals were susceptible (vacSusc), infected, previously vaccinated but not yet immune, vaccine immune (vacVacImmune), or naturally immune prior to vaccination (vacNatImmune).

Calculate the probability that an adequately vaccinated individual will become vaccine immune x days after vaccination for every day in the discrete representation of the user-defined distribution for the time to onset of immunity after vaccination. Call this array of probabilities pOnsetOfImmunityByDay.

For susceptible individuals that were adequately vaccinated:
Based on vacSusc and pOnsetOfImmunityByDay, apply a multinomial distribution to determine when vaccine immunity will develop for all vacSusc individuals.

For infected individuals that were adequately vaccinated:
Do nothing. Adequate vaccination is not effective, and will have no impact on progression of disease.

For previously vaccinated but not yet immune individuals which were adequately vaccinated:
Do nothing. Repeated vaccination will have no effect on time to onset of immunity.

Run submodel for vaccination of immune individuals for naturally immune individuals

Run submodel for vaccination of immune individuals for vaccine immune individuals

Return
Figure 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 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.

a) Time to detection (low contact rate)

b) Time to detection (moderate contact rate)

c) Time to detection (high contact rate)

d) Prevalence of infection at first detection (low contact rate)

e) Prevalence of infection at first detection (moderate contact rate)

f) Prevalence of infection at first detection (high contact rate)