An Introduction to Infectious Disease Modelling for Veterinarians

Mark Stevenson, Anke Wiethoelter
Faculty of Veterinary and Agricultural Sciences
The University of Melbourne
Victoria 3010, Australia

Richard Bradhurst
Centre for Excellence in Biosecurity and Risk Analysis
The University of Melbourne
Victoria 3010, Australia

THE UNIVERSITY OF
MELBOURNE

Contact information:

Mark Stevenson (mark.stevenson1@unimelb.edu.au)
Anke Wiethoelter (anke.wiethoelter@unimelb.edu.au)
Faculty of Veterinary and Agricultural Sciences
University of Melbourne
Victoria 3010
Australia

Richard Bradhurst (richard.bradhurst@unimelb.edu.au)
Centre for Excellence in Biosecurity and Risk Analysis
University of Melbourne
Victoria 3010
Australia

Tel.: +61 (03) 9035 4114
Fax: +61 (03) 8344 7374

URL: fvas.unimelb.edu.au/veam

1 October 2017

An Introduction to Infectious Disease Modelling for Veterinarians

Mark Stevenson* and Anke Wiethoelter†

Faculty of Veterinary and Agricultural Sciences

The University of Melbourne, Parkville Victoria 3010, Australia

Richard Bradhurst‡

Centre for Excellence in Biosecurity and Risk Analysis

The University of Melbourne, Parkville Victoria 3010, Australia

September 29, 2017

Contents

*Email: mark.stevenson1@unimelb.edu.au

†Email: anke.wiethoelter@unimelb.edu.au

‡Email: richard.bradhurst@unimelb.edu.au

1 Introduction

Human ethics, animal welfare, consumer awareness, and trade regulations demand increasing protection and a reduced level of risk against specific health hazards, particularly those arising from contagious pathogens. At the same time, global trade, increasing international travel, and highly specialised production systems lead to more frequent contacts between producers, service providers and markets both nationally and internationally. This provides an increased opportunity for the spread of infectious diseases. Recent examples of large-scale outbreaks of infectious disease include foot and mouth disease, human and avian influenza, SARS, human immunodeficiency virus, human hepatitis, salmonellosis, E. coli O157, and campylobacteriosis.

Because it is difficult and costly to evaluate risks for human and animal health in the complex socio-economic systems in which we live, a multifactorial approach is required. For example, how does the effect of population turnover and how frequently individuals make contact with each other influence how quickly an infectious disease might spread? Disease modelling provides a low-cost means to estimate the likely impact of disease in human and/or animal populations and to estimate the impact of interventions designed to control disease. Disease models help investigators to:

- Better understand a complex system by structuring outcomes and causal components in a logical flow-chart, pathway style.
- Predict the time course and impact of infectious disease epidemics.
- Identify areas of uncertainty where specific knowledge is required.
- Compare the efficiency of interventions for the prevention of adverse outcomes.

1.1 Generic disease models

A diagram showing the progression of events that occur when an individual is exposed to an infectious agent is shown in Figure 1. The interval from infection to recovery can then be divided into three phases: (1) the latent, (2) infectious, and (3) non-infectious periods. The latent period is the interval from the time of infection to the onset of infectiousness. The infectious period is the amount of time the individual remains infectious to others (i.e. transmit disease). The non-infectious period is the period from the cessation of the infectious period to either recovery or death. Following exposure and establishment of infection the period of time that must elapse before the onset of clinical symptoms (in humans) and signs (in animals) is called the incubation period.

The somewhat complicated diagram shown in Figure 1 can be simplified into a more general format as shown in Figure 2. In Figure 2, each of the three boxes corresponds to a state (susceptible, infectious, recovered), while the transitions between them correspond to events. The prevalence of individuals in each state is defined by how many members of the population are distributed among the three boxes at a given point in time. Incidence refers to the flow of individuals from the susceptible to the infected box as a function of time.

The transition from one state to another can be influenced by disease control activities. Preventive measures reduce the flow of individuals from the susceptible to infectious state. One strategy might be to shift individuals from the susceptible state to recovered using immunisation. Therapy tries to increase the rate of flow out of the infectious state. Permanent cure moves individuals from the infectious state to the recovered state. Temporary cure moves individuals from the infectioius state back to the susceptible state. Variations of the generic model framework shown in Figure 2 exist. For example, a susceptible-infectious (SI) model might be used for a disease where recovery does not occur (e.g. bovine spongiform encephalopathy).

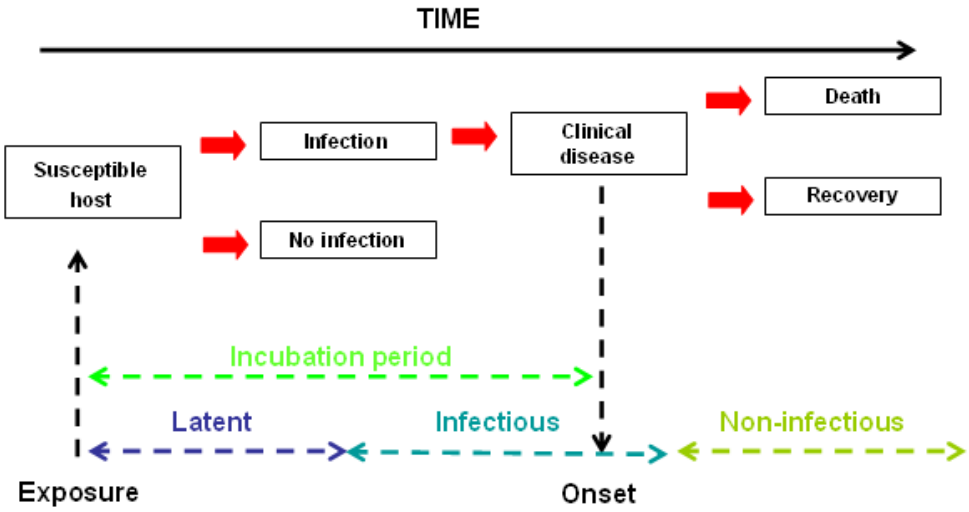


Figure 1: Susceptible, infectious, recovered model of infectious disease.

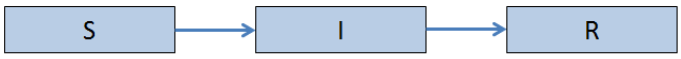


Figure 2: A generic model of disease comprised of susceptible (S), infectious (I) and recovered (R) states.

1.2 Populations

Defined and undefined populations

Relating cases of disease to the base population from which they arose is central to epidemiological thinking. As with case definition, perhaps the most useful way to define a population is to specify the characteristics that its members have in common and that set them apart from non-members. Characteristics include:

1. Individual attributes (e.g. age, sex, breed);
2. Spatial characteristics; and
3. The time or time period in which cases are identified.

Not every group of individuals constitutes a defined population for epidemiologic purposes. Characteristics that might define a population might be too vague to determine in practice and in this situation the population would be classified as undefined. The population specified by the description 'the population of dogs presented to an inner city veterinary clinic' would be typical of an undefined population.

Open and closed populations

Once the characteristics that define a population have been specified, it is easy (in theory) to determine its size and composition at a single point in time. Every individual that meets the defining criteria at that time is a member, and counting them yields the population size. Once we 'start the clock' and monitor a population

over a certain period of time its size and composition may change. If membership of the population remains constant the population is said to be closed. Such a population is also called a fixed cohort. If membership of the population changes (e.g. new members are added as birth and/or if individuals who have not developed disease are removed as deaths) the population is said to be open. Such a population is also called a dynamic population.

Examples of closed populations: passengers on an airplane for the duration of a flight; participants in a clinical trial in which all study procedures and observations are completed in a single encounter; soldiers who fought in a war who are monitored for death from any cause for 25 years after the end of the war (and assuming that ascertainment of deaths is complete).

Examples of open populations: workers employed in a factory during a two-year observation period; residents of Sydney, Australia during 2001.

2 Principles of SIR modelling

The susceptible-infected-resistant (SIR) model provides a relatively simple approach for understanding factors that influence the transmission, spread and time course of infectious disease outbreaks. The components of an SIR model are described below.

2.1 Compartments

We first recognise that any individual in a population of interest can be allocated to one of three compartments at any given point in time (Figure 3):

S_t	the number of susceptible individuals in the population at time t.
I_t	the number of infectious individuals in the population at time t.
R_t	the number of recovered individuals in the population at time t.
N	the total number of individuals in the population.

Correspondingly, we can define the three groups as fractions of the total population N:

s_t	the susceptible fraction of the population at time t.
i_t	the infected fraction of the population at time t.
r_t	the recovered fraction of the population at time t.

Note that each individual in the population can only be in one of the three groups at any time point so $S_t + I_t + R_t = N$ and $s_t + i_t + r_t = 1$.

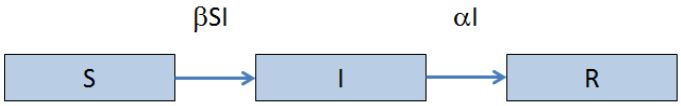


Figure 3: SIR model described by parameters β and α.

2.2 Transition parameters

The number of new infections developing during one time interval depends on the pool of available susceptible individuals (S), the number shedding the agent (infectious, I), and the rate of transmission, represented by a single number called the transmission coefficient, β. The transmission coefficient combines two important properties: (1) the number of contacts between susceptible and infectious individuals, and (2) the ability of the agent to infect a new host once contact has occurred.

If actual contact frequencies are known we can split β into its components $\beta = \gamma\delta$, where γ is the probability of a contact between susceptible and infectious during the time interval and δ is the probability of transmitting infection when such a contact occurs. In real life γ will rarely be observable, therefore a single transmission parameter β is most often used.

While the rate of changing from susceptible to infectious depends on the transmission coefficient β, the number of susceptible individuals and the number of infectious individuals, the change from infectious to resistant depends on the number of infectious individuals (I) and the rate at which they leave the infectious state, α.

The parameter α is equal to the inverse of the duration of the infectious period before becoming resistant. This parameter can be obtained from the literature describing the length of the shedding period of an agent (e.g. infectious bovine rhinotracheitis, bovine virus diarrhoea, avian influenza, rabies) or the period that agents remain alive and infective in the environment, on fomites or in intermediate hosts if infection is transmitted indirectly (e.g. Johne's disease, leptospirosis, babesiosis, and trypanosomiasis).

2.3 Differential equations

If we plot, the number of susceptible, the number of infectious and the number of recovered individuals in a population as a function of time, we might end up with a set of curves similar to that shown in Figure 4. The differential of each curve is equal to the slope of the curve at each time point. The slope of the curve tells us how quickly the number of individuals in each state is changing as a function of time. When the slope of the curve equals zero it means that the number of individuals entering the state is equal to the number leaving the infectious state. When the number of individuals entering the infectious state equals the number leaving the infectious state the system is said to be at equilibrium. In an infectious disease outbreak this is the point in time when the epidemic has reached its peak.

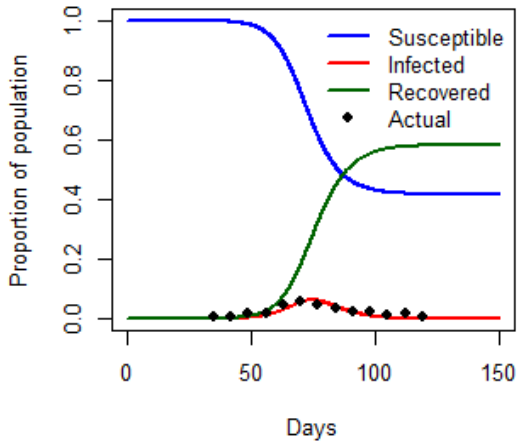


Figure 4: Line plot showing the number of susceptibles, infectious and recovered individuals in a population as a function of time.

In a simple SIR model, the parameters α and β determine 'how quickly' individuals move from one compartment to the next throughout the course of the outbreak. The flow of individuals out of the S compartment and into the I compartment depends on the number of susceptible individuals, the number of infectious individuals, and β the transmission coefficient, -βSI. The flow of individuals into the infectious compartment depends on S, I and β, +βSI; the flow of individuals out of the infectious compartment depends on the number of infectious individuals and α, -αI. Mathematical expressions for these relationships are shown in Equation set 1.

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \alpha I \quad (1)$$
$$\frac{dR}{dt} = -\alpha I$$

This approach can easily be extended to reflect a situation in which there is population turnover (the situation where individuals enter the population as births, transfers or purchases and individuals leave the population as deaths, culls or sales) and where disease is treated, as shown in Figure 5 and Equation set 2.

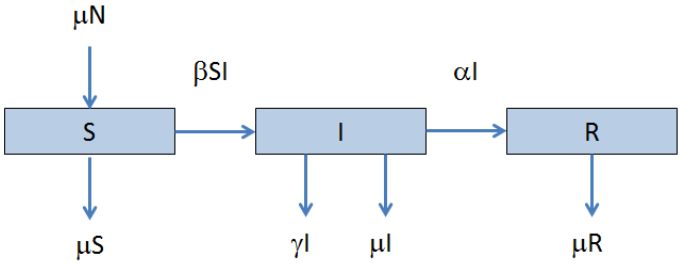


Figure 5: SIR model with the provision to account for population turnover and treatment of infectious individuals.

$$\frac{dS}{dt} = -\beta SI + \mu N - \mu S$$
$$\frac{dI}{dt} = \beta SI - \alpha I - \gamma I - \mu I \quad (2)$$
$$\frac{dR}{dt} = -\alpha I - \mu R$$

2.4 Absolute and relative units

It is important to be aware of the units by which each of the frequencies of change in the above equations are expressed. So far we have used absolute numbers of S and I to quantify the change in the number of infectious individuals per unit time, Equation 3.

$$\frac{dI}{dt} = \beta SI - \alpha I \quad (3)$$

In some situations we may wish to talk in terms of density and frequency dependent transmission (see Begon et al. 2002 for a review). Since the rate of contact varies with the proximity of individuals to each other, the use of units of density scales β by the proportion of infectious individuals in the population and population density, N/A (where A equals the size of the study area). This 'density unit' can be expressed as follows:

$$\frac{dI}{dt} = \beta' S \left(\frac{I}{N} \times \frac{N}{A} \right) - \alpha I$$
$$\frac{dI}{dt} = \frac{\beta' SI}{A} - \alpha I \tag{4}$$

An alternative possibility is that the transmission coefficient does not depend on population density but on the prevalence of infectious individuals (I/N) alone. This 'frequency unit' can be expressed as follows:

$$\frac{dI}{dt} = \frac{\beta" SI}{N} - \alpha I \tag{5}$$

The above expressions can also be readily expressed in terms of population proportions by dividing each of the above equations by N (and remembering that $S = sN$ and $I = iN$):

$$\frac{di}{dt} = \bar{\beta}' siN \text{ (density)}$$
$$\frac{di}{dt} = \bar{\beta}" si \text{ (frequency)} \tag{6}$$

Note that our original β based on absolute numbers has changed to $\bar{\beta}$, because it is now scaled to the proportions s and i.

2.5 Estimation of the transmission coefficient, β

Regression

A challenge for available study resources is the estimation of the transmission coefficient β.

If the number of new infections is known for every interval, β can be estimated using linear regression techniques. Hage et al. (1997) describe a study in which weekly whole-herd serum-sampling was carried out to monitor an outbreak of infectious bovine rhinotracheitis. By interpretation and inference, each cow was allocated to one of three states S, I, R, in each of 8 weeks, Table 1.

If sero-conversion occurred in subsequent weeks, the time of conversion was estimated as 3.5 days before the sample with the positive result (estimated sero-conversion). As an average time from contact to sero-conversion for IBR is about 8 days, the estimated time of effective contact was 8 days prior to the estimated date of seroconversion. By definition, the animal was susceptible up to this date, then became infectious for an average of 10 days (based on repeated virus isolation of the three re-activated carrier animals). Finally, the animal changed over into the resistant state 10 days after the effective contact date. This interpretation was applied to all animals in the herd.

Table 1: Infectious bovine rhinotracheitis in cattle. Counts of animals in the susceptible and infectious state, by week.

Week	S	I	R
1	61	0	
2	61	1	
3	59	2	
4	53	7	
5	28	30	
6	4	45	
7	0	11	
8	0	1	

```
S <- c(61,61,59,53,28,4,0,0)
I <- c(0,1,2,7,30,45,11,1)
SI <- S * I

res.lm <- lm(I ~ -1 + SI)
summary(res.lm)

beta.500 <- res.lm$coefficient
beta.025 <- confint(res.lm, level = 0.95)[1]
beta.975 <- confint(res.lm, level = 0.95)[2]
beta <- matrix(c(beta.025, beta.500, beta.975), dimnames = NULL); beta
```

The estimated transmission coefficient is 0.040 (95% CI 0.002 to 0.079).

If the number of new infections per unit time is not normally distributed, Poisson regression may be more appropriate, possibly with adjustments for repeated measures if the same animals are repeatedly sampled. Regression techniques allow the adjustment for production system parameters and interactions to estimate more representative or more specific values of β for various types of management or population strata.

Secondary attack rates

We call the initially identified infectious individuals the primary or index cases. The secondary attack rate (SAR) is the probability of the occurrence of disease among known (or presumed) susceptible persons following contact with a primary case:

$$\text{SAR} = \frac{\text{number of susceptibles who become infected}}{\text{total number of susceptible, exposed individuals}} \tag{7}$$

The secondary attack rate is actually a proportion (not a rate). It is often defined for exposure to an infective within some small population unit (such as a herd, household, classroom or school). Within this unit, mixing and exposure are assumed to be homogenous.

The first step in assessing the SAR is to define for the disease under investigation the time interval after the index case that would include secondary cases. The presumed beginning of infectiousness of the index case is defined as time 0 for each population unit. Secondary cases are those with time of onset between the end of the minimum incubation period E_1 relative to the beginning of infectiousness of the index case (t = 0) and the end of the maximum incubation period E_2 relative to the time of the maximum infectious period of the primary case, $t = I$. Thus, secondary cases are those occurring in the interval (E_1, $I + E_2$). A case with a recorded onset time less than one minimum incubation period E_1, after that of the index case was presumably no infected by the index case and is called a co-primary case. Tertiary and higher cases are those occurring after the maximum allowable interval for the secondary cases.

The second step in assessing the SAR is to determine for each ascertained case within the population unit whether it is a co-primary, secondary, tertiary or higher generation case. The estimated population unit SAR is the total number of secondary cases in all population units divided by the total number of at-risk susceptibles in all population units (as defined above). Co-primary cases are excluded from the denominator. Tertiary or higher cases are excluded from the numerator but are included in the denominator.

Binomial modelling

The binomial model is often used when susceptibles make more than one potentially infectious contact. The probability of transmission during contact between a susceptible and an infectious individual is denoted by p. The probability of the susceptible individual escaping infection during the contact is $q = (1-p)$. If we suppose that an individual makes n contacts with an infective or different infectives and that the probability of being infected during any contact is independent of previous contacts, then the probability of escaping infection from all of the n potentially infective contacts is $q^n = (1-p)^n$. The probability of being infected after n contacts is $1 - q^n = 1 - (1-p)^n$. The maximum likelihood estimate of the transmission probability under the binomial model is:

$$\hat{p} = \frac{\text{number of susceptibles who become infected}}{\text{total number of contacts with infectives}} \tag{8}$$

Note the difference with the SAR equation. In the binomial model, we count the total number of potentially infectious contacts that susceptible individuals make, while in the SAR approach each susceptible individual is capable of making just one potentially infectious contact with an infective.

Consider a study of HIV transmission conducted on a population of 100 sexually active couples. At the beginning of the study, one partner in each couple was already infected with HIV and the other partner was susceptible. Twenty-five of the susceptible partners became infected during the follow up period.

The total number of sexual encounters reported either up until a person became infected or until the end of the study was 1500. The maximum likelihood estimate of the transmission probability p = 25/1500 = 0.017. The probability of becoming infected after two contacts with an infected person is $1 - (1 - p)^2 = 1 - (1 - 0.017)^2 = 0.034$.

It is possible to estimate the transmission probability even if the infection status of people making contact with susceptibles is not known. An estimate of prevalence P of infection in the pool of potential contacts might be available. The probability of becoming infected from contact with an individual of unknown infection status chosen at random from a population with prevalence P is Pp. Thus, the probability of infection after n contacts is $1 - (1 - Pp)^n$. The transmission probability can be estimated by solving for p, using information on the proportion becoming infected during the study, the total number of contacts, and the prevalence of infection in the pool of contacts.

Sometimes information on the exact number of contacts is not available. Study subjects might give information on the average number of contacts they each make per unit time and from this the expected number of contacts during the study period can be estimated.

3 The basic reproductive number

The reproduction ratio, R_0, is the expected number of new infectious hosts that one infectious host will produce during its period of infectiousness in a large, susceptible population. If R_0 = 9 for measles in a given population, then one person with measles introduced into that population can be expected to produce nine secondary infections before recovering. If the entire population (comprised of N individuals) is susceptible at the beginning of an outbreak it can be shown that:

$$R_0 = (\beta/\alpha) \times N \tag{9}$$

If β and α are scaled to s, i and r then $R_0 = \beta/\alpha$. Note that if there is more than one pathway leading out of the infectious state (e.g. culling) then R_0 is calculated as $[\beta/(\alpha + \mu)] \times N$. R_0 is an important measure of the potential force an agent has to cause an epidemic. If $R_0 > 1$ an epidemic is likely to occur. If $R_0 = 1$ an epidemic is unlikely to occur and if $R_0 < 1$ an epidemic will extinguish itself. R_0 is reduced when:

- β is reduced by a lower contact frequency between susceptibles and infecteds (e.g. application of movement controls during a foot-and-mouth disease epidemic).
- α increases as the duration of infection is reduced (e.g. by treatment).
- μ increases by a process of testing to identify infected individuals and then removing them.

R_0 can be estimated in various ways: (1) using generalised linear models based on observational data, (2) reviewing initial growth rates of an outbreak, (3) from the final size of an outbreak, and (4) for lifetime infections, from demographic data.

3.1 Estimation of the basic reproductive number

Generalised linear models

Counts of susceptible and infectious individuals present at given time points during an epidemic can be used to estimate R_0. Recall that the number of new infectious individuals per unit time is given by $I_t' = \beta S_t I_t$. If we know I_t' and $S_t I_t$ then a generalised linear model can be used to estimate β. Because α equals the inverse of the average duration of infectiousness it will generally be known. R_0 can then be calculated using β, α and N using the expressions described above.

The following data comes from a study of infectious bovine rhinotracheitis in a 116 cow dairy herd. Details of the number susceptible and infectious individuals over a seven week period are as follows:

```
S <- c(61,61,59,53,28,4,0,0)
I <- c(0,1,2,7,30,45,11,1)
```

Estimate `beta` using a linear regression model without an intercept term:

```
SI <- S * I
beta.lm <- lm(I ~ -1 + SI)
summary(beta.lm)

beta.500 <- beta.lm$coefficient
beta.025 <- confint(beta.lm, level = 0.95)[1]
beta.975 <- confint(beta.lm, level = 0.95)[2]
beta <- matrix(c(beta.025, beta.500, beta.975), dimnames = NULL); beta
```

Our estimate of `beta` is 0.040 (95% CI 0.002 – 0.079). Now calculate R_0. From the literature we know that the duration of infectiousness is around 10 days.

```
alpha <- 1/(10/7)
N <- 116
R0 <- (beta / alpha) * N
R0
```

Our estimate of R_0 is 6.71 (95% CI 0.38 – 13.0).

Initial growth rates of an outbreak

If outbreak data are available R_0 can be approximated from the initial multiplication of the number of affected individuals, assuming that a large pool of susceptibles is available:

$$R_0 = 1 + D \times \frac{\ln 2}{t_d} \tag{10}$$

Where D is the length of the infectious period and t_d is the initial doubling time.

During the winter of 1968 – 1969, the United States was swept by a new strain of influenza, named Hong Kong flu after its place of discovery. At that time no flu vaccine was available. Shown below are the weekly totals of 'excess' pneumonia-influenza deaths in New York, that is, the numbers of deaths in excess of the average numbers expected from other sources. While relatively few flu sufferers die from the disease or its complications, even without a vaccine we can reasonably assume that the number of excess deaths in a week was proportional to the number of new cases of flu say, three weeks earlier.

```
week <- seq(from = 5, to = 17, by = 1)
n <- c(14,28,50,66,156,190,156,108,68,77,33,65,24)
flu <- data.frame(week, n)
plot(flu$week, flu$n, xlim = c(0, 20), ylim = c(0, 200), pch = 16, type = "b",
xlab = "Week", ylab = "Number of new flu cases")
```

Initially, the doubling time is one week (7 days). If a person remains infectious for 3 days, then R_0 can be calculated as:

```
inf <- 3; dtime <- 7
R0 = 1 + inf * log(2)/dtime
R0
```

Our estimate of R_0 for this epidemic is 1.3.

Final size of an outbreak

If the proportion of susceptible individuals in a population after an outbreak S_e is known then:

$$R_0 = \frac{1}{S_e/N} = \frac{1}{1 - R_e/N} \tag{11}$$

For example, if 100% of a population were initially susceptible and 20% were unaffected by the end of an epidemic, R_0 = 1/0.2 = 5. This method is applicable to dynamic populations (e.g. when susceptibles are added to the population as mortality reduces total population size). If equilibrium is not established, the proportion of susceptibles left after the outbreak will be underestimated and R_0 will, as a result, be over estimated. In the situation where not all individuals are initially susceptible R_0 can be estimated as:

$$R_0 = \frac{\ln\mu_0 - \ln\mu_\infty}{(\mu_0 - \mu_\infty)} \tag{12}$$

A population is comprised of 120 individuals. If 30 individuals were vaccinated at the start of an epidemic and the total number of infections was also 30 then:

```
mu.0 <- (120 - 30) / 120; mu.0
mu.inf <- (120 - 30 - 30) / 120; mu.inf
```

The proportion of the population initially susceptible is 0.75 (`mu.0`). The proportion of the population still susceptible at the end of the epidemic is 0.5 (`mu.inf`). R_0 is estimated as:

```
R0 <- (log(mu.0) - log(mu.inf)) / (mu.0 - mu.inf); R0
```

Our estimate of R_0 is 1.62. This result is different from the result obtained if the proportion initially susceptible was 100% because it assumes a lower contact rate due to some individuals being resistant at the start of the epidemic.

3.2 Herd immunity

Epidemic equilibrium is reached when the rate of new cases is approximately equal to the rate at which cases are cured or become resistant to disease. This is a steady-state situation where the number of new infectious individuals per unit of time equals the number of recoveries per unit time (that is, the change in the number of infectious individuals per unit time is zero). In this case the proportion of the population that susceptible at the equilibrium state, S_e/N, is given by:

$$\beta S_e I = \alpha I \tag{13}$$

$$S_e = \frac{\alpha}{\beta} \tag{14}$$

$$\frac{S_e}{N} = \frac{\alpha}{\beta N} = \frac{1}{R_0} \tag{15}$$

The threshold theorem states that if S_0/N (the proportion of susceptible individuals in the population at the start of the epidemic) is less than $1/R_0$ then transmission is unlikely to occur, at least not sufficiently to cause an epidemic. Given S_0/N equals the proportion of the population susceptible to disease at the start of an epidemic it follows that the remainder $1 - S_0/N$ is the proportion of the population not susceptible (i.e. immune). $1 - S_0/N$ provides useful information in terms of defining what proportion of the population need to be vaccinated to prevent an epidemic.

Hong Kong flu deaths in New York, 1968 – 1969. Assume that, on average, for every 2500 cases of flu there will be around one flu-related death. Also assume that the initial values for the population variables are `S(0)` = 7,900,000, `I(0)` = 10 and `R(0)` = 0. Also assume `alpha` = 1/3 (the infectious period for flu is around 3 days) and we guess that each infected would make an infecting contact every two days, so `beta` would be 0.5.

```
week <- seq(from = 5, to = 17, by = 1)
n <- c(14,28,50,66,156,190,156,108,68,77,33,65,24)
flu <- data.frame(week, n)
flu$N <- flu$n * 2500
plot(flu$week, flu$n, xlim = c(0, 20), ylim = c(0, 200), pch = 16, type = "b",
xlab = "Week", ylab = "Number of new flu cases")
```

Create a function to compute an SIR model. Here we will use the `lsoda` command in the `deSolve` package to numerically solve the differential equations:

```
library(deSolve)
SIR <- function(t, x, parms){
   S <- x[1]; I <- x[2]
   with(as.list(parms),{
      dS <- -beta * S * I
      dI <- +beta * S * I - (alpha * I)
      dR <- alpha * I
      out <- c(dS, dI, dR)
      list(out)
   })
}

N <- 7900000; S0 = 1; I0 = 10/N; R0 <- 0; alpha = 1/3; beta = 0.5; dt <-
seq(from = 0, to = 150, by = 0.1)
parms <- c(beta = beta, alpha = alpha)
inits <- c(S = S0, I = I0, R = R0)
sim <- as.data.frame(lsoda(inits, dt, SIR, parms = parms))
```

Plot the results:

```
plot(sim$time, sim$S, type = "l", col = "blue", ylim = c(0, 1), xlab = "Days",
ylab = "Number of individuals", lwd = 2)
lines(sim$time, sim$I, type = "l", col = "red", lwd = 2)
lines(sim$time, sim$R, type = "l", col = "darkgreen", lwd = 2)
lines(flu$week * 7, flu$N/N, pch = 16, type = "b")
legend(x = "topright", legend = c("Susceptible", "Infected", "Recovered",
"Actual"), col = c("blue", "red", "darkgreen", "black"), lty = c(1,1,1,NA),
lwd = c(2,2,2,NA), pch = c(NA,NA,NA,16), bty = "n")
```

What proportion of the population would have needed to be vaccinated to prevent an epidemic?

```
prop.vacc <- 1 - (S0 / N)
prop.vacc
```

Virtually the entire population would need to have been vaccinated to prevent an epidemic.

4 Density and frequency dependent infection transmission

These notes focus spefically on the control of canine rabies. Two main methods are used to control canine rabies: (1) vaccination; and (2) measures designed to reduce dog population density (usually by culling and/or sterilisation).

Dog vaccination programmes are often undertaken as annual campaigns that aim to achieve 70% coverage. This target is underpinned by empirical evidence which indicates that 70% coverage achieved during campaigns should maintain population immunity above theoretical critical levels (between 25% and 40%). Culling of dogs is also used, alone or with vaccination based on the assumption that a physical reduction in the number of dogs must reduce the likelihood of rabies transmission and therefore a reduction in the incidence of rabies. While intuitively culling appears to be a logical approach for rabies control there is a body of evidence to show that culling (alone) is a largely ineffective approach. Culling continues to be used as a primary rabies control measure by animal health authorities however, partly because it represents a visible response to public concerns about rabies.

The theoretical basis for rabies control measures involving culling or sterilisation is built on the assumption that the rate of transmission is **density dependent**. Density dependent infection transmission is when the probability of disease transmission increases as the density of the population at risk increases. This scaling of transmission rates occurs under the assumption that the rate of encounters between susceptible and infectious individuals increases with host population density. Under this assumption, increases in host density is associated with an increase in the basic reproductive number R_0.

Frequency dependent infection transmission is when the probability of disease transmission increases (as the name suggests) as the number of contacts between susceptible and infectious individuals increases. With frequency dependent infection transmission rates of transmission are independent of host density and a threshold density for invasion (that is, a concept analogous to R_0) does not exist. Under either frequency- or density-dependent transmission, vaccination equally reduces both the number and proportion of susceptible individuals in a host population, and therefore the opportunities for transmission to occur.

Influenza in humans is a disease where transmission is density dependent. The probability of infection transmission increases as the density of hosts increases.

Sexually transmitted diseases in humans are examples of diseases where transmission is frequency dependent. The probability of infection transmission does not depend on host density — an individual can exist in a population where the prevalence of sexually transmitted disease is high without becoming infected. With sexually transmitted diseases, the probability of infection transmission depends on the number of risky sexual encounters an individual has.

Culling has consistently been shown to be ineffective in controlling rabies in all host species. Rabies persisted in foxes in New York, USA despite 'concentrated reduction campaigns' following an outbreak in 1945. Simultaneous vaccination of dogs and foxes in the 1960s resulted in elimination of the disease (Friend 1968). In response to a rabies outbreak in 1997, nearly 300,000 dogs (approximately half of the population estimated at the start of the outbreak) were culled in Flores, Indonesia over a period of four years. In 2004, rabies was still endemic although the total dog population was still considerably reduced (Windiyaningsih et al. 2004). Culling failed to control canine rabies in Korea (Lee et al. 2001) and Israel (Kaplan, Goor & Tierkel 1954), whereas subsequent vaccination programmes in both countries managed to control the disease.

There are three likely reasons for the lack of success of culling as a means for controlling rabies in domestic dog populations:

1. Rabies transmission in dogs is frequency dependent (as opposed to density dependent);
2. Canine rabies can continue to circulate in areas where the densities of dogs are as low as 1.36 dogs per square kilometre (Hampson 2009) which means that culling programs need to reduce dog densities to effectively zero in order to be effective; and

3. In the face of culling programs by animal health authorities, reactionary translocation and concealment of dogs (Beran & Frith 1988; Denduangboripant et al. 2005; Coetzee & Nel 2007; Kasempimolporn, Jitapunkul & Sitprija 2008; Zinsstag et al. 2009) seriously undermines population control efforts.

5 Exercises

5.1 Theory into practice: Simulating the spread of disease

Recall that in infectious disease modelling S denotes a susceptible individual (an individual who can become infected), I denotes an infectious individual, and R denotes an individual who is recovered (and/or is immune from infection).

In this exercise we will physically simulate an epidemic. We make two assumptions: (1) no individuals die from infection, and (2) once recovered, an individual can't become infected again. We begin our experiment with three members of the class 'infected' with the rest of the class susceptible. Each member of the class will move around the room having 'encounters' with other members of the population. If a susceptible individual meets an infectious individual during an encounter, there is a chance that infection will be transmitted to the susceptible individual, as explained below. The score keeper will keep a tally of the number of susceptible, infectious and recovered individuals on each encounter 'day'.

Once there are no more susceptible individuals in the population the exercise will be complete. We will then plot the numbers of susceptible, infectious and recovered individuals as a function of encounter days and compare our plot to the theoretical plots (as explained in lectures).

Before you start

Before starting the exercise, assign:

- A time keeper, who signals to the class when each encounter should occur.
- A score keeper, who keeps a tally of susceptible, infected, and recovered individuals at each encounter.

Each member of the class should have a coin. When the time keeper anounces START each member of the class is to move freely around the room. When the time keeper anounces ENCOUNTER you are to pair up with the person closest to you. Both parties toss their coin and take action according to the following rules:

- Susceptible encounters a susceptible: no change in status.
- Susceptible encounters an infected: if two heads are rolled on the first toss, the susceptible becomes infected.
- The duration of infection is three encounters. Once an infectious individual passes three encounters they transition to the recovered state.
- Recovered encounters anyone: no change in status.

At the end of each encounter the score keeper will count the number of susceptible, infected, and recovered individuals. Counts will be done by a show of hands with eyes closed (to minimise bias). The score keeper will write these numbers on the board. When the number of infected individuals reaches zero, the experiment stops.

Questions

1. Plot the counts of susceptible, infected, and recovered individuals as a function of time. Describe the results.
2. If we did the experiment again, would we get the same result?
3. What is the estimated value of α and β for this 'epidemic'?
4. What would happen if the duration of infection was increased to 5 encounters? Run the experiment again with these new rules to confirm your predictions.
5. What will be the effect of restricting the amount of movement? Run the experiment again with the rule that you can only take two steps in between encounters. Plot the results to confirm your predictions.

Notes for teachers.

- Don't assume that all students will have coins in their pockets. Bring a collection of (small denomination) coins, distribute them and collect them again as the students leave the tutorial.
- Take a count of the number of students present at the start. At the end of each encounter get the susceptible, infected, and recovered students to stand together (makes counting easier for the score keeper, particularly if you have a big class). Consider using coloured hats to identify status (some students will change their status randomly).
- Some will have trouble keeping track of the number of encounters they have been infected: tell them to use their fingers as counters.

5.2 A simple SIR model using Berkeley Madonna

Consider a measles-like virus spreading in a population of 10,000 (1×10^3) individuals who have never been exposed to the virus before (that is, all individuals in the population are susceptible to infection). The virus is readily transmitted primarily by the airborne route, and we assume that the population mixes homogenously, with no particular subgroup being at increased or reduced risk of infection. Assume the duration of the infectious period is approximately 3.5 days. To begin with we assume lifelong immunity. The life expectancy in the population is 75 years, and the case fatality rate is extremely low.

The model

For this situation, a susceptible-infectious-recovered (SIR) model would be an appropriate place to start. If we ignore the effect of population turnover (i.e. individuals entering the population as births and individuals exiting the population as deaths) a diagramatic representation of the model is shown in Figure 6.

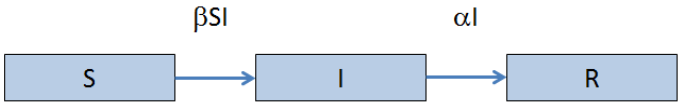


Figure 6: SIR model decribed by parameters β and α.

The equations quantifying the movement of individuals from the susceptible compartment to the infectious compartment and the infectious compartment to the recovered compartment are as follows:

$$\frac{dS}{dt} = -\beta SI \tag{16}$$

$$\frac{dI}{dt} = +\beta SI - \alpha I \tag{17}$$

$$\frac{dR}{dt} = +\alpha I \tag{18}$$

The parameters

First we choose units. We decide to use weeks, with 1 year = 52 weeks = 364 days. The infectious period lasts 0.5 weeks so we set α to (1 ÷ 0.5) = 2. The transmission parameter β is less than obvious. Recall the expression for R_0 can be expressed in terms of α and β.

$$R_0 = \frac{\beta}{\alpha} \times N \tag{19}$$

We can rearrange this equation so β can be expressed in terms of R_0, α and N.

$$\beta = \frac{R_0(\alpha)}{N} \tag{20}$$

Questions

Calculate a value for β assuming R_0 = 3, α = 2 and N = 500.

Answer

Our estimate of β is:

$\beta = (R_0 \times \alpha)$
$\beta = 3 \times 2)000$
$\beta = 0.006$

Start Berkeley Madonna and in a new equation window enter the following code:

```
METHOD RK4
STARTTIME = 0
STOPTIME = 52
DT = 0.02

d/dt(S)= -(beta * S * I)
d/dt(I) = +(beta * S * I) - (alpha * I)
d/dt(R) = +(alpha * I)

N0 = 500
I0 = 1
R0 = 3.0
alpha = 2
beta = 0.012
; beta = (R0 * alpha) / N
N = S + I + R

init S = N0 - I0
init I = I0
init R = 0
```

Run the model by clicking on the `RUN` button at the top of the equation editor window.

Questions

In which week of the epidemic is there the greatest number of infectious individuals? How many individuals were infected by week 10?

Answer

The greatest number of infectious individuals occurs between weeks 1 and 2. By week 10, the total number of recovered individuals was 470.

If you reduce R_0 to 1.5, in which week of the epidemic is there the greatest number of infectious individuals? How many individuals were infected by week 10?

Answer

If you reduce R_0 to 1.5, the greatest number of infectious individuals occurs between weeks 4 and 5. By week 10, the total number of recovered individuals was 286.

5.3 A simple SIR model accounting for population turnover using Berkeley Madonna

Once again we will consider a measles-like virus spreading in a population of 10,000 (1×10^3) individuals who have never been exposed to the virus before. The virus is readily transmitted primarily by the airborne route, and we assume that the population mixes homogenously, with no particular subgroup being at increased or reduced risk of infection. Assume the duration of the infectious period is approximately 3.5 days and once an individual recovers from infection, immunity is lifelong. The life expectancy in this population is 75 years, and the case fatality rate is extremely low.

The model

As for the previous exercies, a susceptible-infectious-recovered (SIR) model would be an appropriate place to start. Accounting for population turnover (i.e. individuals entering the population as births and individuals exiting the population as deaths) a diagramatic representation of the model is shown in Figure 7.

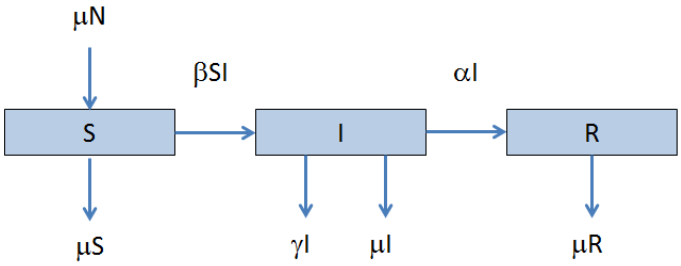


Figure 7: SIR model with the provision to account for population entries (births and purchases) and exits (sales and deaths), decribed by parameters β, α, and μ.

The equations quantifying the movement of individuals from the susceptible compartment to the infectious compartment and the infectious compartment to the recovered compartment are as follows:

$$\frac{dS}{dt} = -\beta SI + \mu N - \mu S \tag{21}$$

$$\frac{dI}{dt} = +\beta SI - \mu I - \alpha I - \gamma I \tag{22}$$

$$\frac{dR}{dt} = +\alpha I - \mu R \tag{23}$$

The parameters

First we choose units. We decide to use weeks, with 1 year = 52 weeks = 364 days.

The natural per-capita mortality rate is $\mu = (75 \times 52)^{-1} = 0.00026 = 2.6 \times 10^{-4}$ per week.

The population size is steady at 10 thousand so the birth rate (b) is $1 \times 10^3 \times 2.6 \times 10^{-4} = 0.26$ per week.

The infectious period lasts 0.5 weeks so $\alpha = 1/0.5 = 2$.

The expression for R_0 can be expressed in terms of α, β and μ:

$$R_0 = \frac{\beta}{(\alpha + \mu)} \times N \tag{24}$$

We can rearrange the expression for R_0 so β can be expressed in terms of R_0, α, μ and N.

$$\beta = \frac{R_0(\alpha + \mu)}{N} \tag{25}$$

For this exercise we will assume (to start with) that the disease is highly infectious with an R_0 equal to 3.

Start Berkeley Madonna and in a new equation window enter the following code:

```
METHOD RK4
STARTTIME = 0
STOPTIME = 52
DT = 0.02

d/dt(S)= -(beta * S * I) + b - (mu * S)
d/dt(I) = +(beta * S * I) - (mu * I) - (alpha * I)
d/dt(R) = +(alpha * I) - (mu * R)

N0 = 500
I0 = 1
R0 = 3.0
alpha = 2
mu = 1 / (75 * 52)
b = N0 * mu
beta = (R0 * (alpha + mu)) / N
N = S + I + R

init S = N0 - I0
init I = I0
init R = 0
```

Run the model by clicking on the `RUN` button at the top of the equation editor window.

Questions

In which week of the epidemic is there the greatest number of infectious individuals? How many individuals were infected by week 50?

Answer

The greatest number of infectious individuals occurs between weeks 1 and 2. By week 50, the total number of recovered individuals was 464.

If you reduce R_0 to 1.5, in which week of the epidemic is there the greatest number of infectious individuals? How many individuals were infected by week 50?

Answer

If you reduce R_0 to 1.5, the greatest number of infectious individuals occurs between weeks 4 and 5. By week 50, the total number of recovered individuals was 290.

What modifications would you need to make to this model to allow it to be used to model the spread of rabies in a population of dogs?

Answer

6 Selected papers

Elsevier
ELSEVIER
0264-410X(95)00197-2
Vaccine, Vol. 14, No. 3, pp. 185–186, 1996

Printed in Great Britain
0264-410X/96 $15+0.00

Short Papers

Immunization coverage required to prevent outbreaks of dog rabies

Paul G. Coleman* and Christopher Dye*†

WHO recommends that 70% of dogs in a population should be immunized to eliminate or prevent outbreaks of rabies. This critical percentage (p_c) has been established empirically from observations on the relationship between vaccination coverage and rabies incidence in dog populations around the world. Here, by contrast, we estimate p_c by using epidemic theory, together with data available from four outbreaks in urban and rural areas of the USA, Mexico, Malaysia and Indonesia. From the rate of increase of cases at the beginning of these epidemics, we obtain estimates of the basic case reproduction number of infection, R_0, in the range 1.62–2.33, implying that p_c lies between 39% and 57%. The errors attached to these estimates of p_c suggest that the recommended coverage of 70% would prevent a major outbreak of rabies on no fewer than 96.5% of occasions.

Keywords: Rabies; dog; basic case reproduction number; vaccination coverage; epidemic

About 95% of all reported animal cases worldwide are in dogs, and over 90% of human rabies fatalities are attributable to rabid dogs[1]. Mass vaccination is one of the principal methods of dog rabies control (with restriction of dog movement and the elimination of strays), and the critical percentage of dogs which need to be vaccinated (p_c) to prevent or control an outbreak is said to be 70%[2,3]. This criterion apparently originated as the consensus among veterinary practitioners in New York State during the 1940s[4], and is therefore purely empirical. Observations worldwide on the relation between vaccination coverage and the reduction in rabies incidence have increased confidence in this figure[3], but p_c obtained by trial-and-error needs to be underpinned by calculations based on epidemic theory.

We begin with a simple compartmental model of dog rabies in which all animals (population size N) are assumed to be susceptible (S), latently infected (L) or infective (I). The per capita rate at which susceptibles acquire rabies virus from infectives is β, so newly infected animals arise at a rate βSI/week. Infected animals remain in the latent class for a period $l=1/\sigma$ weeks (σ is the rate at which latent animals become infective), and infective animals have a life expectancy of $f=1/\gamma$ weeks (γ is the death rate of rabid dogs). Deaths from other causes and births are both negligible on the timescale of a rabies epidemic, and can safely be ignored. The generation time, g, in this model is $1+f=1/\sigma+1/\gamma$ weeks, and the basic case reproduction number of infection[5], R_0, is $\beta N/\gamma$. R_0 depends explicitly on N, so we expect R_0 to be greater in larger (and probably higher density) dog populations. If R_0 varies from one population to another then so too will p_c, which immediately questions the view, implicit in much of the literature[1–3], that the same criterion can be applied to dog populations everywhere.

With these definitions and assumptions, we can write down formally a set of coupled, first order, non-linear differential equations describing rabies dynamics, as follows:

$$\frac{dS}{dtu} = -\beta SI$$

$$\frac{dL}{dt} = \beta SI - \sigma L$$

$$\frac{dI}{dt} = \sigma L - \gamma I.$$

These may be solved to show that the incidence of cases is expected to grow exponentially during the early stages of an epidemic (when $S \approx N$) at a rate roughly equal to $(R_0-1)/g$. More precisely, $\gamma(t) \approx k\exp(rt)$, where $\gamma(t)$ is the incidence between times t and $t-1$, k is a constant, and to a good approximation $R_0=1+r(rlf+g)$. We can therefore estimate r by fitting the first of these two equations to data describing the exponential growth in incidence during an outbreak, and get R_0 by using the second. The percentage to be immunized then comes from the well-known relation[5] $p_c=100(1-1/R_0)$. Where an outbreak occurs in a partially vaccinated dog population, estimates of R_0 and p_c obtained this way will be too low; R_0 needs to be corrected upwards by dividing by the fraction of dogs (s) which were unvaccinated prior to the outbreak.

Foggin[6] has provided the best estimates of latent and infective periods, and therefore generation time, because his data come from natural rather than experimental

*Department of Medical Parasitology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. †To whom correspondence should be addressed. (Received 6 February 1995; revised 31 August 1995; accepted 12 September 1995)

Table 1 Estimates of R_0, p_c and upper 95% confidence limits for p_c, calculated using data from four studies of dog rabies epidemics

Study	Country	Region	Setting	Weeks of exponential growth	Number of observations	r	S.E.(r)	S	R_0	S.E.(R_0)	p_c	95% upper confidence limit for p_c
7	USA	Memphis and Shelby County, Tennessee	Urban and rural	11	11	0.172	0.046	0.840	2.334	0.556	57.1	71.0
8	Mexico	Hermosillo	Urban	~22	5	0.175	0.023	1.000	1.981	0.418	49.5	64.5
9	Indonesia	Central Java	Rural	12	12	0.144	0.057	1.000	1.789	0.451	44.1	62.8
10	Malaysia	Kuala Lumpur	Urban	~17	4	0.116	0.028	1.000	1.627	0.302	38.5	55.2

infections. He presents the intervals between biting and the appearance of clinical signs for 68 dogs attacked by other dogs or jackals, from which we calculate a mean of 4.18 (S.E. 0.27) weeks and a median of 3.45 (S.E. 0.21) weeks. We use the mean here because it gives more conservative (larger) estimates of R_0 than the median (it is also longer than obtained from most experimental infections). Although there is some evidence[1] that dogs are infective before signs develop, transmission is more likely when dogs behave rabidly, so we assume that latent and incubation periods are equal. With regard to the infective period, Foggin unfortunately gives only the mean (0.81 weeks) and range (0.29–1.71 weeks). We adopt his mean, but we cannot calculate the variance, so our estimates of S.E. (R_0) below exclude this source of error.

Four studies of dog rabies epidemics in the USA[7], Mexico[8], Indonesia[9] and Malaysia[10] give the incidence of cases through time (*Table 1*). The first of these outbreaks occurred despite an ongoing vaccination campaign, though the data in Ref. 7 suggest that no more than 16% of dogs were protected. The regression analyses leading to estimates of R_0 and p_c were carried out in GLIM[11] assuming a Poisson error distribution, and restricting the data to confirmed cases of dog[8–10] or animal[7] rabies. R_0 varies from 1.63 to 2.33, and hence p_c lies in the range 39–57%. None of the estimates in *Table 1* differs significantly from any other (see S.E.s in *Table 1*), so the variation could be due to chance alone. There is no evidence to suggest, for example, that R_0 is greater in larger dog populations, though we might expect to see such an effect in a larger set of data (see above).

We are interested not only in the point estimates of p_c, but also in the upper confidence limits. The upper 95% limits fall between 55% and 71%, that is, generally below 70%. Put another way, if the errors surrounding the point estimate of R_0 are roughly normal, we expect a coverage of 70% to prevent a major outbreak from occurring on no fewer than 96.5% of occasions. These data and our analysis therefore suggest that immunizing 70% of dogs, following the current WHO recommendation, will indeed be sufficient to prevent or control outbreaks of dog rabies.

ACKNOWLEDGEMENTS

PGC is supported by a MRC research studentship.

REFERENCES

1 Fekadu, M. Canine rabies. In: *The Natural History of Rabies* (Ed. Baer, G.M.), 2nd edn. CRC Press, Boca Raton, 1991, pp. 367–378
2 World Health Organization. *Guidelines for Dog Rabies Control.* VPH/83.43 Rev. 1. WHO, Geneva, 1987
3 Beran, G.W. Urban rabies. In: *The Natural History of Rabies* (Ed. Baer, G.M.), 2nd edn. CRC Press, Boca Raton, 1991, pp. 427–443
4 Korns, R.F. and Zeissig, A. Dog, fox and cattle rabies in New York State. *Am. J. Publ. Hlth* 1948, **38,** 50–65
5 Anderson, R.M. and May, R.M. *Infectious Diseases of Humans.* Oxford University Press, Oxford, 1991
6 Foggin, C.M. Rabies and rabies-related viruses in Zimbabwe: historical, virological and ecological aspects (dissertation). University of Zimbabwe, Harare, 1988
7 Tierkel, E.S., Graves, L.M., Tuggle, H.G. and Wadley, S.L. Effective control of an outbreak of rabies in Memphis and Shelby County, Tennessee. *Am. J. Publ. Hlth* 1950, **40,** 1084–1088
8 Eng, T.R., Fishbein, H.E., Talamante, H.E. *et al.* Urban epizootic of rabies in Mexico: epidemiology and impact of animal bite injuries. *Bull. WHO* 1993, **71,** 615–624
9 Waltner-Toews, D., Maryono, A., Akoso, B.T., Wisynu, S. and Unruh, D.H.A. An epidemic of canine rabies in Central Java, Indonesia. *Preventive Vet. Med.* 1990, **8,** 295–303
10 Wells C.W. The control of rabies in Malaya through compulsory mass vaccination of dogs. *Bull. WHO* 1954, **10,** 731–742
11 Becker, N.G. *The Analysis of Infectious Disease Data.* Chapman and Hall, London, 1989

Journal of Animal Ecology

Journal of Animal Ecology 2013, **82,** 6–14 doi: 10.1111/j.1365-2656.2012.02033.x

REVIEW

Evidence-based control of canine rabies: a critical review of population density reduction

Michelle K. Morters[1]*, Olivier Restif[1], Katie Hampson[2], Sarah Cleaveland[2], James L. N. Wood[1] and Andrew J. K. Conlan[1]

[1]*Department of Veterinary Medicine, University of Cambridge, Cambridge, UK; and* [2]*Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow, UK*

Summary

1. Control measures for canine rabies include vaccination and reducing population density through culling or sterilization.
2. Despite the evidence that culling fails to control canine rabies, efforts to reduce canine population density continue in many parts of the world.
3. The rationale for reducing population density is that rabies transmission is density-dependent, with disease incidence increasing directly with host density. This may be based, in part, on an incomplete interpretation of historical field data for wildlife, with important implications for disease control in dog populations. Here, we examine historical and more recent field data, in the context of host ecology and epidemic theory, to understand better the role of density in rabies transmission and the reasons why culling fails to control rabies.
4. We conclude that the relationship between host density, disease incidence and other factors is complex and may differ between species. This highlights the difficulties of interpreting field data and the constraints of extrapolations between species, particularly in terms of control policies.
5. We also propose that the complex interactions between dogs and people may render culling of free-roaming dogs ineffective irrespective of the relationship between host density and disease incidence.
6. We conclude that vaccination is the most effective means to control rabies in all species.

Key-words: culling, density, dog, sterilisation, vaccination

Introduction

Canine-mediated rabies is a serious zoonosis causing an estimated 55 000 human deaths per year (Knobel *et al.* 2005). Mortality from rabies is highest in developing communities in Africa and Asia where domestic dogs are predominately free-roaming (Ezeokoli & Umoh 1987; Butler & Bingham 2000; Kitala *et al.* 2002; Kayali *et al.* 2003; Windiyaningsih *et al.* 2004; Kasempimolporn, Jitapunkul & Sitprija 2008). Social, economic and political factors contribute to the inadequate control of rabies in domestic dog populations (WHO 2004), accentuated by an incomplete understanding of disease dynamics. Knowledge of the factors that drive the transmission of rabies is needed for the development of effective, sustainable disease control measures.

*Correspondence author. E-mail: mm675@cam.ac.uk

Two main methods are used to control canine rabies: vaccination (Cleaveland *et al.* 2003; WHO 2004; Schneider *et al.* 2005; Cleaveland *et al.* 2006) and measures aiming to reduce dog population density, usually by culling (i.e. the widespread killing of dogs regardless of infection status) (Beran & Frith 1988; Windiyaningsih *et al.* 2004) but also by sterilization (WHO 2004; Reece & Chawla 2006). Dog vaccinations are often undertaken as annual campaigns that aim to achieve 70% coverage (WHO 2004). This target coverage is supported by empirical evidence and theory, which indicates that a 70% coverage achieved during campaigns should maintain population immunity above the critical levels (25–40%) required to interrupt rabies transmission (Coleman & Dye 1996; Cleaveland *et al.* 2003; Hampson *et al.* 2009). This additional coverage above the critical level compensates for the loss in coverage arising from an increase in susceptible and loss of immune dogs through demographic and immunological processes (Hampson *et al.* 2009). Culling

of dogs is also used, alone or with vaccination (Kaplan, Goor & Tierkel 1954; Larghi *et al.* 1988), based on the assumption that a physical reduction in the number of dogs must reduce the incidence of rabies, despite evidence suggesting that it is ineffective (Beran & Frith 1988; WHO 2004; Windiyaningsih *et al.* 2004). Culling is still used, partly as a visible response to public concerns about rabies. It is also perceived to be easier to implement than annual vaccination of 70% of dogs, particularly if many are free-roaming and poorly socialized, and in areas where veterinarians and animal health workers have relatively little experience or confidence in handling dogs. In some areas, sterilizations are carried out together with vaccinations, on the basis that this is a more humane and culturally acceptable approach to reducing dog population density.

The theoretical basis for rabies control measures involving culling or sterilization is the assumption that rates of transmission are density-dependent (Anderson *et al.* 1981; Wandeler *et al.* 1988; Cleaveland 1998; Hampson *et al.* 2007). This scaling of transmission rates occurs if the rate of encounters between susceptible and infectious individuals increases with host population density. Under this assumption, we expect that disease incidence will also increase with host density, as will the basic reproductive number (R_0) that characterizes the maximum reproductive potential of a pathogen. R_0 is defined as the average number of secondary infections produced when one infected individual is introduced into a wholly susceptible population (Anderson & May 1991). For an epidemic to spread, R_0 must, by definition, be >1. Hence, under density-dependent transmission, there will exist a threshold density below which disease cannot invade a population. This contrasts with frequency-dependent disease transmission where the rate of contact and subsequent rates of transmission are assumed to be independent of host density and a threshold density for invasion does not exist (Begon *et al.* 2002; Lloyd-Smith *et al.* 2005).

Under either frequency- or density-dependent transmission, vaccination equally reduces both the number and proportion of susceptible individuals in a host population, and thus, the opportunities for transmission to occur. Therefore, the assumption that rabies transmission is density-dependent has little consequence for the efficiency of vaccination programmes. Conversely, the assumption is of critical importance with regard to control measures that aim to reduce dog population density. The net impact of culling and sterilization on subsequent rates of rabies transmission depends on the degree to which transmission scales with population density. Under the assumption of frequency dependence, density reduction will have no impact on the rate of transmission. Conversely, when transmission is density-dependent, there will be a threshold for disease invasion, and density reduction alone has the potential to achieve disease eradication. However, stochastic effects and antagonistic biological processes may complicate these simple relationships.

Establishing the relationships between host density, disease incidence and other processes is therefore not only important for refinement of epidemiological models for rabies transmission, but also has serious practical implications for the utility of density reduction in controlling rabies. In this study, we review current understanding of the role of density and other factors in rabies transmission in dogs to encourage reappraisal of the most appropriate and effective means of rabies control. Within the literature, and during the development of policy, extrapolations are often made between species, in particular between wildlife and domestic dogs. We therefore extend our review to rabies transmission in wildlife and highlight the differences and similarities with dog populations. We also compare the utility of various lines of evidence between species. This discussion will focus on fox rabies in particular, as empirical data on the local transmission of wildlife rabies are largely confined to this host species.

Evidence for density-dependent transmission of rabies

It is difficult to determine the direct relationship between disease incidence, host density and transmission under field conditions, particularly for wildlife given their inaccessibility (Wandeler *et al.* 1974b; Macdonald & Voigt 1985; Beyer *et al.* 2010). Consequently, we are left with interpreting indirect and somewhat conflicting evidence regarding the role of density in rabies transmission in wildlife and dogs. In this section, we examine four key lines of evidence about the functional forms of rabies transmission.

CYCLES IN DISEASE INCIDENCE

Cycles in disease incidence have motivated some of the most effective applications of population modelling in ecology (Anderson & May 1991; Begon, Harper & Townsend 1996). Mathematical models can explore how different biological hypotheses relate to the expected amplitude and period of cycles, providing insights into the drivers of transmission. Perhaps, the most successful examples of this have been in the study of childhood infectious diseases (Earn *et al.* 2000; Altizer *et al.* 2006) where detailed historical records have allowed the application of sophisticated methods of statistical inference (Bjornstad, Finkenstadt & Grenfell 2002; Grenfell, Bjornstad & Finkenstadt 2002). However, even in the absence of detailed data, models can provide useful insights simply through the ability of a given mechanism to generate periodic dynamics.

Cycles have been observed for wildlife (Friend 1968; Bogel *et al.* 1974; Childs *et al.* 2000; Courtin *et al.* 2000; MacInnes *et al.* 2001) and canine rabies (Ernst & Fabrega 1989; Bingham *et al.* 1999a; Widdowson *et al.* 2002; Hampson *et al.* 2007), although periodicity in incidence is not a consistent finding (Macdonald & Voigt 1985;

Zinsstag *et al.* 2009). The mechanistic driver of these cycles is widely assumed to be the interaction of density-dependent transmission, rabies-induced mortality and other demographic processes (Bogel *et al.* 1974; Steck & Wandeler 1980; Anderson *et al.* 1981; Childs *et al.* 2000; Hampson *et al.* 2007). However, it is important to determine wether this assumption is correct given its implications for culling.

Deterministic compartmental models have been used to describe rabies dynamics in wildlife (Anderson *et al.* 1981; Coyne, Smith & McAllister 1989) and domestic dogs (Cleaveland & Dye 1995; Coleman & Dye 1996; Kitala *et al.* 2002; Hampson *et al.* 2007; Carroll *et al.* 2010). These models assume random mixing, neglecting the spatial and social heterogeneity that exists in real populations. Within such 'well-mixed' models, frequency-dependent transmission of fatal diseases inevitably leads to rapid die-out of the host population (Keeling & Rohani 2008). Under frequency dependence, the average reproductive potential of the pathogen is unchanged during the spread of an epidemic. With no mechanism to arrest the spread of disease, transmission continues and the host and parasite populations go extinct. In contrast, under the assumption of density-dependent transmission, epidemics will subside when the host density falls below the invasion threshold (where $R_0 = 1$). The time delay between epidemic peak and replenishment of the host population generates damped epidemic cycles through delayed density dependence. The assumption of density-dependent transmission is therefore the most parsimonious mechanism by which stable epidemic cycles for rabies can be supported within deterministic random mixing models. However, in structured populations, epidemic cycles may be generated by alternative mechanisms even when the transmission rate is frequency-dependent.

Age structure is one such potential mechanism. Attack rates for rabies appear to vary considerably with age, with reported incidence in foxes in Europe (Wandeler *et al.* 1974b) and raccoons in Ontario (Rosatte *et al.* 2006) concentrated within adult age classes. Within an age-structured model, the net reproductive ratio of rabies will not only depend on the rates of transmission, but also on the age distribution in the population (Anderson & May 1991). If the basic reproductive ratio is only above unity for a core group of high-risk individuals, the epidemic can recede when this core group is exhausted. The delay between depletion of the core group and replenishment through births can generate cycles in incidence that may be sustained by seasonal birth pulses (Davis & Wood 1959; Lloyd *et al.* 1976).

Deterministic thresholds are not the only possible mechanism by which endemic coexistence of rabies could be maintained within frequency-dependent transmission models. An important limitation of deterministic models is that they do not account for the probability of local extinction of disease following an epidemic. In areas where rabies in foxes is not actively controlled, 3–4 yearly cycles in incidence are observed at regional levels [around 1000 km^2 in Europe and at the county level in Canada] (Johnston & Beauregard 1969; Bogel *et al.* 1974) and are out of phase between regions (Johnston & Beauregard 1969; Bogel *et al.* 1974; Macdonald & Voigt 1985). Epidemics have been associated with considerable reductions in host populations by up to 50% (Bogel *et al.* 1974). This reduction in the density of the host species within a region and the corresponding reduction in the instantaneous numbers of infective individuals will increase the chances of rabies becoming locally extinct before the host population is exhausted. Stochastic population thresholds for persistence of rabies can exist irrespective of the mode of transmission (Lloyd-Smith *et al.* 2005). Stochastic extinction and re-introduction of rabies following the local restructuring of host populations (Steck & Wandeler 1980; Anderson *et al.* 1981; Macdonald & Voigt 1985), consistent with metapopulation dynamics, are also viable alternative mechanisms to generate these dynamics.

In conclusion, cycles in rabies incidence observed in wildlife could be supported by density- or frequency-dependent transmission when stochasticity and the heterogeneous structure of real populations are accounted for.

Although deterministic density-dependent models have been used to describe rabies dynamics in domestic dogs, reactive vaccination can also drive cycles in incidence (Hampson *et al.* 2007). For example, in Zimbabwe between 1950 and 1995, the amplitude and interval of peaks in rabies varied (from 75 to 350 cases per year and interepidemic periods from 4 to 20 years) with the level of vaccination delivered during national vaccination campaigns (Bingham *et al.* 1999a). These observations provide little insight into the processes driving local disease dynamics for dogs. Rather, other evidence for the functional forms of transmission of canine rabies will be considered in the next sections.

THE RELATIONSHIP BETWEEN R_0 AND HOST DENSITY

As discussed above, R_0 is expected to increase with density for density-dependent transmission and remains constant irrespective of density for frequency-dependent transmission. R_0 may be estimated from the (exponential) rate of growth early in an epidemic prior to significant susceptible depletion or implementation of control measures (Heffernan, Smith & Wahl 2005; Wallinga & Lipsitch 2007). Using this method, Hampson *et al.* (2009) obtained estimates of R_0 for canine rabies, across a wide geographical range, of between 1·05 and 1·72. The range of these estimates is similar to the statistical uncertainty in simulated epidemics when the biting behaviour of rabid dogs is accounted for. Dog population densities were reported for only four of these locations, ranging from 1·36 dogs km^{-2} in rural Tanzania to 110 unrestricted dogs per km^2 in urban Mexico. However, other locations cited in the study are likely to represent even higher

densities, with the highest reported density in the general literature being 2388 dogs km^{-2} in Guayquil, Ecuador (Beran & Frith 1988). The absence of any correlation between R_0 and host density across such a large range of densities is consistent with earlier studies (Coleman & Dye 1996; Kitala *et al.* 2002) and suggests that if a relationship between transmission and dog density does exist, it must be quite weak.

Equivalent data are not available for wildlife. Compared to canine rabies, incidence records generally have a lower temporal resolution (typically quarterly or annually) (Macdonald & Voigt 1985; Rhodes *et al.* 1998; Bingham *et al.* 1999b; Rosatte *et al.* 2006), and the ranges of host densities are narrower: 0·8–1·2 jackals km^{-2} during the breeding season on commercial farmland in Zimbabwe (Rhodes *et al.* 1998), 5·4–9·1 racoons km^{-2} (averaged over a 4 year period) for rural Ontario (Rosatte *et al.* 2007) and 0·5–1·8 adult foxes km^{-2} in central Europe (Lloyd *et al.* 1976).

This apparent lack of relationship between R_0 and host density is most consistent with frequency-dependent transmission. However, as previously discussed, random mixing models with frequency-dependent transmission of rabies predict host extinction as soon as R_0 exceeds unity. This prediction is inconsistent with the very low attack rates reported for canine rabies compared to wildlife rabies and with the absence of large declines in population densities from rabies-induced mortality (Hampson *et al.* 2007). Estimates of the incidence, or average monthly attack rates, are typically below 0·5% and rarely exceed 2% (Waltner-Toews *et al.* 1990; Windiyaningsih *et al.* 2004; Zinsstag *et al.* 2009; Tenzin *et al.* 2010; Putra *et al.* 2011; Tenzin *et al.* 2011).

This incongruity between attack rates and the apparent scaling of R_0 may be resolved by considering a more complex relationship between rabies dynamics in dogs and anthropogenic factors than has previously been assumed. Suspect rabid and in-contact dogs are often identified and killed swiftly by the community (Hampson *et al.* 2007, 2009), a practice hereafter referred to as 'selective removal'. This reduces the effective infectious period in dogs (Hampson *et al.* 2009) and could contribute to the relatively lower incidence as compared to wildlife. The selective removal of infectious and in-contact dogs was thought to have contributed to the control of rabies in eastern Bhutan (Tenzin *et al.* 2011) and the United Kingdom (Pastoret & Brochier 1998). Indeed, euthanasia (WSPA 2012) of infected dogs is advocated to control rabies (WHO 2004). Such behavioural responses to the spread of epidemics are rarely considered in epidemiological models (Ferguson 2007; Funk *et al.* 2009) but are likely to play a particularly important role in disease transmission within owned, and managed, populations. Selective removal may conceal the existence of density-dependent transmission processes if the rate of intervention also scales with density.

We thus hypothesize that selective removal itself might be density-dependent for several reasons. First, rabid dogs may be more quickly spotted and selectively removed from areas with more people present. Second, given that most dogs are owned (WHO & WSPA 1990; Cleaveland & Dye 1995; Butler & Bingham 2000; Windiyaningsih *et al.* 2004), dog and human population densities are expected to correlate (Oboegbulem & Nwakonobi 1989; Matter *et al.* 1998; Butler & Bingham 2000). Finally, other anthropogenic factors that may interfere with contact processes, such as traffic or urban infrastructure, are also likely to scale with human and dog density. Therefore, the effective infectious period, as reduced by selective removal, could scale inversely with human, and thus dog, population density. The estimates of R_0 discussed above are conditional on the assumption of a fixed infectious period. Any systematic variation in the infectious period with population density could counteract the impact of density-dependent contact rates and result in R_0 appearing density-independent. Under this hypothesis, density-dependent transmission could not be ruled out unequivocally for canine rabies.

As a final consideration, stochastic fade-out is expected with low attack rates. However, rabies often appears to persist in dog populations. This may be because selective removal and stochastic processes are offset by the continual translocation of dogs (some of them infected) by people (Beran & Frith 1988; Denduangboripant *et al.* 2005; Coetzee & Nel 2007; Kasempimolporn, Jitapunkul & Sitprija 2008; Zinsstag *et al.* 2009) consistent with metapopulation dynamics (Hanski & Gaggiotti 2004; Beyer *et al.* 2010). In conclusion, more intensive study of the mechanisms underlying rabies transmission and persistence in domestic dog populations is warranted to understand these empirical patterns.

THRESHOLDS FOR INVASION AND INCREASING INCIDENCE WITH POPULATION DENSITY

The existence of a threshold in host population density below which infection cannot spread (i.e. where $R_0 < 1$) would be direct evidence in support of density-dependent transmission. Such invasion thresholds in wildlife and domestic dog populations have been proposed based on a limited number of studies that compared disease incidence between different geographical locations with different host densities (Steck & Wandeler 1980; Beran & Frith 1988; Cleaveland & Dye 1995). However, as discussed below, it is not possible to establish the relationship between host density and disease incidence based on these data.

Threshold densities for invasion have been suggested to occur where canine rabies is observed to change from sporadic disease at lower densities to persistence at higher densities (Beran & Frith 1988; Cleaveland & Dye 1995). However, these observations could also be explained by increased stochastic fade-out of disease at lower densities where there are lower numbers of infected dogs. In general, the probability of stochastic fade-out will decrease

with an increase in R_0 or in the number of infected individuals (Lloyd-Smith *et al.* 2005). This effect may be particularly relevant to dogs where more infected individuals may be introduced into larger or more dense populations by people (Denduangboripant *et al.* 2005; Kasempimolporn, Jitapunkul & Sitprija 2008; Zinsstag *et al.* 2009). Consequently, the probability of stochastic fade-out is predicted to decrease with an increase in population size or density. Even when R_0 is invariant between populations of different sizes or densities, stochastic effects may give the impression of a deterministic threshold for invasion where one does not exist. This is particularly likely when R_0 is low. Should a deterministic threshold for invasion exists, it may be obscured by these processes and be lower than estimated empirically.

The key data used to support the existence of a threshold density in foxes are expressed in terms of the hunting indicator of population density (HIPD) (Steck & Wandeler 1980). HIPD is an indirect estimate of density, with well-known biases (Wandeler 1980; Macdonald & Voigt 1985). However, there are two specific issues with the use of these data to support a threshold density for fox rabies. First, HIPD estimates below the purported threshold density for invasion were not recorded, thus precluding any conclusion of an invasion threshold. Second, the observed positive correlation between the annual number of animal rabies cases per km^2 per year and the HIPD has been wrongly interpreted as evidence for density-dependent transmission. Assuming the HIPD correlates with host density, such a relationship would be expected whether transmission depends on fox density or not. Determining the mode of transmission would require an evaluation of disease incidence as a proportion of the total population size or density (Rothman, Greenland & Lash 2008), which cannot be inferred from HIPD.

IMPACTS OF DENSITY REDUCTION

Density reduction, particularly culling (i.e. the widespread killing of hosts regardless of infection status), has been undertaken to reduce the incidence of rabies and therefore eliminate the disease on the basis that transmission is density-dependent. As previously discussed, the assumption of density dependence originates from the interpretation of cycles in wildlife rabies and thresholds for the invasion for foxes and dogs. However, the fact that culling has failed to achieve sustained control of rabies in wildlife and dogs (Kaplan, Goor & Tierkel 1954; Anderson *et al.* 1981; Macdonald & Voigt 1985; Anderson 1986; Beran & Frith 1988; WHO 2004; Windiyaningsih *et al.* 2004; Cleaveland *et al.* 2006) may be the best evidence that a simple relationship between disease incidence and host population density does not exist for rabies. We now discuss evidence from culling programmes (dogs and wildlife) followed by more limited evidence on sterilization campaigns.

Culling

Culling has been shown to be ineffective in controlling rabies in all host species. Rabies persisted in foxes in New York State despite 'concentrated reduction campaigns' following an outbreak in 1945, while simultaneous vaccination of dogs in the State eliminated rabies from this species (Friend 1968). Similarly, in Denmark in 1964, culling did not prevent rabies outbreaks in foxes; however, rabies did not occur where dogs in the same region had been vaccinated (Muller 1966, 1971). In response to a rabies outbreak in 1997, nearly 300 000 dogs, approximately half of the population estimated at the start of the outbreak, were culled in Flores, Indonesia over a period of 4 years. However, in 2004, rabies was still endemic although the total dog population was still considerably reduced (Windiyaningsih *et al.* 2004). Culling failed to control canine rabies in Korea (Lee *et al.* 2001) and Israel (Kaplan, Goor & Tierkel 1954), whereas subsequent vaccination in both countries controlled the disease.

Culling has been used to control ongoing outbreaks and to prevent the invasion of rabies in foxes. Declines in rabies cases have followed outbreaks irrespective of active culling (Bogel *et al.* 1974), with stochastic extinction expected (Anderson *et al.* 1981) particularly where disease-induced mortality is substantial (Bogel *et al.* 1974). Within a given area, culling might be expected to amplify these processes, increasing the probability of stochastic extinction regardless of density dependence. Indeed, rabies appeared to die-out in some areas where fox dens were gassed (Wandeler *et al.* 1974b). However, the limited data available are unclear regarding how culling interacts with disease-induced mortality during an epidemic and how it may change disease dynamics (Wandeler *et al.* 1974b). Other processes may also counter the effect of density reduction on disease incidence. Examples include social perturbations, as demonstrated in badger populations (Woodroofe *et al.* 2006a,b), and interactions between the level of culling, age structure (Bolzoni, Real & De Leo 2007) and demographic processes (Choisy & Rohani 2006).

Culling has also failed to prevent outbreaks of rabies in foxes in previously unaffected areas or the recurrence of the disease in areas where it had died-out, as observed in southern Denmark (Muller 1971). Where density-dependent transmission has been assumed, invasion thresholds are reported to vary and to be low (i.e. <1 fox km^{-2} in Europe and $<0{\cdot}4$ foxes km^{-2} in Ontario). Thus, even if transmission were density-dependent, reductions in density to below an invasion threshold may not be achievable practically or be sustainable (Wandeler *et al.* 1974a; Anderson *et al.* 1981).

Culling has generally failed to eliminate outbreaks of rabies in dogs. In our review of the scaling of rabies transmission rates with density (in the previous sections), we have found no conclusive evidence to support either the frequency-dependent or density-dependent assumption

for canine rabies. We are therefore unable to unequivocally conclude that the ineffectiveness of culling is because transmission is frequency-dependent. An alternative explanation is that reductions in densities to below invasion thresholds are not achievable practically. Canine rabies can circulate where densities are as low as 1·36 dogs km^{-2} (Hampson 2009), which is substantially lower than the densities reported for most free-roaming dog populations. Under the assumption of density-dependent contact rates, culling and vaccination should have similar impacts on disease incidence. Thus, given estimated values of $R_0 < 2$, control should be achieved by culling at most half the population. Yet, in Flores, Indonesia, rabies persisted after this level of culling was achieved (Windiyaningsih *et al.* 2004). More generally, the stochastic persistence of canine rabies despite low attack rates and considerable density reduction is interesting irrespective of the mode of transmission.

The fact that rabies often persists despite culling may be a function of human factors. The continual translocation of dogs (some infected) with people (Beran & Frith 1988; Denduangboripant *et al.* 2005; Coetzee & Nel 2007; Kasempimolporn, Jitapunkul & Sitprija 2008; Zinsstag *et al.* 2009) may offset the selective removal of infectious and in-contact dogs and stochastic extinctions. Where culling occurs simultaneously, translocation may also offset any reductions in the incidence of rabies. In addition, translocation may be exacerbated in response to culling campaigns. For example, within a few days of a village-wide cull in Kelusa, Bali, where rabies had not occurred previously, two residents brought in unvaccinated, potentially infected puppies from outside the village to replace their culled, vaccinated adult dogs. As attack rates are typically very low, culling predominately removes healthy dogs, and some of these may be vaccinated and hence unlikely to become infected. Other compensatory mechanisms may also offset reductions in host density. These include concomitant reductions in mortality from reduced competition for food (although the actual intensity of competition in free-roaming dogs is unknown), reductions in the dumping of surplus puppies/unwanted dogs and improved care of dogs. To address these issues, we are currently investigating the effects of human behaviour in response to culling on dog population dynamics and disease transmission in Kelusa.

The ethics of culling healthy, free-roaming animals in conjunction with vaccination programmes are also debatable. Raccoons have been culled on Wolfe Island, Ontario, as a means to reduce the number of animals that needed to be trapped and vaccinated (Rosatte *et al.* 2007). The same justification may be extended to dogs, and a variable degree of culling of free-roaming dogs, historically regarded as 'strays', has often been undertaken alongside mass vaccination programs (Wells 1954; Cheuk 1969; Larghi *et al.* 1988; Ernst & Fabrega 1989). However, despite appearances, the vast majority of free-roaming dogs in most societies globally are owned (WHO & WSPA 1990; Cleaveland & Dye 1995; Butler & Bingham 2000; Windiyaningsih *et al.* 2004) and in reasonable health. Not only are these dogs more accessible to vaccination than commonly recognized, but culling healthy animals can result in unintended negative consequences on both animal welfare and disease control.

Sterilization

The use of immunological and chemical sterilization has been modelled for the control of rabies in wildlife and in dogs (Suppo *et al.* 2000; Smith & Cheeseman 2002; Carroll *et al.* 2010). However, only surgical sterilization has been used in dogs under field conditions. Sterilizations are usually carried out by nongovernmental organizations and local authorities, which aim to vaccinate and simultaneously sterilize at least 70% of the dog population (Totton 2009). Limited data suggest that these programs reduce the incidence of rabies and may stabilize or gradually reduce population density over time-scales of several years (Reece & Chawla 2006; Totton 2009; Totton *et al.* 2010). However, the respective impacts of vaccination and sterilizations have not been assessed. Reductions in population density may plausibly reduce the number of dogs that require vaccination, although timely reductions in density may be constrained by resources and population dynamics (Hemachudha 2005). As with culling, the demand for dogs by communities may result in an increase in dog importation where local supply has been reduced by sterilization. Thus, we are studying the effect of human behaviour in response to sterilization on dog population dynamics and disease transmission in Antiga, Bali.

Conclusion

There is still considerable uncertainty surrounding the role of density in the transmission of rabies in animal host species. Density has been assumed to be the key factor that drives transmission, with important implications for the use of population reduction as a means to control rabies. However, it is evident that the relationship between host density, disease incidence and other factors is complex and varies between species. Further research to determine the factors that drive rabies transmission would not only enhance development of epidemiological models but also inform the development of effective, sustainable disease control measures.

Determining the effect of density in the transmission of rabies in wildlife hosts is constrained by the lack of high-resolution data exhibiting sufficient variability in both disease incidence and host densities. We have discussed how cycles in the incidence of rabies in foxes and raccoons can occur under either frequency- or density-dependent transmission, and how both model structures could account for the failure of culling to control rabies.

Although still limited, better quality data for dogs suggest a more complicated relationship between contact

rates and host density. The evidence indicates that not only is reducing dog density ineffective at controlling rabies, but culling in particular often has unintended negative consequences. We advocate more systematic investigation of the human factors that could affect the dynamics of rabies in dogs, to understand possible contrasts with the situation in wildlife.

In contrast to culling, vaccination programmes against rabies in dogs (Cleaveland *et al.* 2003; WHO 2004; Schneider *et al.* 2005; Cleaveland *et al.* 2006; Davlin & VonVille 2012) and wildlife (Wandeler *et al.* 1988; Brochier *et al.* 1991; MacInnes *et al.* 2001; Rosatte *et al.* 2007) have proven efficacy and feasibility across a wide range of settings and raise far fewer ethical or welfare issues.

Acknowledgements

Michelle Morters is supported by a grant from the International Fund for Animal Welfare (IFAW) and the World Society for the Protection of Animals (WSPA), with additional support from the Charles Slater Fund and the Jowett Fund. Olivier Restif is supported by the Royal Society, Katie Hampson by the Wellcome Trust and James Wood by the Alborada Trust. James Wood, Olivier Restif and Katie Hampson receive support from the Research and Policy for Infectious Disease Dynamics program of the Science and Technology Directorate, Department of Homeland Security, Fogarty International Centre, National Institutes of Health. The authors also thank T.J. McKinley for useful discussions and the reviewers for critical feedback on the manuscript.

References

Altizer, S., Dobson, A., Hosseini, P., Hudson, P., Pascual, M. & Rohani, P. (2006) Seasonality and the dynamics of infectious diseases. *Ecology Letters*, **9**, 467–484.

Anderson, R.M. (1986) Vaccination of wildlife reservoirs. *Nature*, **322**, 304–305.

Anderson, R.M. & May, R.M. (1991) *Infectious Diseases of Humans – Dynamics and Control*. Oxford University Press, New York.

Anderson, R.M., Jackson, H.C., May, R.M. & Smith, A.M. (1981) Population dynamics of fox rabies in Europe. *Nature*, **289**, 765–771.

Begon, M., Harper, J.L. & Townsend, C.R. (1996) *Ecology*, 3rd edn. Blackwell Science Limited, Oxford, UK.

Begon, M., Bennett, M., Bowers, R.G., French, N.P., Hazel, S.M. & Turner, J. (2002) A clarification of transmission terms in host-microparasite models: numbers, densities and areas. *Epidemiology and Infection*, **129**, 147–153.

Beran, G.W. & Frith, M. (1988) Domestic animal rabies control: an overview. *Reviews of Infectious Diseases*, **10**, S672–S677.

Beyer, H.L., Hampson, K., Lembo, T., Cleaveland, S., Kaare, M. & Haydon, D.T. (2010) Metapopulation dynamics of rabies and the efficacy of vaccination. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **278**, 2182–2190.

Bingham, J., Foggin, C.M., Wandeler, A.I. & Hill, F.W.G. (1999a). The epidemiology of rabies in Zimbabwe. 1. Rabies in dogs (Canis familiaris). *Onderstepoort Journal of Veterinary Research*, **66**, 1–10.

Bingham, J., Foggin, C.M., Wandeler, A.I. & Hill, F.W.G. (1999b) The epidemiology of rabies in Zimbabwe. 2. Rabies in jackals (*Canis adustus* and *Canis mesomelas*). *Onderstepoort Journal of Veterinary Research*, **66**, 11–23.

Bjornstad, O.N., Finkenstadt, B.F. & Grenfell, B.T. (2002) Dynamics of measles epidemics: estimating scaling of transmission rates using a time series SIR model. *Ecological Monographs*, **72**, 169–184.

Bogel, K., Arata, A.A., Moegle, H. & Knorpp, F. (1974) Recovery of reduced fox populations in rabies control. *Zentralblatt fur Veterinarmedizin Reihe B*, **21**, 401–412.

Bolzoni, L., Real, L. & De Leo, G. (2007) Transmission heterogeneity and control strategies for infectious disease emergence. *PLoS ONE*, **8**, e747.

Brochier, B., Kieny, M.P., Costy, F., Coppens, P., Bauduin, B., Lecocq, J. P., Languet, B., Chappius, G., Desmettre, P., Afiademanyo, K., Libois, R. & Pastoret, P.-P. (1991) Large-scale eradication of rabies using recombinant vaccinia-rabies vaccine. *Nature*, **354**, 520–522.

Butler, J.R.A. & Bingham, J. (2000) Demography and dog-human relationships of the dog population in Zimbabwean communal lands. *The Veterinary Record*, **147**, 442–446.

Carroll, M.J., Singer, A., Smith, G.C., Cowan, D.P. & Massei, G. (2010) The use of immunocontraception to improve rabies eradication in urban dog populations. *Wildlife Research*, **37**, 676–687.

Cheuk, H. (1969) A review of the history and control of rabies in Hong Kong. *Agricultural Science Hong Kong*, **1**, 141–147.

Childs, J.E., Curns, A.T., Dey, M.E., Real, L.A., Feinstein, L., Bjornstad, O.N. & Krebs, J.W. (2000) Predicting the local dynamics of epizootic rabies among raccoons in the United States. *Proceedings of the National Academy of Sciences*, **97**, 13666–13671.

Choisy, M. & Rohani, P. (2006) Harvesting can increase severity of wildlife disease epidemics. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **273**, 2025–2034.

Cleaveland, S. (1998) Epidemiology and control of rabies. The growing problem of rabies in Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **92**, 131–134.

Cleaveland, S. & Dye, C. (1995) Maintenance of a microparasite infecting several host species: rabies in the Serengeti. *Parasitology*, **111**, S33–S47.

Cleaveland, S., Kaare, M., Tiringa, P., Mlengeya, T. & Barrat, J. (2003) A dog rabies vaccination campaign in rural Africa: impact on the incidence of dog rabies and human dog-bite injuries. *Vaccine*, **21**, 1965–1973.

Cleaveland, S., Kaare, M., Knobel, D. & Laurenson, M.K. (2006) Canine vaccination – providing broder benefits for disease control. *Veterinary Microbiology*, **117**, 43–50.

Coetzee, P. & Nel, L.H. (2007) Emerging epidemic dog rabies in coastal South Africa: a molecular epidemiological analysis. *Virus Research*, **126**, 186–195.

Coleman, P.G. & Dye, C. (1996) Immunization coverage required to prevent outbreaks of dog rabies. *Vaccine*, **14**, 185–186.

Courtin, F., Carpenter, T.E., Paskin, R.D. & Chomel, B.B. (2000) Temporal patterns of domestic and wildlife rabies in central Namibia stock-ranching area, 1986–1996. *Preventive Veterinary Medicine*, **43**, 13–28.

Coyne, M.J., Smith, G. & McAllister, F.E. (1989) Mathematic model for the population biology of rabies in raccoons in the mid-Atlantic. *American Journal of Veterinary Research*, **50**, 2148–2154.

Davis, D.E. & Wood, J.E. (1959) Ecology of foxes and rabies control. *Public Health Reports*, **74**, 115–118.

Davlin, S.L. & VonVille, H.M. (2012) Canine rabies vaccination and domestic dog population characteristics in the developing world: a systematic review. *Vaccine*, **30**, 3492–3502.

Denduangboripant, J., Wacharapluesadee, S., Lumlertdacha, B., Ruankaew, N., Hoonsuwan, W., Puanghat, A. & Hemachudha, T. (2005) Transmission dynamics of rabies virus in Thailand: implications for disease control. *BMC Infectious Diseases*, **5**, 52.

Earn, D.J.D., Rohani, P., Bolker, B.M. & Grenfell, B.T. (2000) A simple model for complex dynamical transitions in epidemics. *Science*, **287**, 667–670.

Ernst, S.N. & Fabrega, F. (1989) A time series analysis of the rabies control programme in Chile. *Epidemiology and Infection*, **103**, 651–657.

Ezeokoli, C.D. & Umoh, J.U. (1987) Epidemiology of rabies in northern Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 268–272.

Ferguson, N. (2007) Capturing human behaviour. *Nature*, **446**, 733.

Friend, M. (1968) History and epidemiology of rabies in wildlife in New York. *New York Fish and Game Journal*, **15**, 71–97.

Funk, S., Gilad, E., Watkins, C. & Jansen, V.A.A. (2009) The spread of awareness and its impact on epidemic outbreaks. *Proceedings of the National Academy of Sciences*, **106**, 6872–8677.

Grenfell, B.T., Bjornstad, O.N. & Finkenstadt, B. (2002) Dynamics of measles epidemics. II. Scaling noise, determinism and predictability with the time series SIR model. *Ecological Monographs*, **72**, 185–202.

Hampson, K., Dushoff, J., Bingham, J., Bruckner, G., Ali, Y.H. & Dobson, A. (2007) Synchronous cycles of domestic dog rabies in sub-Saharan Africa and the impact of control efforts. *Proceedings of the National Academy of Sciences*, **104**, 7717–7722.

Hampson, K., Dushoff, J., Cleaveland, S., Haydon, D.T., Kaare, M., Packer, C. & Dobson, A. (2009) Transmission dynamics and prospects for the elimination of canine rabies. *PLoS Biology*, **7**, 462–471.

Hanski, I. & Gaggiotti, O.E. (2004) *Ecology, Genetics and Evolution of Metapopulations: Standard Methods for Inventory and Monitoring*. Elsevier Academic Press, London.

Heffernan, J.M., Smith, R.J. & Wahl, L.M. (2005) Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, **2**, 281–293.

Hemachudha, T. (2005) Rabies and dog population control in Thailand: success or failure? *Journal of the Medical Association of Thailand*, **88**, 120–123.

Johnston, D.H. & Beauregard, M. (1969) Rabies epidemiology in Ontario. *Bulletin of the Wildlife Disease Association*, **5**, 357–370.

Kaplan, M.M., Goor, Y. & Tierkel, E.S. (1954) A field demonstration of rabies control using chicken-embryo vaccine in dogs. *Bulletin of the World Health Organization*, **10**, 743–752.

Kasempimolporn, S., Jitapunkul, S. & Sitprija, V. (2008) Moving towards the elimination of rabies in Thailand. *Journal of the Medical Association of Thailand*, **91**, 433–437.

Kayali, U., Mindekem, R., Yemadji, N., Oussiguere, A., Naissengar, S., Ndoutamia, A.G. & Zinsstag, J. (2003) Incidence of canine rabies in N'Djamena, Chad. *Preventive Veterinary Medicine*, **61**, 227–233.

Keeling, M.J. & Rohani, P. (2008) *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press, Princeton, NJ.

Kitala, P.M., McDermott, J.J., Coleman, P.G. & Dye, C. (2002) Comparison of vaccination strategies for the control of dog rabies in Machakos District, Kenya. *Epidemiology and Infection*, **129**, 215–222.

Knobel, D.L., Cleaveland, S., Coleman, P.G., Fevre, E.M., Meltzer, M. I., Miranda, M.E.G., Shaw, A., Zinsstag, J. & Meslin, F.-X. (2005) Re-evaluating the burden of rabies in Africa and Asia. *Bulletin of the World Health Organization*, **83**, 360–368.

Larghi, O.P., Arrosi, J.C., Nakajata-A, J. & Villa-Nova, A. (1988) Control of urban rabies. *Rabies* (eds J.B. Campbell & K.M. Charlton), pp. 407–422. Kluwer Academic Press, Boston, MA.

Lee, J.H., Lee, M.J., Lee, J.B., Kim, J.S., Bae, C.S. & Lee, W.C. (2001) Review of canine rabies prevalence under two different vaccination programmes in Korea. *The Veterinary Record*, **148**, 511–512.

Lloyd, H.G., Jensen, B., van Haaften, J.L., Niewold, F.J.J., Wandeler, A., Bogel, K. & Arata, A.A. (1976) Annual turnover of fox populations in Europe. *Zentralblatt fur Veterinarmedizin Reihe B*, **23**, 580–589.

Lloyd-Smith, J.O., Cross, P.C., Briggs, C.J., Daugherty, M., Getz, W.M., Latto, J., Sanchez, M.S., Smith, A.B. & Swei, A. (2005) Should we expect population thresholds for wildlife disease? *Trends in Ecology and Evolution*, **20**, 511–519.

Macdonald, D.W. & Voigt, D.R. (1985) The biological basis of rabies models. *Population Dynamics of Rabies in Wildlife* (ed. P.J. Bacon), pp. 71–108. Academic Press, London.

MacInnes, C.D., Smith, S.M., Tinline, R.R., Ayers, N.R., Bachmann, P., Ball, D.G.A., Calder, L.A., Crosgrey, S.J., Fielding, C., Hauschildt, P., Honig, J.M., Johnston, D.H., Lawson, K.F., Nunan, C.P., Pedde, M. A., Pond, B., Stewart, R.B. & Voigt, D.R. (2001) Elimination of rabies from red foxes in eastern Ontario. *Journal of Wildlife Diseases*, **37**, 119–132.

Matter, H.C., Schumacher, C.L., Kharmachi, H., Hammami, S., Tlatli, A., Jemli, J., Mrabet, L., Meslin, F.X., Aubert, M.F.A., Neuenschwander, B.E. & El Hicheri, K. (1998) Field evaluation of two bait delivery systems for the oral immunization of dogs against rabies in Tunisia. *Vaccine*, **16**, 657–665.

Muller, J. (1966) The reappearance of rabies in Denmark. *Bulletin of the Wildlife Disease Association*, **65**, 21–29.

Muller, J. (1971) The effect of fox reduction on the occurence of rabies. Observations from two outbreaks of rabies in Denmark. *Bulletin of the World Health Organization*, **75**, 763–776.

Oboegbulem, S.I. & Nwakonobi, I.E. (1989) Population density and ecology of dogs in Nigeria: a pilot stdy. *Revue Scientifique et Technique-Office International*, **8**, 733–745.

Pastoret, P.P. & Brochier, B. (1998) Epidemiology and elimination of rabies in Western Europe. *The Veterinary Journal*, **156**, 83–90.

Putra, A.A.G., Mardiana, I.W., Scott-Orr, H., Hiby, E., Hampson, K., Haydon, D., Girardi, J., Knobel, D. & Townsend, S. (2011) Progress of a rabies elimination program in Bali, Indonesia. Rabies in Asia Conference. Colombo, Sri Lanka.

Reece, J.F. & Chawla, S.K. (2006) Control of rabies in Jaipur, India, by the sterilisation and vaccination of neighbourhood dogs. *The Veterinary Record*, **159**, 379–383.

Rhodes, C.J., Atkinson, R.P.D., Anderson, R.M. & Macdonald, D.W. (1998) Rabies in Zimbabwe: reservoir dogs and the implications for disease control. *Philosophical Transactions of the Royal Society of London B*, **353**, 999–1010.

Rosatte, R., Sobey, K., Donovan, D., Bruce, L., Allan, M., Silver, A., Bennett, K., Gibson, M., Simpson, H., Davies, C., Wandeler, A. & Muldoon, F. (2006) Behaviour, movements and demographics of rabid raccoons in Ontario, Canada: management implications. *Journal of Wildlife Diseases*, **42**, 589–605.

Rosatte, R., MacDonald, E., Sobey, K., Donovan, D., Bruce, L., Allan, M., Silver, A., Bennett, K., MacDonald, K., Gibson, M., Buchanan, T., Stevenson, B., Davies, C., Wandeler, A. & Muldoon, F. (2007) The elimination of raccoon rabies from Wolfe Island, Ontario: animal density and movements. *Journal of Wildlife Diseases*, **43**, 242–250.

Rothman, K.J., Greenland, S. & Lash, T.L. (2008) *Modern Epidemiology*, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, PA.

Schneider, M.C., Belotto, A., Ade, M.P., Correa, E., Tamayo, H., Medina, G. & Rodrigues, M.J. (2005) Epidemiological situation of human rabies in Latin America in 2004. *Epidemiological Bulletin/Pan-American Health Organization*, **26**, 2–4.

Smith, G.C. & Cheeseman, C.L. (2002) A mathematical model for the control of diseases in wildlife populations: culling, vaccinations and fertility control. *Ecological Modelling*, **150**, 45–53.

Steck, F. & Wandeler, A. (1980) The epidemiology of fox rabies in Europe. *Epidemiologic Reviews*, **2**, 71–96.

Suppo, C., Naulin, J.-M., Langlais, M. & Artois, M. (2000) A modelling approach to vaccination and contracpetion programmes for rabies control in fox populations. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **267**, 1575–1582.

Tenzin, Sharma, B., Dhand, N.K., Timsina, N. & Ward, M.P. (2010) Reemergence of rabies in Chhukha District, Bhutan, 2008. *Emerging Infectious Diseases*, **16**, 1925–1930.

Tenzin, Dhand, N.K., Dorjee, J. & Ward, M.P. (2011) Re-emergence of rabies in dogs and other domestic animals in eastern Bhutan, 2005–2007. *Epidemiology and Infection*, **139**, 220–225.

Totton, S.C. (2009) *Stray Dog Population Health and Demographics in Jodhpur, India, Following a Spay/Neuter/Rabies Vaccination Program*. PhD thesis, University of Guelph, Guelph, Ontario, Canada.

Totton, S.C., Wandeler, A.I., Zinsstag, J., Bauch, C.T., Ribblw, C.S., Rosatte, R.C. & McEwen, S.A. (2010) Stray dog population demographics in Jodhpur, India following a population control/rabies vaccination program. *Preventive Veterinary Medicine*, **97**, 51–57.

Wallinga, J. & Lipsitch, M. (2007) How generation intervals shape the relationship between growth rates and reproductive numbers. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, **274**, 599–604.

Waltner-Toews, D., Maryono, A., Akoso, B.T., Wisynu, S. & Unruh, D. H.A. (1990) An epidemic of canine rabies in central Java, Indonesia. *Preventive Veterinary Medicine*, **8**, 295–303.

Wandeler, A. (1980) Hunters and foxes. *Habitat Classification, Fox Populations and Rabies Spread*. Institute of Terrestrial Ecology, Institute of Terrestrial Ecology, Huntingdon, UK.

Wandeler, A.I., Muller, J., Wachendorfer, G., Schale, W., Forster, U. & Steck, F. (1974a) Rabies in wild carnivores in central Europe. III. Ecology and biology of the fox in relation to control operations. *Zentralblatt fur Veterinarmedizin Reihe B*, **21**, 765–773.

Wandeler, A.I., Wachendorfer, G., Forster, U., Krekel, H., Schale, W., Muller, J. & Steck, F. (1974b) Rabies in wild carnivores in central Europe. I. Epidemiological studies. *Zentralblatt fur Veterinarmedizin Reihe B*, **21**, 735–756.

Wandeler, A.I., Capt, S., Gerber, H., Kappeler, A. & Kipfer, R. (1988) Rabies epidemiology, natural barriers and fox vaccination. *Parassitologia*, **30**, 53–57.

Wells, C.W. (1954) The control of rabies in Malaya through compulsory mass vaccination of dogs. *Bulletin of the Wildlife Disease Association*, **10**, 731–742.

WHO (2004) *World Health Organization Expert Consultation on Rabies First Report*. WHO Technical Report Series 931. WHO, Geneva.

WHO & WSPA (1990) *Guidelines for Dog Population Management*. WHO/ZOON/90.166. World Health Organization (WHO) and World Society for the Protection of Animals (WSPA), Geneva.

Widdowson, M.-A., Morales, G.J., Chaves, S. & McGrane, J. (2002) Epidemiology of urban canine rabies, Santa Cruz, Bolivia, 1972–1997. *Emerging Infectious Diseases*, **8**, 458–461.

Windiyaningsih, C., Wilde, H., Meslin, F.-X., Suroso, T. & Widarso, H.S. (2004) The rabies epidemic on Flores Island, Indonesia (1998–2003). *Journal of the Medical Association of Thailand*, **87**, 1389–1393.

Woodroofe, R., Donnelly, C.A., Cox, D.R., Bourne, F.J., Cheeseman, C. L., Delahay, R.J., Gettinby, G., McInerney, J.P. & Morrison, W.I. (2006a) Effects of culling on badger *Meles meles* spatial organization: implications for the control of bovine tuberculosis. *Journal of Applied Ecology*, **43**, 1–10.

Woodroofe, R., Donnelly, C.A., Jenkins, H.E., Johnston, W.T., Cox, D. R., Bourne, F.J., Cheeseman, C.L., Delahay, R.J., Clifton-Hadley, R.S., Gettinby, G., Gilks, P., Hewinson, R.G., McInerney, J.P. & Morrison, W.I. (2006b) Culling and cattle controls influence tuberculosis risk for badgers. *Proceedings of the National Academy of Sciences*, **103**, 14713–14717.

WSPA (2012) http://www.rabiesblueprint.com/IMG/pdf/Link72_Euthanasia_WSPA.pdf [accessed 17 May 2012].

Zinsstag, J., Durr, S., Penny, M.A., Mindekem, R., Roth, F., Menendez Gonzalez, S., Naissengar, S. & Hattendorf, J. (2009) Transmission dynamics and economics of rabies control in dogs and humans in an African city. *Proceedings of the National Academy of Sciences*, **106**, 14996–15001.

Received 21 December 2011; accepted 31 July 2012
Handling Editor: Mike Boots

Feature Series Article

Application of modelling to determine the absence of foot-and-mouth disease in the face of a suspected incursion

C Heuer[*§], NP French[*], R Jackson[*] and GF Mackereth[†]

Abstract

AIM: To use disease modelling to inform a response team about the number of animals per herd/flock to be examined, and the start date and duration of clinical surveillance required to be confident that foot-and-mouth disease (FMD) was not present on an island in New Zealand with a population of approximately 1,600 cattle, 10,000 sheep and a small number of pigs, goats and alpacas.

METHODS: Because the probability of detecting clinical disease in (the) primary case(s) in larger herds and flocks was extremely low, deterministic and stochastic mathematical SLIR (susceptible, latent, infectious, recovered) models for the transmission of infection were constructed to estimate the date when clinical lesions in herds and flocks would be detected with 95% confidence. Surveillance targeted the first wave of infections following a suspect index case.

RESULTS: If 70 cattle in herds of about 400 cattle were examined it was estimated it would take approximately 13 (90% stochastic range 9–19) days from first exposure before it would be possible to achieve 95% confidence for detecting clinical signs for a low-virulence virus, and 9 (7–14) days for a high-virulence virus. The duration of sufficiently accurate clinical detection was 17 (15–19) days and 13 (12–14) days for low- and high-virulence viruses, respectively. A sample of 70 sheep from flocks of >1,000 would be required to achieve clinical detection at about the same time but with a shorter period of detection than for cattle. The duration of effective detection could be increased by examining a larger sample in most sheep flocks, however the small size of many cattle herds in the study population limited the confidence of detecting group-level disease in cattle, therefore necessitating repeated herd inspections. The model suggested that group-level detection was not feasible if it was based on elevated body temperature alone because of short durations of fever in infected animals.

CONCLUSION AND CLINICAL RELEVANCE: Simulation modelling is a useful and powerful tool for informing ongoing surveillance activities in the face of an exotic disease incursion. Results of modelling suggested to start clinical inspection activities at 4 days and to continue regular inspection twice a week for about 35 days after the date of first exposure, to satisfy the required 95% confidence threshold of clinical detection of FMD in cattle herds and sheep flocks.

[*] EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North, New Zealand.
[†] Biosecurity New Zealand, Ministry of Agriculture and Forestry, Investigation and Diagnostic Centre Wallaceville PO Box 40742, Upper Hutt, New Zealand.
[§] Author for correspondence. Email: c.heuer@massey.ac.nz

KEY WORDS: *Foot-and-mouth disease, incursion response, surveillance, stochastic state transition modelling*

Introduction

On 10 May 2005, a letter was received by the Prime Minister of New Zealand stating that FMD virus had been deliberately released on Monday 09 May 2005 on Waiheke Island, by exposing one or more cattle and sheep to virus-contaminated hay. The Exotic Disease Response (EDR) team of Biosecurity New Zealand, Ministry of Agriculture and Forestry, New Zealand, immediately mobilised all required and available resources to detect and contain any disease and prevent a major outbreak. A contingency plan for the detection of disease in sheep or cattle was developed, and a sampling plan was issued by the National Centre for Disease Investigation on 22 May 2005. The plan aimed to detect with 95% confidence clinical signs of infection in so-called management groups, which were defined as mobs of animals which were managed separately on each farm. A property could therefore have more than one management group. On farms with >100 sheep, the estimated average number of management groups was 2.5, and according to official national census data about 99% of the island's sheep were kept on seven farms, ranging from 218 to 12,000 sheep per farm. Cattle were generally kept as one management group per farm. However, a census carried out during response operations revealed that the actual ruminant population of Waiheke Island comprised 1,618 cattle in 30 herds, comprising 1–454 animals per herd, and 10,491 sheep in 36 flocks, comprising 1–5,250 animals per flock. A few other domestic livestock (pigs, 30 alpacas (*Lama pacos*), 47 goats) and some susceptible wildlife (mainly feral pigs and feral goats) were also present. As a sampling approach was applied to sheep and cattle but all other susceptible species were clinically inspected, this study aimed to develop a surveillance strategy only for these two species.

The initial surveillance plan included a complete description of procedures for whole-herd inspection, examination of potentially exposed animals, including measurement of rectal temperatures, sampling of vesicular fluid from affected animals, and submission of specimens from animals with a fever or clinical signs of FMD.

AP	Apparent prevalence
EDR	Emerging Disease Response
FMD	Foot-and-mouth disease
HSe/FSe	Herd sensitivity/flock sensitivity
Ro	Basic dissemination rate
Se	Sensitivity
SLIR	Susceptible, latent, infectious, recovered
TP	True prevalence

Herd and flock inspections were scheduled to start immediately upon arrival of the response team. All animals from small farms with up to 40 animals per management group, and 40–70 animals in larger management groups of 40–1,000 animals, were to be clinically inspected.

However, after considering the transmission dynamics of FMD it became apparent that detection of the initially exposed index case(s) ('needle in the haystack') was highly unlikely and that a more effective approach would be to focus surveillance activities on the most likely time after the release of the virus for the appearance of clinical signs in secondary cases.

Several detailed reviews of the epidemiology of FMD were available (Sanson 1994; Hughes et al 2002; Alexandersen et al 2003). In the FMD outbreak in the United Kingdom (UK) in 2001, only 73% of infected sheep developed clinical signs (which were mild and lasted only 2 days), and 93% of the one to four lesions per animal were small and occurred on the feet (Hughes et al 2002). The disease in sheep needed careful clinical inspection to be detectable (Hughes et al 2002). It has also been postulated that sheep might not shed and disseminate sufficient virus to propagate infection and cause an outbreak (Donaldson 2000, non-peer-reviewed). However, recent experimental studies in lambs indicated that outbreaks can occur, albeit under artificial conditions and following intranasal inoculation of specific amounts of virus (Orsel et al 2007b). In the latter study, sheep shed significant amounts of virus for an average of 4.5 (range 0–14) days, yet approximately 50% of in-contact animals became infected and only 50% of infected animals showed clinical signs. However, this information was not available at the time of the incident on Waiheke Island.

Detection of FMD in cattle appears to be much easier. Cattle are highly susceptible to respiratory infection and almost all infected cattle develop clearly visible clinical signs. Infection via the oral route as it was inferred from the letter to the Prime Minister, is harder to establish and may result in a longer latent period than respiratory infection. Infection acquired orally requires a viral dose of 10^5–10^6 tissue-culture-infectious-dose-50, which is about 100–1 million times higher than that required for infection via the respiratory route (Sanson 1994; Alexandersen et al 2003).

The incubation time for FMD is highly variable, and depends on the strain and dose of virus, route of transmission, animal species, and husbandry conditions. The incubation period was described as 2–14 days (Anonymous 2005), but may be as short as 24 h in some animals. When transmission is occurring within a herd or flock, the incubation period is typically 2–6 days, but for between-farm spread it may take 2–14 days from infection on the source farm to clinical signs on the target farm (Alexandersen et al 2003). Subsequent clinical signs (vesicles and lesions) normally last for variable periods of 2–6 days in cattle and sheep, but lasted 8.5 days on average in lambs in recent experimental studies (Orsel et al 2007b). After a latent period of 1–2 days, shedding of large amounts of virus starts 2–4 days before the appearance of clinical signs. About 50% cattle and sheep become carriers and continue to shed virus for more than 4 weeks. A decline in viral excretion and load occurs around Day 4–5 of the clinical disease, by which time a significant antibody titre may be detectable. Generally, all secretions and excretions (except oesophageal-pharyngeal fluid in ruminants) will be free from detectable virus at 10–14 days (Hughes et al 2002; Alexanderson et al 2003).

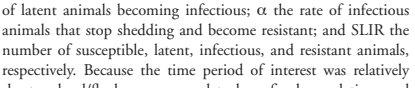
Transmission rates depend in part on the strain of the virus, frequency of contact, and conditions of ventilation, since most transmission is by the respiratory route. Animals on pasture will transmit the virus at a lower rate than animals housed indoors, especially when stocking rates are low and no crowding occurs (Hughes et al 2002). Whereas the estimation of transmission parameters usually requires extensive sampling and testing, they can be derived from reported basic reproduction ratios (Woolhouse et al 1996).

The purpose of this study was to provide guidance to the EDR team on the number of animals per herd/flock to be clinically examined, the starting date of clinical surveillance, and for how long it would be required before being sure that FMD was not present on the island. This advice was required within a few days after the incident was first reported. Situations like this may occur frequently elsewhere, for example when minor outbreaks occur that are likely to have originated from a common source, such as in early August 2007 in the UK. Thus this approach was assessed for its usefulness in informing surveillance policy in the face of a potential FMD outbreak.

Materials and methods

Model structure

Density-dependent (assuming constant area) deterministic and stochastic SLIR models were developed to estimate changes in the prevalence of occurrence of clinically detectable signs (Begon et al 2002). The additional state C (clinical) was linked with the SLIR model, as described below, to include the rate of development of clinical signs in groups of animals within a herd/flock. A schematic representation of the model is shown below:



where β is the parameter of transmission of infection; γ the rate of latent animals becoming infectious; α the rate of infectious animals that stop shedding and become resistant; and SLIR the number of susceptible, latent, infectious, and resistant animals, respectively. Because the time period of interest was relatively short, a herd/flock was assumed to be a fixed population, and there was no consideration of withdrawals or additions. The following coupled differential equations described the transmission process:

$d/dt\ (S) = -\beta^*S^*I$

$d/dt\ (L) = \beta^*S^*I - \gamma^*L$

$d/dt\ (I) = \gamma^*L - \alpha^*I$

$d/dt\ (R) = \alpha^*I$

where d is the number of animals changing from one state to the next, dt the time period, and capital letters representing the number of animals in each state.

The latent period was assumed to be 2 days for both cattle and sheep, resulting in $\gamma = 1/L = 0.5$. The infectious period was 6 days for cattle and 4 days for sheep, thus $\alpha = 1/6 = 0.1667$ for cattle, and $1/4 = 0.25$ for sheep. Referenced estimates for latent, infectious and incubation periods and the duration of clinical signs are shown in Table 1.

Table 1. Epidemiologically relevant parameters for foot-and-mouth disease in cattle and sheep.

Parameter	Cattle	Sheep	Reference
Latent period of orally exposed index case	2.5 days	2.5 days	Inferred from Sanson 1994
Latent period of in-contact animals	1–2 days	1–2 days	Orsel et al 2007ab
Incubation period	2–6 days	2–6 days	Alexanderson et al 2003
	4.5 days	4.5 days	Orsel et al 2007b
Shedding period	2–6 days	2–4 days	Sanson 1994; Hughes et al 2002
Clinical period (skin lesions)	3–6 days	2.2–6 days	Alexanderson et al 2003; Hughes et al 2002
		8.5 days	Orsel et al 2007b
Duration of elevated body temperature	12–24 h	12–24 h	Hughes et al 2002
No. secondary infections per index case	2–12	2–12	Woolhouse et al 1996; Tsutsui et al 2003
(basic dissemination rate Ro)		1–2	Orsel et al 2007b

In all scenarios, clinical signs were assumed to become evident on average 2 days into the infectious period and last for 3 days, thus shedding commenced 2 days before the onset of clinical signs. The average time from contact to the onset of clinical signs (incubation period) was therefore assumed to be 4 days. The clinical state (C) was modelled by assuming that individuals in the infectious state became clinical after 2 days, and remained both clinical and infectious for a further 3 days. The transmission parameter, β, depended on the species-dependent infectious period ($1/\alpha$), a scenario-specific dissemination rate (Ro), and herd size (N), and was calculated as $\beta = Ro^*\alpha/N$.

This model produced the number of animals in a clinical state of infection at every time point. Since all cattle but only 73% sheep would develop clinical signs (Hughes et al 2002), the true prevalence (TP) of clinically affected animals was the number affected divided by herd size, multiplied by 1 for cattle and by 0.73 for sheep. Consequently, the apparent prevalence (AP) of clinically affected animals detected by inspection was the TP multiplied by the sensitivity (Se) of detection of clinical signs, which was assumed to be 1 for cattle and 0.8 for sheep, i.e. AP = TP*Se. The specificity of detection was set to 1 because every animal that was regarded as infected with FMD virus based on clinical inspection was followed-up by sampling and testing for serum antibody (indirect enzyme-linked immunosorbent assay Bommeli; De Diego et al 1997) and virus RNA in swabs from suspected lesions (fluorogenic real-time polymerase chain reaction; Reid et al 2003). In addition, an entire random herd/flock sample would be re-inspected for clinical signs and tested for serum antibody. Finally, the sensitivity of detecting at least one infected animal in a sample size of n animals at the herd/flock sensitivity (HSe/FSe) level was calculated as $HSe/FSe = 1-(1-AP)^n$.

The stochastic model assumed that individuals moved from one state to another, and the following Poisson-distributed average number (μ) changed state in the small time interval t to t + dt, where dt = 0.0001 days:

Event	Distribution (μ)
(S,L) ⟶ (S–1, L + 1)	Poisson ($\beta^*S^*I^*dt$)
(L,I) ⟶ (L–1, I + 1)	Poisson (γ^*L^*dt)
(I,R) ⟶ (I–1, R + 1)	Poisson (α^*I^*dt)

The time step was chosen such that only one animal changed state (in much less than 1% of the time steps were there two events in the same time step). Since the Poisson distribution models integers, only entire animals could change states, so the model simulated the fate of each animal in the herd/flock in each 0.0001-day interval (8.6 seconds) using stochastic selection of inter-event time. It was assumed that a single animal was infected on Day 1 (thus in latent stage), as this reflected the most challenging scenario for surveillance. The number in the clinical state was calculated as for the deterministic model. Berkeley Madonna v8.0.1 (RI Macey and GF Oster, University of California, Berkeley, USA, 1997–2000), a software package specifically designed to model transition processes, was used for both deterministic and stochastic simulations (code available on request).

The key output parameters of interest were the starting date and the length of the period during which the confidence of detection of FMD at the herd/flock level was ≥95%.

Sensitivity analysis

The deterministic model was used to evaluate several scenarios. Firstly, the small difference between detection in cattle and sheep was presumably due to a different sample size or sampling fraction used in the eight scenarios described above (sample/herd size: 40/50 *vs* 70/100 in small, 70/400 *vs* 70/1,000 in large groups). Moreover, the minimum sample size required for effective clinical detection was of interest for logistic reasons, and prudent and efficient use of personnel and financial resources.

Since much lower dissemination rates were proposed recently by researchers (Orsel et al 2007ab) than those considered in this study, these new findings were evaluated in hindsight, to consider them for future incursion events. Thus, the effect of Ro on clinical detection was simulated in flocks of 1,000 sheep, and a sample of 70 sheep inspected clinically (all other parameters as before).

Reported incubation periods from two infection experiments under different conditions turned out to be remarkably similar to each other (Hughes et al 2002; Orsel et al 2007b). Therefore, average incubation periods of 2 and 4 days were evaluated, which were in reported ranges. Other evaluated parameters were the latent period and the sensitivity of clinical detection.

Results

Figure 1 shows model outputs (flock-level confidence of detection, TP, AP, and clinical prevalence) for a scenario using Ro=6, a flock size of 1,000, a random sample of 70 sheep, 73% probability of sheep developing clinically detectable symptoms, and a detection sensitivity of 80%. Table 2 summarises these findings, which are explained below in more detail for cattle and sheep.

Table 2. Time after release of the foot-and-mouth disease virus until clinical symptoms were detected with 95% confidence ('clinical detection'), and duration of detection: median of 100 stochastic model runs (numbers in brackets = 90% credible intervals).

Species	Ro	Herd or flock size /sample size	Herd or flock size /sample size
Cattle		50/40	400/70
Post-release interval to first clinical detection (days)			
	6	8.7 (5.0–14.4)	12.6 (8.9–19.3)
	12	6.6 (4.0–11.6)	8.7 (6.5–14.3)
Duration of clinical detection (days)			
	6	14.5 (11.9–17.9)	17.3 (15.4–19.3)
	12	11.0 (8.9–13.4)	12.9 (11.8–14.1)
Outbreak probability[a]			
	6	0.83	0.91
	12	0.92	0.96
Sheep		100/70	1,000/70
Post-release interval to first clinical detection (days)			
	6	9.2 (6.4–17.2)	13.2 (10.0–19.8)
	12	6.7 (4.4–10.1)	9.6 (7.4–13.8)
Duration of clinical detection (days)			
	6	12.2 (10.6–14.8)	12.5 (11.9–13.2)
	12	9.8 (8.3–11.1)	9.9 (9.3–10.4)
Outbreak probability[a]			
	6	0.91	0.83
	12	0.91	0.91

[a] Defined as the number of stochastic model runs that resulted in a noticeable secondary wave of infected animals during a 100-day period post- release of the virus
Ro = basic dissemination rate

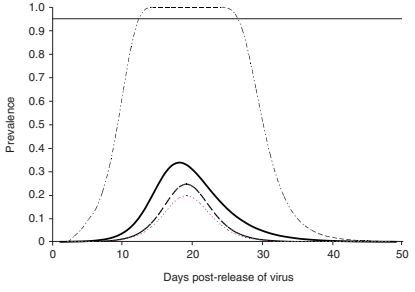


Figure 1. Model outputs for a scenario of a flock of 1,000 sheep, after release of foot-and-mouth-disease virus, comprising a sample size of 70 sheep selected randomly. Prevalence of sheep with detected clinical symptoms at 80% sensitivity (···), prevalence of sheep with clinical symptoms in 73% of infected sheep (– –), prevalence of infection (——), and confidence of detecting at least one sheep with clinical symptoms in the sample (– · – · –). The horizontal line depicts the minimum confidence for detection of 95%.

Cattle

The suggested sample sizes of 40 for small herds and 70 for large herds were sufficient to achieve the desired 95% confidence level for the detection of FMD by clinical inspection for both assumed dissemination rates (Ro=6 and 12). Ability to clinically detect disease in large herds was 2–5 days later than in small herds. Across ranges of herd size (50 and 400) and dissemination rates (Ro=6 or 12), detection became feasible about 7–13 days after the release of the virus, and the 90% stochastic range was 4–19 days.

The duration of detection lasted for a median of about 11–15 (90% stochastic range 9–18) days in small herds/small samples, and 13–17 (90% stochastic range 12–19) days in larger herds/large samples. However, the stochastic model showed that the duration could be as short as 2 days. The duration was 3.5–4.4 days shorter when the dissemination rate, Ro, was doubled. Ro explained 18%, and sample size 44%, of the variability in duration. A larger sample size (70 *vs* 40) increased the duration of clinical detection by 1.9–2.8 days.

Not every release of virus resulted in an outbreak. The stochastic model indicated that the probability that one infected animal would result in an outbreak was 83–96%, thus there was early fade-out or no transmission in 4–17% of the simulations. In summary, the models supported a strategy of starting clinical surveillance in cattle 4–5 days after the supposed release of the virus and continuing for 35 days (19 days for a late start + 16 days average duration of detecting a slow-spreading virus), to cover the entire period of high-detection probability.

Despite a longer shedding period in cattle than in sheep, clinical examination based on signs such as elevated body temperature, which would only be present for about 24 h, resulted in herd sensitivity being too low for reliable detection. Sampling 70 cattle resulted in too few animals with an increase in temperature, which would be present at any given time in herds of 50–400 cattle. Under such circumstances, reliable detection was possible using a 2-fold increase in sample size and inspection at least twice a week.

Sheep

Trends seen in cattle generally held for sheep, i.e. larger flocks took more time until first becoming clinically detectable and had higher dissemination rates reducing this interval. Clinical signs were detectible 2.9–4.0 days later in large flocks than in small

flocks, and a higher dissemination rate reduced the time until detection by 2.5–3.6 days.

However, due to shorter shedding periods, a lower proportion of animals developing clinical signs, and a lower sensitivity for detecting them, the sheep model indicated that the duration of clinical detection was 2–5 days shorter in sheep than in cattle, especially in large flocks. Ro explained 28% of the variability in duration of detection whereas flock size was unrelated to duration.

The data suggested that surveillance should start at the earliest 4 days after the supposed release of the virus and be continued at the most for 32 days (20 days until start +12 days average duration of detecting a slow-spreading virus). As in cattle, the flock sensitivity for the detection of a 24-h elevated body temperature was below the threshold of 95%, and only with a high dissemination rate was detection possible for 3 days, using body temperature as the leading clinical sign. This suggests that to be an effective indicator of disease, body temperature would have to be measured from 70 sheep selected randomly at least twice a week, starting in the second week after the release of the virus. Increasing the sample size had little effect on flock sensitivity based on body temperature.

Figure 2 illustrates the stochastic dispersion of flock sensitivity, and Figure 3 shows the cumulative distribution of the output of the stochastic model (100 model runs). The figures reveal that small flocks would be detected earlier due to a 10-fold higher sampling fraction, but that the duration of detection was much more variable and shorter in small than in large flocks. Thus, achieving the same confidence of detecting disease in small flocks was more difficult than in large flocks despite the same absolute sample size. A higher dissemination rate increased the speed of the intra-herd epidemic, and thus reduced the area under the detection curve, with the effect of achieving a higher confidence for clinical detection, albeit for a shorter duration.

Sensitivity analysis

The result of the sensitivity analysis (Figure 4) showed that whereas a sample of n≥20 was required for cattle it needed to be larger for sheep flocks (n≥30) to provide an adequate duration of detection. It was clear that the period during which the disease would be clinically detectable in a flock of sheep was considerably shorter. Varying the size of the flock while holding the sample constant hardly affected the confidence of clinical detection, thus it was the larger absolute sample size and not the proportion sampled from the herd/flock that compensated for the greater difficulty of detection in sheep in the selected scenarios.

Detection with a very low dissemination rate (Ro=2) was feasible only for an extremely short period, but for all higher dissemination rates a sample of 70 sheep per flock provided sufficient confidence of detection of disease at the flock level (Figure 5). A slight increase of the sample size from 70 to 80 achieved 95% confidence for clinical detection over a reasonable period of time at a low Ro of 2.

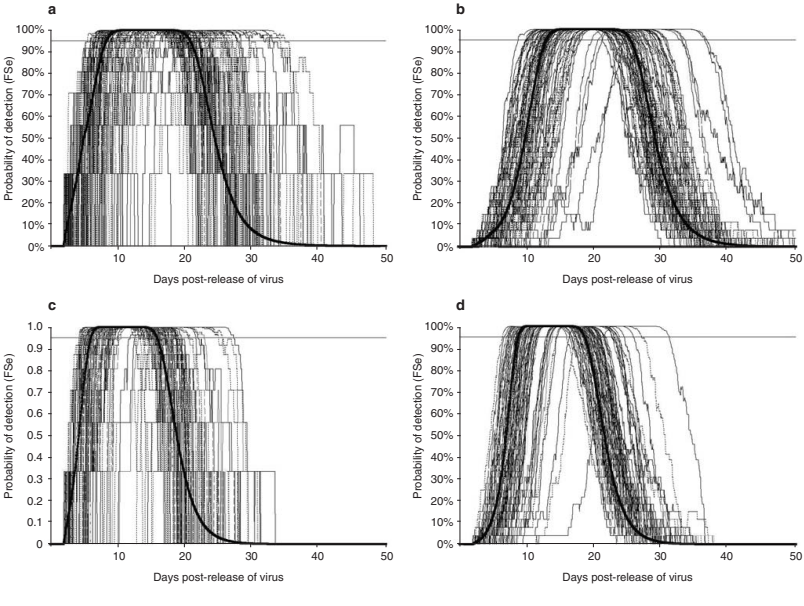


Figure 2. Flock sensitivity (FSe) in sheep after release of foot-and-mouth-disease. Distribution of 100 stochastic model runs for four scenarios, namely (a) flock size (FS)=100, basic dissemination rate (Ro)=6, sample size (n)=70; (b) FS=1,000, Ro=6, n=70; (c) FS=100, Ro=12, n=70; and (d) FS=1,000, Ro=12, n=70 (bold line = deterministic model; horizontal line = minimum probability detection required).

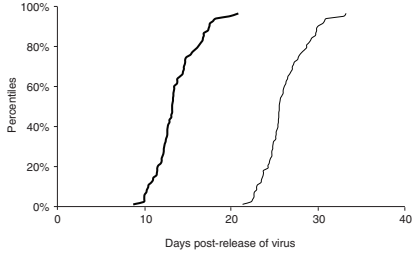


Figure 3. Cumulative distribution of the start (left) and end (right) of clinical detection of foot-and-mouth disease at the flock level in sheep, with 95% confidence (83/100 stochastic model runs with outbreaks; basic dissemination rate Ro=6, n=70, flock size=1,000).

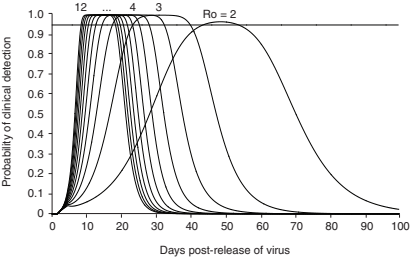


Figure 5. Effect of the basic dissemination rate (Ro) of 2 to 12 on clinical detection of foot-and-mouth-disease in diseased sheep flocks (flock size=1,000; n=70; curves shifting left with increasing Ro; horizontal line = surveillance target).

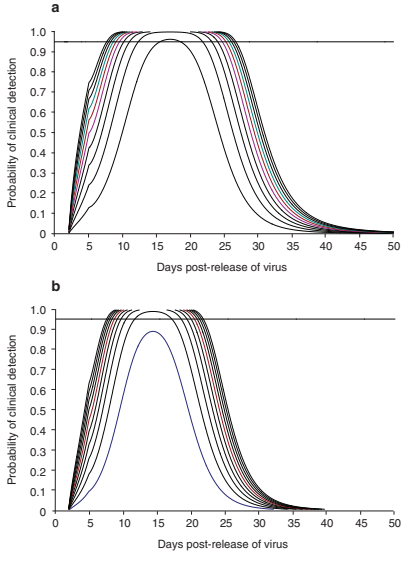


Figure 4: Effect of sample size on the probability of clinical detection of foot-and-mouth-disease by days after the release of the virus for (a) cattle, and (b) sheep; samples in steps of 10 from 10 to 100 in a group of 100 cattle/sheep (smallest curve at n=10; largest curve at n=100; horizontal line = targeted minimum for clinical detection).

The model suggested that short incubation periods of 2 *vs* 4 days, combined with a high dissemination rate (Ro=12), had almost no effect on the confidence of clinical detection. Effects from variability of latent periods appeared to be relatively small. Latent periods >2 days slowed the epidemic down and increased the time to the start and the duration of clinical detection, but did not reduce the confidence of detection.

Clinical detection depended on the accuracy (sensitivity) of clinical detection. The assumed 80% sensitivity of clinical detection in individual sheep provided sufficient flock-level confidence of detection. In fact, a minimum sensitivity of 30% was required in the slow-spread scenario for sheep (Ro=6, n=70, 4 days' incubation, 27% without clinical signs) to achieve acceptable detection at the flock level.

Discussion

We evaluated the timing and duration of clinical surveillance as part of the process for development of prudent guidelines for surveillance in the face of a deliberate or incidental FMD incursion. An initial presumption was that a possible single index case would most likely not be detected, but that surveillance would target the first wave of secondary cases in any infected herd. State transition modelling was used for simultaneous consideration of the most important epidemiological parameters. The resulting epidemic curve of the prevalence of clinical signs during the critical post-release period of the virus was the basis for calculating the confidence of detection of disease at the herd and flock level.

The most significant outcome of this exercise was that the guidelines initially used for surveillance needed to be revised and become more targeted. Consequently, the confidence in negative findings from the field increased. In this context, modelling was the basis for risk-based surveillance in the incursion incident described. We believe the approach has wide application. The most recent example is an FMD incursion in the UK in early August 2007, for which a point source was hypothesised and surveillance was initiated to investigate freedom from FMD within a surveillance zone. The approach presented here may assist the design of such response activities.

State transition models have previously been used and applied to FMD situations, both at individual animal (Woolhouse et al 1996; Tsutsui et al 2003) and herd (Haydon et al 1997) levels. Whereas deterministic modelling is useful for evaluating the relative merits of various components such as detection sensitivity, dissemination rate, or sample size, they lack the ability to give an accurate account of start and finish dates for surveillance teams in the field in the event that good prior information about the day of the incursion is available. Insights into the variability of the assumed parameters and of chance events, such as whether or not infection will take place during a time interval, was more re-

alistically approached using the stochastic process, that effectively allowed inter-event time to vary. As would be expected in real life, this resulted in various proportions of no-outbreak or fade-out runs, and by moderate differences in the outcome between median stochastic and average deterministic models. Moreover, the stochastic outcome was not symmetrically distributed around the deterministic result. A few stochastic runs revealed outbreaks that occurred with a much longer delay than the majority of runs, thus simulating situations where the index case did not have a sufficient contact until about 8–10 days after the release of the virus (Figure 2).

Our mathematical approach was different from the stochastic method used by Tsutsui et al (2003), which was based on an @Risk (C Palisade Corporation, Ithaca NY, USA 14850, http://www.palisade.com) spreadsheet, where stochasticity was approximated by random draws from continuous distributions of parameters. Our method used random draws from a Poisson distribution of inter-event time independently for each transition, and a short time period that allowed only one animal to change state for each transition. On the other hand, the stochastic process we used held parameters constant (Ro, α, and γ; β depending on herd/flock size; proportion of animals developing clinical signs; animal-level sensitivity). In the absence of information on parameter variability, we decided to use sensitivity analysis to examine the impact of parameter changes on model outcomes. These were therefore evaluated in the sensitivity analysis, as recommended by Christensen and Gardner (2000).

The chance of detecting disease by active clinical surveillance in small (cattle) herds was relatively low, even if almost the entire herd was inspected. This was simply a matter of too few animals with clinical symptoms. Depending on prevalence, a maximum of 12 animals with clinical symptoms would be present in a sample of 40.

The critical prevalence for detection was 5%. Considering the scatter of days when animals were in a clinical state, including days when there were no animals with lesions despite ongoing infection, in theory at least three clinically affected animals were required to be present at any point in time to detect disease in a herd of 50 cattle for inspection to be sufficiently accurate. Due to biological variation and chance, this critical number of three clinical cases may often not be reached. Therefore, when herds are small, and much more so at low contact rates (as is often the case on pasture), or when Ro is low (e.g. low-pathogenicity virus strains), surveillance can fail to detect infected herds, despite signs in cattle being easy to detect. This could be compensated by repeated inspection of the same herd. However, the confidence of clinical detection in small herds may have been underestimated by the model because the formula for herd sensitivity (Martin et al 1992) is not continuity-corrected. The approach by Cameron and Baldock (1998), who derived an exact but complex, iterative probability estimation to be used for small populations, would be more appropriate, but it was difficult to incorporate into the model and would have required extreme processing time because the process would have to be repeated at each time step.

The estimated confidence of detection may in reality be higher because people handling animals, especially when alerted about the possibility of an imminent outbreak, would be expected to report symptoms and thereby increase the chance of detection. For example, McClaws et al (2006) found that clinical cases were more likely to be laboratory-positive if they were reported by farmers (especially dairy farmers) *vs* active surveillance. We ignored this additional pathway to detection because the interest was in the worst case scenario, and it would have been hard to quantify the probability of farmer-detection.

The speed of the spread of disease, which was a function of Ro, and period of shedding in the model, is considered to be much greater in cattle than in small ruminants (Hughes et al 2002). In New Zealand, however, clinical detection in sheep is not limited by sample size because sheep flocks are much larger than cattle herds. Detection will, theoretically therefore, not be as difficult as in cattle, except for a relatively low number of small flocks.

It is doubtful that ≥80% sensitivity of clinical inspection can be realised under field conditions in individual animals because only one to three small lesions, if any, can be expected in sheep (Hughes et al 2002). Since a sensitivity of <30% often led to failure of detection in a flock, clear instructions are required for the clinical examination of individual animals. Immobilisation, cleaning of hooves, and close inspection are probably mandatory if 80% is to be achieved. Such an approach would require animals to be crowded for flock inspection, and thus dramatically increase contact rates, and impose stress, and consequently accelerate transmission. For the purpose of surveillance, increased transmission induced by crowding would benefit recognition of disease (and thus a higher confidence in negative flock inspections), but inspected flocks would have to be reinspected after an incubation period of 4–5 days at least once to determine whether crowding had triggered a dormant infection. Again, this supports repeated inspection of the same herd/flock about twice a week.

An increase in the dissemination rate (Ro) beyond the chosen value of 12 had surprisingly little effect on detection of disease at the herd level because large, easy-to-detect outbreaks would occur when Ro>12. Whether or not extreme values of Ro>70, as suggested by Woolhouse et al (1996), are realistic, they did not much affect the accuracy of detection. Conversely, low dissemination rates of 2 or lower (Orsel et al 2007ab) delayed the time until reaching the 95% confidence level of detection to about 44 days after the suspected release of the virus, and detection lasted for 10 days. To achieve sufficient confidence of detection, a slightly larger sample (n=100) and an extended surveillance period would be required, combined with campaigns to increase farmer awareness for intensive observations of their flocks, and self-reporting.

The stochastic model predicted that 4–17% herds/flocks would not experience an outbreak even if one infected index case was present. Considering the fact that the oral route of infection is hard to establish (Sanson 1994; Alexandersen et al 2003), the chance of producing an index case was probably quite low. However, the enormous economic consequences of an introduction into New Zealand would justify any cost and intensity for surveillance, especially as the immediate population at risk on Waiheke Island was small.

At the onset of surveillance, apparently ill animals were targeted for clinical inspection. This may help to identify FMD-infected animals and increase the chance of detection. However, such an approach may bias away from animals with FMD because animals with clinical disease other than FMD may be less exposed to contact with others than healthy animals. Their lower contact rates would make them less likely to become infected in the presence of shedders. Moreover, it was recommended to measure

the body temperature of those animals that were apparently ill. However, the model suggested that body temperature may not lead to detection at the group level because the probability and the period of increased body temperature are relatively small (Hughes et al 2002; Orsel et al 2007a). We assumed a 2-day latent period for the index case. This may not be appropriate, especially for the oral route of infection. The period until detection shown in Table 2 may therefore have to be increased by 1–2 days.

In conclusion, stochastic SLIR modelling was a useful tool to assist ongoing surveillance activities in the face of a suspected deliberate incursion in real time. Contrary to initial expectations, it suggested that only secondary cases could be detected by clinical surveillance, and that measuring body temperature alone was not a reliable tool to detect FMD infection in cattle herds and sheep flocks ranging from 50–400 and 100–1,000 heads, respectively. Infection was less likely to be detected in small herds <40 cattle than in larger herds, but this could be compensated by repeated inspection of the same herd/flock about twice a week. Stochastic modelling indicated that situations could occur wherein infection was not apparent until about 3 weeks after the release of the virus, although it may already have passed through other herds or flocks by that time. Based on the variability of stochastic outputs, clinical inspection activities are best started at 4 days and continued for about 35 days after the date of first exposure, to achieve at least 95% confidence of clinical detection of FMD in herds and flocks.

Acknowledgements

The continued support of the head of the incursion response team, Matthew Stone, and his colleagues, throughout the development of the surveillance strategy is highly appreciated. The study also greatly benefitted from the specialist knowledge of Reinhold Kittelberger and Rick Clough on technicalities and accuracy of antibody and antigen follow-up tests which were vital to achieve 100% specificity for the follow-up examination of animals and herds/flocks suspected to be infected with FMD virus.

References

Alexandersen S, Zhang Z, Donaldson AI, Garland AJM. The pathogenesis and diagnosis of foot-and-mouth disease. *Journal of Comparative Pathology* 129, 1–36, 2003

Anonymous. Foot-and-mouth disease. *Terrestrial Animal Health Code*. 14th Edtn. Office International des Épizooties Standards Commission. Paris, France, 2005

Begon M, Bennett M, Bowers RG, French NP, Hazel SM, Turner J. A clarification of transmission terms in host-microparasite models: numbers, densities and areas. *Epidemiology and Infection* 129, 147–53, 2002

Cameron AR, Baldock FC. A new probability formula for surveys to substantiate freedom from disease. *Preventive Veterinary Medicine* 34, 1–17, 1998

Christensen J, Gardner IA. Herd-level interpretation of test results for epidemiologic studies of animal diseases. *Preventive Veterinary Medicine* 45, 83–106, 2000

De Diego M, Brocchi E, Mackay D, De Simmone F. The non-structural polyprotein 3ABC of foot-and-mouth disease virus as a diagnostic antigen in ELISA to differentiate infected from vaccinated cattle. *Archives of Virology* 142, 2021–33, 1997

Donaldson A. *The Role of Sheep in the Epidemiology of Foot-and-Mouth Disease and Proposals for Control and Eradication in Animal Populations with a High Density of Sheep*. European Commission for the Control of Foot-and-Mouth Disease of the Food and Agriculture Organization of the United Nations, 5–8 September 2000, Borovets, Bulgaria. Pp 107–16, 2000

Haydon DT, Woolhouse MEJ, Kitching RP. An analysis of foot-and-mouth-disease epidemics in the UK. *IMA Journal of Mathematics Applied in Medicine and Biology* 14, 1–9, 1997

Hughes GJ, Mioulet V, Kitching RP, Woolhouse MEJ, Alexandersen S, Donaldson AI. Foot-and-mouth disease virus infection of sheep: implications for diagnosis and control. *Veterinary Record* 150, 724–7, 2002

Martin SW, Shoukri M, Thorburn MA. Evaluating the health status of herds based on tests applied to individuals. *Preventive Veterinary Medicine* 14, 33–43, 1992

McClaws M, Ribble C, Martin W, Stephen C. Factors associated with the clinical diagnosis of foot-and-mouth disease during the 2001 epidemic in the UK. *Preventive Veterinary Medicine* 77, 65–81, 2006

Orsel K, de Jong MCM, Bouma A, Stegeman JA, Dekker A. The effect of vaccination on foot-and-mouth disease virus transmission among dairy cows. *Vaccine* 25, 327–35, 2007 a

Orsel K, Dekker A, Bouma A, Stegeman JA, de Jong MCM. Quantification of foot-and-mouth disease virus excretion and transmission within groups of lambs with and without vaccination. *Vaccine* 25, 2673–9, 2007 b

Reid S, Grierson S, Ferris N, Hutchings G, Alexandersen S. Evaluation of automated RT-PCR to accelerate the laboratory diagnosis of foot-and-mouth disease virus. *Journal of Virological Methods* 107, 129–39, 2003

Sanson RL. The epidemiology of foot-and-mouth disease: implications for New Zealand. *New Zealand Veterinary Journal* 42, 41–53, 1994

Tsutsui T, Minami N, Koiwai M, Hamaoka T, Yamane I, Shimura K. A stochastic-modeling evaluation of the foot-and-mouth-disease survey conducted after the outbreak in Miyazaki, Japan in 2000. *Preventive Veterinary Medicine* 61, 45–58, 2003

Woolhouse ME, Haydon DT, Pearson A, Kitching RP. Failure of vaccination to prevent outbreaks of foot-and-mouth disease. *Epidemiology of Infection* 116, 363–71, 1996

Submitted 04 September 2007

Accepted for publication 24 October 2007

Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001

R. S. MORRIS, J. W. WILESMITH, M. W. STERN, R. L. SANSON, M. A. STEVENSON

A spatial simulation model of foot-and-mouth disease was used in March and early April 2001 to evaluate alternative control policies for the 2001 epidemic in Great Britain. Control policies were those in operation from March 20, 2001, and comprised a ban on all animal movements from February 23, 2001, and a stamping-out policy. Each simulation commenced with the known population of infected farms on April 10, 2001, and ran for 200 days. For the control policy which best approximated that actually implemented from late March, the model predicted an epidemic of approximately 1800 to 1900 affected farms, and estimated that the epidemic would be eradicated between July and October 2001, with a low probability of continuing beyond October 2001. This policy included the slaughter-out of infected farms within 24 hours, slaughter of about 1·3 of the surrounding farms per infected farm within a further 48 hours, and minimal interfarm movements of susceptible animals. Delays in the slaughter of animals on infected farms beyond 24 hours after diagnosis slightly increased the epidemic size, and failure to achieve pre-emptive slaughter on an adequate number of at-risk farms substantially increased the expected size of the epidemic. Vaccination of up to three of the most outbreak-dense areas carried out in conjunction with the adopted control policy reduced the predicted size of the epidemic by less than 100 farms. Vaccination of buffer zones (designed to apply available vaccine and manpower as effectively as possible) carried out in place of the adopted control policy allowed the disease to spread out of control, producing an epidemic involving over 6000 farms by October 2001, with no prospect of immediate eradication.

Veterinary Record (2001) **149,** 137-144

R. S. Morris, MVSc, PhD, FAmerCE, FACVSc, FRSNZ, **M. W. Stern, M. A. Stevenson,** MVSc, MACVSc, EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11-222 Palmerston North, New Zealand
J. W. Wilesmith, BVSc, MRCVS, HonMFPHM, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, University of London, Keppel Street, London WC1E 7HT
R. L. Sanson, BVSc, PhD, MACVSc, AgriQuality New Zealand, PO Box 1654 Palmerston North, New Zealand

Professor Wilesmith is also at Epidemiology Department, Veterinary Laboratories Agency – Weybridge, New Haw, Addlestone, Surrey KT15 3NB

THE British foot-and-mouth disease (FMD) epidemic which commenced with a confirmed outbreak on February 20, 2001, has devastated the British livestock industries, and it will take several years for full recovery to occur. Reports of the evolution of the epidemic have been provided on the Ministry of Agriculture, Fisheries and Food (now the Department for Environment, Food and Rural Affairs) website (MAFF 2001) and in *The Veterinary Record* (see, for example, Anon 2001a). The epidemic was already well established and disseminated by the time it was diagnosed, and retrospective evaluation of the epidemiological data shows that at least 29 farms were infected but undiagnosed at the date of the initial confirmation. This was determined by including all farms with estimated dates of infection before this date and diagnosis dates after the date of diagnosis of the index case.

In managing such an epidemic and allocating resources appropriately, modelling can be a very useful tool since it can separately predict numbers of infected and confirmed farms, and can predict forward into the future the expected effect of alternative control strategies (Carpenter and Thieme 1980, Carpenter and Dilgard 1983, Habtemariam and others 1983, Barlow 1991, Beal 1993). This can provide decision makers with guidance on the likely scale and (for geographically structured models) the spatial pattern of the epidemic under different control scenarios. Analyses can also be rapidly re-run in response to new information, which may include revised parameter settings which make use of data from the emerging epidemic. Various recent modelling studies have examined aspects of FMD control (Howard and Donnelly 2000, Ferguson and others 2001, Kao 2001).

As part of the development of the EpiMAN information system for emergency disease control (Sanson 1993), a fully spatial national model of FMD termed 'InterSpread' was developed in the early 1990s (Sanson and others 1999). It has progressively been refined and generalised, and during its design and testing extensive use was made of the detailed epidemiological records of the 1967/68 epidemic of FMD in the UK, and of a detailed review of published papers and other sources of epidemiological evidence (Sanson 1993). The model has been used for FMD policy evaluation in Europe (Jalvingh and others 1995) and has subsequently been adapted to model classical swine fever and other contagious diseases (Vonk Noordegraaf and others 1997, Staerk and others 1998, Jalvingh and others 1999, Nielen and others 1999).

At the end of February 2001, InterSpread was populated with the available UK geographical and farm livestock enterprise information to enable it to realistically represent the British livestock population. Epidemiological data for all farms diagnosed as infected, which were being collated and stored in the EpiMAN database, were transferred to InterSpread for modelling studies. This database was maintained by the FMD Epidemiology Team at the headquarters of the State Veterinary Service, and will be described in more detail in a future publication These studies have been conducted as joint undertakings by Great Britain and New Zealand members of the team regularly since early March 2001, and are continuing. This paper describes analyses of alternative control strategies which were conducted in late March and early April 2001, at the time when policy decisions were being made on potential modifications to the control strategy in place at that time. The control policies evaluated were those of interest at March 20, 2001, but because a more comprehensive national farms database became available in early April, were then re-simulated using case reports to April 10, 2001. The results reported are for this second set of model runs.

MATERIALS AND METHODS

Model description

InterSpread (Sanson and others 1999) is a computer program which can be used to model a FMD epidemic using Monte Carlo simulation. This involves representing biological processes (including their inherent variability) by sampling on statistical distributions. As its base population InterSpread uses the spatial location of all farms and animal markets, in combination with other relevant data such as the coordinates of any control zones. It can use either the surveyed shape of farms if these are available – as it is in the AgriBase system in New Zealand (Sanson and Pearson 1997) – or the easting and

northing coordinates of a single identifying point on the farm (such as the centroid) if this is the best information available. This population of farms in a defined study area is then populated with counts of the number of pigs, cattle, sheep, goats and deer present at the start of a FMD epidemic, as best these can be estimated at the time. The model run can either be initiated from the index case in the outbreak, or it can use the recorded history of the sequence of specific farms already confirmed with the disease to a chosen date, which represents the start of the simulation period (Table 1). The model predicts the spatial and temporal spread of the FMD epidemic by identifying which of the population of farms at risk are likely to experience the disease for each day throughout the simulation period.

A synopsis of InterSpread's logic is as follows. The model provides separate representations of the epidemiological transmission processes and effects of control measures for each susceptible species, and represents the interactions among species which produce the characteristic behaviour of the disease. For each farm confirmed with FMD, the infection date (if known) is used to commence the simulation of transmission from that farm. Where the date of infection is not known, an estimated infection date is determined by subtracting a species-specific incubation period from the date on which clinical signs were first observed. Each farm is assumed to begin producing virus (and therefore becomes infectious to other farms) on or just before the date of appearance of clinical signs, depending on the species present. Between-farm spread of the virus occurs by one of four mechanisms:

TABLE 1: Epidemic history file details from the EpiMAN database, as used by InterSpread. This file contains a list of farms confirmed with foot-and-mouth disease (FMD) and those suspected of having FMD

Variable	Details
Farm identifier	Unique farm identifier
Date infected	Estimate of the date that the farm became infected
Source farm identifier	Unique identifier for the farm that was responsible for this farm's infection (if known)
Date of earliest clinical signs	Date that clinical signs first appeared on this farm
Date of diagnosis	Date that FMD was confirmed on this farm
Date slaughter completed	Date on which all susceptible animals on this farm were slaughtered
Stock numbers	Estimate of the number of sheep, cattle, pigs, goats and deer present on the farm when FMD was diagnosed

TABLE 2: Epidemiological parameters used by InterSpread

Item	Details
1	Probability look-up table to define the distribution of the number of days to onset of clinical signs
2 – 4	Probability look-up table to define the distribution of the number of days to diagnosis for sheep, cattle and pigs
5 – 7	Average number of high-, medium- and low-risk movements off farm per day
8 – 9	Average number of high- and medium- risk movements to saleyards off farm per day
10	Average number of extra farm contacts generated by each saleyard movement
11	Probability look-up table to define the distribution of the distance of movement from a source farm to a destination farm
12 – 14	Probability of infection occurring on a destination farm from a high-, medium- and low-risk movement
15	Table of probabilities that a neighbouring farm will be infected by an infected farm, given the number of days relative to onset of clinical signs and distance from the property
16	Local spread multiplier for item 15. Where local spread is the only transmission mechanism in operation, the probabilities in item 15 will be multiplied by this value
17 – 19	Pig, cattle and sheep multiplier for item 15. When the source farm has each of these species, the probabilities in item 15 will be multiplied by this value. If a farm has more than one species, the largest multiplier of these species will be used
20 – 23	Codes to determine the behaviour of airborne spread
24	Proportion of dairy farms with lactating dairy cattle
25	Maximum length of tanker routes, expressed in metres
26	Probability of farm being selected for particular tanker route
27 – 28	Mean and standard deviation of the number of farms on a dairy tanker route in the disease-free zone (that is, in the non-movement-controlled area)
29 – 30	Mean and standard deviation of the number of farms on a dairy tanker route inside the infected area
31	Number of days taken to slaughter the animals on an infected farm
32	Number of diagnosed farms that cause a resourcing problem
33	Number of days before the onset of clinical signs that foot-and-mouth disease virus appears in the milk
34 – 35	Number of days taken for immunity to be reached after vaccination for cattle and pigs
36 – 38	Hours taken to trace low-, medium- and high-risk movements
39	Days taken to identify an infected farm by back tracing
40	Number of dairy tanker pick ups per week
41 – 43	Probability that a farm manager forgets to report a low-, medium- and high-risk movement
44 – 45	Probability of a farm being infected from a medium- and low-risk dairy tanker contact
46	Code to indicate whether separate local and airborne spread are to be assumed, or the two combined
47	Number of days after the onset of clinical signs that disease transmission via medium- or low-risk movements from an infected farm will occur
48	Look-up table to define the distribution of the days from clinical signs to diagnosis during the period before the first case has been diagnosed
49	Proportion of local spread that continues to occur after a farm has been placed on surveillance
50	Code to indicate if all epidemiologically significant dates or only infection dates are to be used by InterSpread
51	Code to indicate if a separate look-up table to represent the delay to diagnosis before the finding of the first infected farm is to be used by InterSpread
52 – 54	Airborne susceptibility modifier for cattle, sheep and pigs. Whenever airborne spread is modelled, the probability of infecting a farm by airborne spread will be multiplied by this value if the respective species are present

TABLE 3: Control strategy procedural definitions used by InterSpread

Item	Details
1	Number of infected areas (disease zones within which blanket movement restrictions were implemented), their date of activation and the coordinates defining each infected area
2	Description of vaccination buffers used (number of buffers, their coordinates, species to be vaccinated)
3	Description of pre-emptive slaughter-by-risk control procedures to be implemented
4	Description of pre-emptive slaughter-by-area control procedures to be implemented
5	Description of within-infected area movement control strategies selected
6	Description of through-infected area movement control strategies selected
7	Description of off-surveillance farm movement control strategies selected
8	Description of off-vaccinated farm movement control strategies selected
9	Description of surveillance level control strategies selected
10	Description of surveillance length control strategies selected
11	Description of patrol zone controls selected
12	Code to indicate if flexible infected areas are used, and if used, their description
13	Description of the size and designated control function of radial control zones specified to be used
14	Description of pre-emptive slaughter strategy including: whether or not manpower is to be limited, which species are to be slaughtered, the number of animals able to be processed per day (if manpower is limited), and the number of days required to process the pre-emptive slaughter (if manpower is unlimited)
15	Description of vaccination strategy including: whether or not manpower is to be limited, which species are to be vaccinated, the number of animals able to be processed per day (if manpower is limited), and the number of days required to complete vaccination (if manpower is unlimited)
16	Description of movement control strategy including: number of days after initial diagnosis to activate movement control, number of days to maintain movement control, list of proportions of movements allowed within the specified zone by risk (low, medium and high), list of proportions of movements allowed out of the zone by risk (low, medium and high), list of proportions of movements allowed into the zone by risk (low, medium and high)
17	Description of surveillance strategy including: number of days after diagnosis to activate surveillance, number of days to maintain surveillance, proportion of farms in zone to put on surveillance, level of surveillance expressed as a risk rating (low, medium and high)
18	Description of vaccination strategy where implemented based on a specific criterion (if used) including: criteria for the initiation of vaccination (based on the total number of outbreaks, the interval between outbreaks, outbreaks ratio or epidemic day), whether or not manpower is unlimited, which species are to be vaccinated, the number of animals able to be processed per day (if manpower, as specified in item 15, is limited), and the number of days required to complete vaccination (if manpower, as specified in item 15, is unlimited)
19	Number of tracing delay modifiers defined, date that the tracing modifier is activated, value to multiply the modelled tracing delay for each risk category (low, medium and high)

(1) movement of animals as a result of sales to other farms or to markets; (2) local spread to nearby farms on fomites and personnel; (3) long-distance windborne spread if meteorological conditions are conducive to this pathway; and (4) spread from dairy tanker movements. Once FMD has been confirmed on a farm, infectivity continues until control measures have been completed, and varies according to the stage both of the disease process and implementation of control procedures. InterSpread uses a set of transmission parameters to govern how FMD spreads throughout the area of study (Sanson and others 1993, Sanson 1994, Sanson and Morris 1994), and a set of control options to define the details of the proposed control strategy to be investigated. Variables defined in each of these parameter sets are shown in Tables 2 and 3, respectively.

Simulation models use a random number generator to determine the outcome of each probability assessment, and the sequence of random numbers generated is determined by the 'seed' used to start the generator. In InterSpread each of the component processes is independently seeded, so the model is made to produce the same underlying epidemic

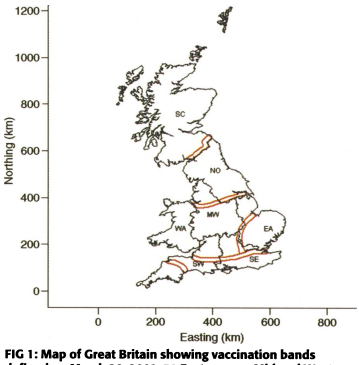


FIG 1: Map of Great Britain showing vaccination bands defined on March 20, 2001. EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

process, which is then influenced in its degree of manifestation by the control measures applied. Each replicate simulation for a particular strategy is seeded differently, so that an element of biological variability is built into the evaluation process.

Study population

The unit of interest in this study was every farm containing cattle, sheep, pigs, goats or deer recorded on the 2000 agricultural census conducted by MAFF in England and Wales (MAFF 2000) and the Scottish Executive Rural Affairs Department in Scotland (SERAD 2000). Census data for each farm included a unique identifier, the easting and northing coordinate of the centroid of the farm and the numbers of pigs, cattle, sheep, goats and deer present on the farm at the date of census (June 30, 2000). For farms in England and Wales, census data was collected for all farms employing at least one labour unit and a random sample of farms employing less than one labour unit. In Scotland, census data was collected for all farms. Because only the centroid of each farm was recorded, it was not possible to determine contiguity of farms, and inter-centroid distance was used as a proxy for close contact.

Control strategies evaluated

Details of FMD-affected farms confirmed up to April 10, 2001, were used to seed InterSpread and assess the effectiveness of a series of possible enhanced FMD control strategies, which operated within the model from March 20, 2001. The impact of the prior control strategy applied from initial diagnosis was represented in the initial information provided to the model. The model thus represented the official movement control policy, except that it did not consider the MAFF-licensed movements allowed for welfare reasons to represent a risk of transmission (MAFF 2001), and it allowed for the occurrence of a low level of potentially risky illegal movements.

In the first series of strategies, the effects of varying the speed of stamping-out, and the number of farms pre-emptively slaughtered around each farm diagnosed as infected were jointly assessed. InterSpread depopulated infected farms first, and then progressively slaughtered neighbouring farms to the scale specified. Pre-emptive slaughter was conducted radially from each infected farm to eliminate varying numbers of surrounding farms specified as level 1 (negligible elim-

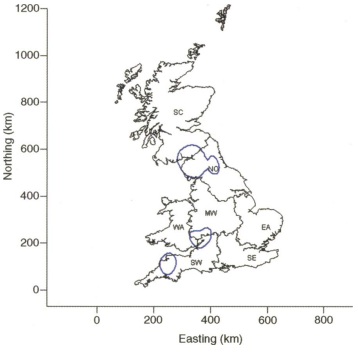


FIG 2: Map of Great Britain showing areas where, for the period April 1 to April 15, 2001, there were more than 50 newly confirmed FMD-affected farms per 100 km². These contours were used to define areas for implementation of cattle vaccination, as reported in Table 7. EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

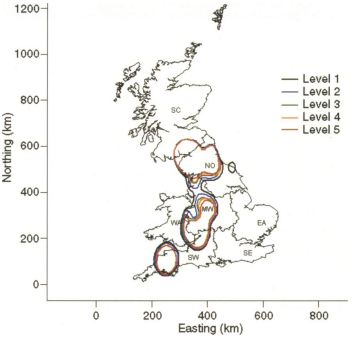


FIG 3: Map of Great Britain showing the spatial distribution of FMD-positive farms at June 30, 2001, predicted by the 24-hour slaughter of infected farms strategy shown in Table 4. Contour lines show areas where the density of FMD-positive farms was predicted to be greater than 50 per 100 km². EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

ination) to level 5 (substantial removal of herds). Because farm density varies between areas, ratios of pre-emptively slaughtered farms to infected farms actually achieved in model runs were calculated from model outputs for comparison with field data. All animals of all susceptible species were slaughtered on farms subject to the pre-emptive slaughter policy. In this series, depopulation of the infected holding occurred within 24 hours of confirmation and depopulation of farms within the pre-emptive slaughter list occurred within 72 hours of confirmation.

In the second series of strategies, the effect of increasing the time to slaughter of infected farms was assessed. Pre-emptive slaughter rules around infected farms were applied as before, but longer delays were built into the slaughter process, with depopulation of the infected holding occurring within 48 hours of confirmation and depopulation of pre-emptive slaughter farms occurring within 72 hours.

In the third series of strategies, the effect of vaccination alone as a control measure was assessed. The spatial distribution of FMD-affected farms confirmed up to March 20, 2001, provided the basis for defining a series of FMD vaccination 'bands' across the country, positioned to create a barrier between FMD-affected and FMD-unaffected areas, on a scale which was feasible to achieve (Fig 1). At the time there was public discussion of the merits of abandoning stamping out and using vaccination to control the disease, and this policy was defined to realistically assess how such a policy might be implemented and what its effects might be, given likely supplies of vaccine and manpower to vaccinate cattle. As vaccination of cattle was the policy under discussion, the model simulated the effects of vaccinating cattle in these defined areas starting from March 20, 2001, with 8000 head being processed within each specified area per day, continuing until the population of cattle in the area was fully vaccinated. No other species were vaccinated.

In the fourth series of strategies, the effectiveness of a combination of vaccination and slaughter was assessed. Areas of Great Britain where the incidence of FMD was greater than 50 farms per 100 km² for the period April 1 to April 15, 2001, were defined (Fig 2). There were three of these areas: the first in Cumbria, the second in Devon and the third in Gloucestershire. Vaccination of cattle was introduced in conjunction with pre-emptive slaughter of infected farms within 24 hours at the levels described in Table 4. Three variations of this strategy were assessed: the first where only the Cumbria high outbreak density zone was vaccinated, the second where the Cumbria and Devon high-density zones were vaccinated and the third where the Cumbria, Devon and Gloucestershire high-density zones were vaccinated. Vaccination of cattle was carried out in these defined areas starting from April 10, 2001, with 8000 head being processed within each area per day. Vaccination was assumed to fully protect farms against becoming infected from seven days after administration.

Each of the specified strategies was simulated for 200 days commencing from April 10, 2001, and five iterations of each variant were produced using five sets of random number seeds. The effectiveness of each strategy was assessed in terms of: (1) the total number of farms which became infected within 200 days; (2) the mean date of eradication (calculated for replicates where eradication was achieved within the 200-day modelling horizon); and (3) the proportion of iterations where eradication was achieved within 200 days.

RESULTS

Table 4 shows the mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for the 24-hour slaughter of infected farms strategy. The spatial distribution of FMD-positive farms at June 30, 2001, predicted by each of the variations of this strategy is shown in Fig 3.

TABLE 4: Mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for control strategies where pre-emptive slaughter zones were negligible (level 1) to substantial (level 5), and where depopulation of infected farms occurred within 24 hours of confirmation and depopulation of farms within the pre-emptive slaughter zone occurred within 72 hours of confirmation

Pre-emptive slaughter level	Mean (range) Farms affected	Eradication date	Eradication
1	3604 (2966–3974)	Oct 23 (Oct 22–Oct 25)	4 of 5
2	2343 (2124–2515)	Sept 18 (Sept 2–Oct 3)	3 of 5
3	1845 (1702–1973)	Aug 9 (Jul 14–Oct 1)	5 of 5
4	1768 (1682–1973)	July 18 (June 8–Aug 10)	4 of 5
5	1703 (1625–1896)	Aug 16 (June 8–Oct 19)	5 of 5

TABLE 5: Mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for control strategies where pre-emptive slaughter zones were negligible (level 1) to substantial (level 5), and where depopulation of infected farms occurred within 48 hours of confirmation and depopulation of farms within the pre-emptive slaughter zone occurred within 72 hours of confirmation

Pre-emptive slaughter level	Mean (range) Farms affected	Eradication date	Eradication
1	5568 (3958–7134)	–	0 of 5
2	2786 (2477–2997)	Sept 28 (Sept 12–Oct 26)	5 of 5
3	1995 (1775–2194)	Aug 24 (July 18–Oct 11)	5 of 5
4	1856 (1766–2010)	July 26 (June 20–Aug 21)	4 of 5
5	1769 (1622–1998)	July 29 (June 10–Sept 26)	5 of 5

Table 5 shows the mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for the 48-hour slaughter of infected farms strategy. The spatial distribution of FMD-positive farms at June 30, 2001, predicted by each of the variations of this strategy is shown in Fig 4, pooled and averaged over five replicates.

Table 6 shows the mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for the vaccination-only strategy. The spatial distribution of FMD-positive farms at June 30, 2001, predicted by this strategy is shown in Figure 5.

Table 7 shows the mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for the vaccination plus slaughter strategy. The spatial distribution of FMD-positive farms at June 30, 2001, predicted by the variations of this strategy is shown in Fig 6.

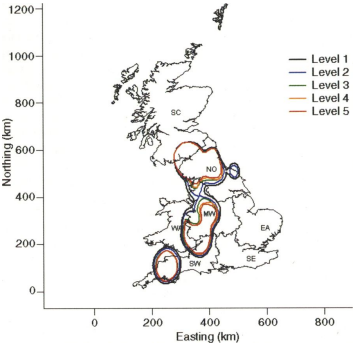


FIG 4: Map of Great Britain showing the spatial distribution of FMD-positive farms at June 30, 2001, predicted by the 48-hour slaughter of infected farms strategy shown in Table 5. Contour lines show areas where the density of FMD-positive farms was predicted to be greater than 50 per 100 km². EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

DISCUSSION

Specific roles of different modelling methods

Computer modelling can provide valuable assistance in making rapid and informed decisions about the relative merits of different control strategies in emergency disease control, provided that the model has been developed and tested, and is ready for immediate application. Although InterSpread had not been populated with British farm data before the FMD epidemic, prior experience of team members allowed the model to be populated within a week, and adjusted to handle special requirements such as the unusually prominent role of sheep movements in this epidemic (Anon 2001b).

An alternative approach is mathematical modelling, in which mathematical equations are formulated to represent the biological processes, and these are processed repeatedly through time to predict the behaviour of the epidemic under different control scenarios (Bailey 1975, Anderson and May 1979, 1991, Pech and Hone 1988). Typically, such models are deterministic – the outcome of any single analysis will always be the same, because the modelling approach does not have built-in consideration of variability. This approach has been used by other workers during this epidemic, and the results have been reported recently (Ferguson and others 2001). Such models can be very useful as a source of broad insights into the biological behaviour of diseases in populations. However,

TABLE 6: Mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved using vaccination alone, in the areas shown in Fig 1

	Mean (range) Farms affected	Eradication date	Eradication
Protective vaccination bands	6423 (4502–7960)	–	0 of 5

TABLE 7: Mean number of farms affected, the mean date of eradication and the number of iterations where eradication was achieved for control strategies where a combination of vaccination and pre-emptive slaughter at level 3 was adopted

Details	Mean (range) Farms affected	Eradication date	Eradication
Cumbria	1846 (1712–1931)	Aug 9 (July 14–Oct 1)	5 of 5
Cumbria, Devon	1853 (1720–1937)	Aug 9 (July 14–Oct 1)	5 of 5
Cumbria, Devon, Gloucestershire	1822 (1709–1910)	July 30 (June 25–Oct 1)	5 of 5

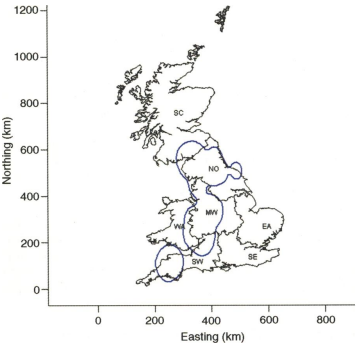


FIG 5: Map of Great Britain showing the spatial distribution of FMD-positive farms at June 30, 2001, predicted by the vaccination-only strategy shown in Table 6. Contour lines show areas where the density of FMD-positive farms was predicted to be greater than 50 per 100 km². EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

they are by their inherent nature simplified mathematical abstractions of biological reality, and, as such, suffer a range of limitations as tools for making policy decisions in the face of a disease which has complex biological interactions among the various species involved, and for which spatial relationships among farms strongly influence the probability of disease transmission between them. It is also important to consider for policy purposes the inherent biological variability in disease epidemics, and to provide decision makers with soundly derived ranges of expected outcomes, rather than single predictions which fail to recognise that an outcome which is favourable on average may have a probability of (say) 20 per cent of producing a very adverse result, which would lead to its exclusion from the feasible options.

A method which is widely used to overcome these limitations in standard mathematical modelling is Monte Carlo simulation modelling. In this approach, a representation of the biological processes involved is constructed, in which the outcome of events and decisions is in each case determined by sampling on probability distributions derived from epidemiological knowledge of the disease (Marsh 1986). Multiple runs are carried out to measure the expected variation in outcome arising from chance influences – just as in reality. Simulation models can also accurately represent the geography of the region being modelled (Saarenmaa 1988) and can incorporate data items from external data sources, such as true spatial coordinates of farms. Hence, they can predict the spatial evolution of the epidemic, as well as its temporal development – the former being much more challenging to achieve than the latter.

However, simulation models take considerably longer to develop than mathematical models, and cannot usually be developed in the face of an immediate need. It is possible to produce relatively generic models which are applicable to different diseases and different geographical regions and which can be rapidly applied to new situations in response to a disease emergency, as was done in this case with InterSpread. Simulation models are also more complex in design, and hence need more parameters than mathematical models. Obtaining adequate estimates of these parameters requires access to data (which, in this case, was obtained from the 1967/68 FMD epidemic in the UK plus a review of the literature). It may also be possible to produce very similar results with different sets of parameter values, because changes in one parameter may compensate for changes in another. Validation procedures and sensitivity analysis help to provide confidence in the robustness of a model, and comparison of model predictions with subsequent field experience will also be valuable.

Because models of the type exemplified by InterSpread are relatively stable in behaviour, five replicates were used to assess each control policy, in the interests of rapid processing. Larger numbers of runs would reduce confidence intervals on the means, and eliminate problems such as chance variation in the predictions which are not entirely consistent across control policies (Table 5). However, given the uncertainties in data and parameter estimates, comparison of different numbers of replicates led to the conclusion that five runs would give adequate estimates of variability, while allowing rapid processing.

Comparison of alternative control policies

The analyses support historical field experience in reinforcing the crucial value of the slaughter of all susceptible animals on affected farms as rapidly as possible after diagnosis, and especially the benefits of pre-emptive slaughter of high-risk farms before signs of disease can appear. FMD is exceptionally transmissible because of the large quantities of virus excreted and the fact that animals commonly become infectious before clinical signs appear (Sanson 1994). This massive

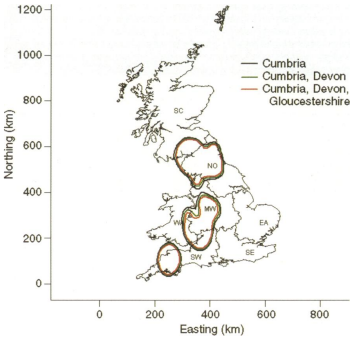


FIG 6: Map of Great Britain showing the spatial distribution of FMD-positive farms at June 30, 2001, predicted by the vaccination and slaughter strategies shown in Table 7. Contour lines show areas where the density of FMD-positive farms was predicted to be greater than 50 per 100 km². Contour lines for the three variations of this strategy overlap. EA Eastern, MW Mid and West, NO Northern, SC Scotland, SE South east, SW South west, WA Wales

virus production is compounded by the very low infective dose for susceptible species, the differences in key epidemiological features of the disease between the various species, the ease with which the virus can be transmitted on fomites and the capacity for long-distance windborne spread in bursts when appropriate meteorological conditions coincide with large-scale excretion of virus, especially by pigs.

A study of FMD outbreaks in unvaccinated European livestock populations between 1965 and 1982 by Lorenz (1986) showed that the median outbreak size was 29 farms, but the mean size was 1048 farms. Thus, most outbreaks of FMD in temperate climates can be controlled rapidly, but a small proportion of outbreaks occur under conditions which are exceptionally favourable for virus transmission, and in such cases massive epidemics ensue. The 2001 British epidemic was one such case, where lengthy delays in the reporting of the apparent source pig herd, combined with extensive movement of sheep from the area surrounding this farm through markets and on to a wide area of the country, produced the explosive epidemic form of the disease. The situation was made worse by the fact that these events took place in January and February when environmental conditions were most favourable for virus survival and transmission. This can be contrasted with the circumstances in tropical and subtropical countries in which FMD is endemic, where the disease typically smoulders continuously with occasional upsurges, rather than producing a 'wildfire' as it did in Britain.

By early March 2001, the scale of the outbreak had seriously outstripped available resources and the options of using vaccination either instead of or in conjunction with stamping out were being widely debated. The analyses described here were undertaken to help make decisions on the true merits of such policies.

If the goal is to eradicate the disease most rapidly and cost effectively and to restore normal domestic livestock trading and export capacity, then the provision of additional resources to allow intensification of the stamping-out policy was clearly the best solution identified by the modelling. This achieved eradication in the model in almost all cases if pre-emptive slaughter was used on a sufficient scale (at least 1·0 high-risk farm per infected farm), with a total epidemic size of around 1800 diagnosed infected farms. Eradication was predicted to be achieved between July and October, although one of 15 iterations of the model produced an epidemic which was not eradicated within the 200-day run time. The number of farms in the model is a mild under-representation

of the true number of farms because of limitations of the population-at-risk data which could be used. In addition, the use of data from the annual agricultural censuses, which are conducted in June of each year, results in an underestimate of the number of farms which would have had sheep temporarily agisted from home farms at the time of the ban on movements. This is because a proportion of these would not have had sheep present at the time of the census in June. Thus, all model predictions may be mild underestimates in relation to the true population at risk.

As only point data were available for farms rather than complete bounding polygons, the pre-emptive slaughter policy applied cannot be taken as strictly based on distance from an infected farm, but rather as a measure of increasing scale of pre-emptive slaughter from negligible (coded as level 1) to substantial (coded as level 5). A comparison of the ratio of pre-emptively slaughtered farms to infected farms in the model with the true ratio from field data is the best way to interpret the scale of pre-emptive slaughter. Field data to April 18, 2001, gave a ratio of between 1·0:1 and 1·3:1, depending on the definitions used of what is a true pre-emptively slaughtered farm based on distance from an infected farm (as against slaughter on suspicion, because of dangerous contacts and so on). Model runs gave ratios of 0·1 (level 1), 0·5 (level 2), 1·0 (level 3), 1·4 (level 4), and 2·3 (level 5). Thus, the policy followed in the field seems to approximate to a pre-emptive slaughter ratio of level 3 to 4, which implies that on average 1 to 1·4 farms were slaughtered pre-emptively for every diagnosed infected farm. Because many infected farms were in close proximity due to local spread, in numerous cases farms were slaughtered pre-emptively because of contiguity to a number of infected farms, so the ratio does not imply that high-risk farms were missed.

Allowing some infected farms to wait up to 48 hours between diagnosis and slaughter raised the total number of farms in the outbreak by about 5 per cent if pre-emptive slaughter was conducted on an adequate scale, but enlarged the scale of the epidemic substantially in the absence of effective pre-emptive slaughter. This represents the situation which developed early in the epidemic when resources were very limited, and demonstrates that this would have been a much larger epidemic had extra resources provided by the British Army and additional veterinarians not been applied to reduce the time from reporting to slaughter.

Considerable public discussion took place in March and April about the merits of switching to a vaccination policy, as the epidemic grew rapidly. It proved impossible to find a vaccination strategy which was achievable within an acceptable time period, and which would have favourably influenced the course of the epidemic to a worthwhile extent. Substituting vaccination for stamping-out in realistically achievable buffer zones resulted in a massive epidemic, with little prospect of achieving eradication in less than several years. Using vaccination in conjunction with stamping-out was predicted to reduce the size of the epidemic slightly, but the direct cost was high and the adverse trading consequences large. Thus, introduction of vaccination would have been a very high-risk strategy which was unlikely to have yielded a favourable result either in economic terms or in usefully reducing the scale or the duration of the epidemic. Additionally, it would have made it more difficult for Britain to prove freedom from the disease in the aftermath of the epidemic.

The results reported here predict a smaller and earlier-peaking epidemic than that predicted by Ferguson and others (2001) and subsequent field evidence has been compatible with the InterSpread predictions. The differences appear to be principally due to the lack of species specificity and full spatial representation in the model reported by Ferguson and others.

InterSpread was used by Jalvingh and others (1999) in a retrospective modelling study of the Dutch classical swine fever epidemic in 1997/98, and in that case produced an expected epidemic size of 381 farms and 95 per cent confidence intervals of 231 to 1787 farms, in comparison with the true epidemic size of 429 farms. That study found benefits for more rapid slaughter after diagnosis, enhanced destruction capacity and adequate scale of pre-emptive slaughter which were broadly similar to those reported here for FMD. While all of these principles are well recognised from past decades of experience with epidemic disease control, the difficulty in practice usually lies in gaining approval for marshalling the required resources before the need for them is clearly demonstrable – despite the fact that this is when they will provide the largest payoff. InterSpread has a potential role in aiding early recognition of the warning signs of an impending major epidemic. To do this, an appropriate information system needs to be in operation from day 1 of the epidemic, to provide data of sufficient accuracy and completeness to permit forward predictions to be undertaken with confidence from an early stage of the disease outbreak.

These studies were undertaken to assist in policy decisions during the period when the epidemic was rising to its peak. The model has subsequently been run daily to reassess progress and results of this later work will be reported at a future date.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance provided by the British Ministry of Agriculture, Fisheries and Food foot-and-mouth disease epidemiology team, and by personnel at the Massey University EpiCentre, New Zealand including Susanne Karsten and Helen Benard. They would also like to thank Professor M. E. Hugh-Jones, of Louisiana State University, USA, for providing the detailed epidemiological records of the 1967/68 FMD outbreaks in the UK. The authors are grateful for funding from the Department for Environment, Food and Rural Affairs (formerly MAFF) for this study.

References

ANON (2001a) Foot-and-mouth disease: waiting for the peak. *Veterinary Record* **148**, 322-324

ANON (2001b) Foot-and-mouth disease: two weeks and counting. *Veterinary Record* **148**, 286-288

ANDERSON, R. M. & MAY, R. M. (1979) Population biology of infectious diseases. Part I. *Nature* **280**, 361-367

ANDERSON, R. M. & MAY, R. M. (1991) Infectious Diseases of Humans: Dynamics and Control. Oxford, Oxford University Press

BAILEY, N. T. J. (1975) The Mathematical Theory of Infectious Diseases and its Applications. London, Charles Griffin

BARLOW, N. D. (1991) The role of modelling in policy and control decisions. Proceedings of a Symposium on Tuberculosis. Palmerston North, New Zealand, April, 1991. pp 251-265

BEAL, V. C. (1983) The use of mathematical models in animal disease program evaluation. Proceedings of the 87th Annual Meeting of the United States Animal Health Association. Las Vegas, Nevada, USA, October 16 to 21, 1983. pp 386-402

CARPENTER, T. E. & DILGARD, P. (1983) An application of computerized decision analysis in animal health economics. Proceedings of the 3rd International Symposium on Veterinary Epidemiology and Economics. Arlington, Virginia, USA, September 6 to 10, 1982. pp 408-414

CARPENTER, T. E. & THIEME, A. (1980) A simulation approach to measuring the economic effects of foot-and-mouth disease in beef and dairy cattle. Proceedings of the 2nd International Symposium on Veterinary Epidemiology and Economics. Canberra, Australia, May 7 to 11, 1979. pp 511–516

FERGUSON, N. M., DONNELLY, C. A. & ANDERSON, R. M. (2001) The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. *Science* **292**, 1155-1160
HABTEMARIAM, T., RUPPANNER, R., RIEMANN, H. P. & THEIS, J. H. (1983) Evaluation of trypanosomiasis control alternatives using an epidemiological simulation model. *Preventive Veterinary Medicine* **1**, 147-156
HOWARD, S. C. & DONNELLY, C. A. (2000) The importance of immediate destruction in epidemics of foot-and-mouth disease. *Research in Veterinary Science* **69**, 189-196
JALVINGH, A. W., NIELEN, M., MAURICE, H., STEGEMAN, A. J., ELBERS, A. R. W. & DIJKHUIZEN, A. A. (1999) Spatial and stochastic simulation to evaluate the impact of events and control measures on the 1997-1998 classical swine fever epidemic in The Netherlands. I. Description of simulation model. *Preventive Veterinary Medicine* **42**, 271-295
JALVINGH, A. W., NIELEN, M., MEUWISSEN, M. P. M., DIJKHUIZEN, A. A. & MORRIS, R. S. (1995) A computerised decision support system for contagious animal disease control. *Pig News and Information* **16**, 9N-12N
KAO, R. R. (2001) Landscape fragmentation and foot-and-mouth disease transmission. *Veterinary Record* **148**, 746-747
LORENZ, R. J. (1986) Economic evaluation of foot-and-mouth disease vaccination programme in the Federal Republic of Germany. Tubingen, Federal Research Centre for Virus Diseases in Animals
MAFF (2000) Agricultural Statistics – United Kingdom. London, The Stationery Office
MAFF (2001) Ministry of Agriculture, Fisheries and Food (MAFF) website: http://www.maff.gov.uk. Accessed April 2, 2001, and subsequently (now http://www.defra.gov.uk)
MARSH, W. E. (1986) Economic decision making on health and management in livestock herds: examining complex problems through computer simulation. PhD thesis, University of Minnesota
NIELEN, M., JALVINGH, A. W., MEUWISSEN, M. P. M., HORST, S. H. & DIJKHUIZEN, A. A. (1999) Spatial and stochastic simulation to evaluate the impact of events and control measures on the 1997-1998 classical swine fever epidemic in The Netherlands. II. Comparison of control strategies. *Preventive Veterinary Medicine* **42**, 297-317
PECH, R. P. & HONE, J. (1988) A model of the dynamics and control of an outbreak of foot-and-mouth disease in feral pigs in Australia. *Journal of Applied Ecology* **25**, 63-77
SAARENMAA, H. (1988) Model-based reasoning in ecology and natural resource management. Proceedings of the International Symposium on Advanced Technology in Natural Resource Management. Fort Collins, Colorado, USA, June 20 to 23, 1988. pp 141-158
SANSON, R. L. (1993) The Development of a Decision Support System for an Animal Disease Emergency. PhD thesis, Massey University
SANSON, R. L. (1994) The epidemiology of foot-and-mouth disease: implications for New Zealand. *New Zealand Veterinary Journal* **42**, 41-53
SANSON, R. L. & MORRIS, R. S. (1994) The use of survival analysis to investigate the probability of local spread of foot-and-mouth disease: an example study on the United Kingdom epidemic of 1967-1968. Proceedings of the 7th International Symposium on Veterinary Epidemiology and Economics. Nairobi, Kenya, August 15, 1994. pp 186-188
SANSON, R. L., MORRIS, R. S. & STERN, M. W. (1999) EpiMAN-FMD a decision support system for managing epidemics of vesicular disease. *Revue Scientifique et Technique – Office International des Epizooties* **18**, 593-605
SANSON, R. L. & PEARSON, A. (1997) AgriBase – a national spatial farm database. Proceedings of the 8th International Symposium on Veterinary Epidemiology and Economics. Paris, France, July 7 to 11, 1997. pp 12.16.1-12.16.3
SANSON, R. L., STRUTHERS, G., KING, P., WESTON, J. F. & MORRIS, R. S. (1993) The potential extent and transmission of foot-and-mouth disease: a study of the movement of animals and materials in Southland, New Zealand. *New Zealand Veterinary Journal* **41**, 21-28
SCOTTISH EXECUTIVE RURAL AFFAIRS DEPARTMENT (2000) Agricultural Statistics – Scotland. Edinburgh, Department of Agriculture, Environment and Fisheries
STAERK, K. D. C., MORRIS, R. S., BENARD, H. J. & STERN, M. W. (1998) EpiMAN-SF: a decision support system for managing swine fever epidemics. *Revue Scientifique et Technique – Office International des Epizooties* **17**, 682-690
VONK NOORDEGRAAF, A., BUITELS, J. A. A. M., DIJKHUIZEN, A. A., FRANKEN, P., STEGEMAN, J. A. & VERHOEFF, J. (1997) An epidemiological and economic simulation model to evaluate the spread and control of infectious bovine rhinotracheitis in dairy cattle. Proceedings of the 8th International Symposium on Veterinary Epidemiology and Economics. Paris, France, July 7 to 11, 1997. pp 13.09.1-13.09.3

Veterinary Record (2001) **149**, 144-147

Dissecting aneurysm of the carotid artery as a cause of respiratory distress in adult cattle

K. J. CHANDLER, D. C. BARRETT, H. THOMSON, P. E. MCNEIL, J. L. FITZPATRICK

A two-and-a-half-year-old Friesian cow and a five-year-old Charolais cow developed severe respiratory distress and palpable swellings to the left of the larynx as a result of a dissecting aneurysm of the common carotid artery. Neither cow responded to medical treatment. The underlying pathogenesis of the condition was uncertain, but direct trauma to the carotid artery was a possible contributory factor. Aneurysms of the common carotid artery should be considered when swelling occurs in the region of the larynx or when respiratory distress is due to laryngeal compression.

K. J. Chandler, BVMS, CertEP, MRCVS,
D. C. Barrett, BSc, BVSc, DBR, DCHP, MRCVS,
J. L. Fitzpatrick, BVMS, PhD, MRCVS, Department of Veterinary Clinical Studies,
H. Thomson, BVMS, PhD, MRCVS,
P. E. McNeil, BVMS, PhD, MRCVS,
Department of Veterinary Pathology, University of Glasgow Veterinary School, Bearsden Road, Bearsden, Glasgow G61 1QH

Mr Chandler's present address is Department of Veterinary Clinical Studies, Royal (Dick) School of Veterinary Studies, The University of Edinburgh Large Animal Practice, Easter Bush Veterinary Centre, Roslin, Midlothian EH25 9RG

AN aneurysm is a localised and permanent abnormal dilatation of a blood vessel (Robinson and Maxie 1993, Van Vleet and Ferrans 1995). In man, aneurysms occur most commonly as a result of atherosclerosis. They can be classified pathologically on the basis of either the composition of the wall of the aneurysm, that is, true or false, or their gross appearance, for example, saccular or fusiform, or the pathological mechanism which results in the formation of the aneurysm, for example, mycotic, dissecting or congenital (Titus and Kim 1990). A dissecting aneurysm is one in which blood enters the wall of an artery through a tear in the intima, dissects between the medial layers and creates a cavity within the arterial wall (Robinson and Maxie 1993, Jones and others 1997).

In domestic animals, the best known cause of aneurysms is the equine parasite *Strongylus vulgaris*, which commonly causes lesions in the cranial mesenteric artery (Urquhart and others 1996). Another parasite, *Onchocerca armillata,* causes lesions in the aorta of cattle in the Middle East, Africa and India, although not in the UK (Urquhart and others 1996). With the exception of these parasitic lesions, aneurysms are rare and usually restricted to individual cases in domestic animals.

In ruminants, the commonest aneurysm develops in the pulmonary artery as a consequence of thrombosis of the posterior vena cava in cattle (Breeze and others 1976). A single case of an aneurysm of the left internal iliac artery has been

Available online at www.sciencedirect.com
SCIENCE DIRECT
ELSEVIER
Preventive Veterinary Medicine 74 (2006) 212–225
PREVENTIVE VETERINARY MEDICINE
www.elsevier.com/locate/prevetmed

Simulation analyses to evaluate alternative control strategies for the 2002 foot-and-mouth disease outbreak in the Republic of Korea

H. Yoon [a], S.-H. Wee [a], M.A. Stevenson [b,*], B.D. O'Leary [b], R.S. Morris [b], I.-J. Hwang [a], C.-K. Park [a], M.W. Stern [b]

[a] *National Veterinary Research and Quarantine Service, Veterinary Epidemiology Division, 480 Anyang 6-dong, Anyang, Gyeonggi-do 430-824, Republic of Korea*
[b] *EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11-222, Palmerston North, New Zealand*

Received 15 December 2004; received in revised form 10 November 2005; accepted 2 December 2005

Abstract

Using the stochastic and spatial simulation model of between-farm spread of disease, InterSpread Plus, we evaluated the effect of alternative strategies for controlling the 2002 epidemic of foot-and-mouth disease (FMD) in the Republic of Korea. InterSpread Plus was parameterised to simulate epidemics of FMD in the population of farms containing susceptible animal species in the Korean counties of Yongin, Icheon, Pyongtaek, Anseong, Eumseong, Asan, Cheonan, and Jincheon. The starting point of our analyses was the simulation of a reference strategy, which approximated the real epidemic. The results of simulations of alternative epidemic-control strategies were compared with this reference strategy. Ring vaccination (when used with either limited or extended pre-emptive depopulation) reduced both the size and variability of the predicted number of infected farms. Reducing the time between disease incursion and commencement of controls had the greatest effect on reducing the predicted number of infected farms.

Keywords: Foot-and-mouth disease; Simulation models; Disease control; Evaluation; Republic of Korea

* Corresponding author. Tel.: +64 6 3505915; fax: +64 6 3505716.
E-mail address: m.stevenson@massey.ac.nz (M.A. Stevenson).

0167-5877/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.prevetmed.2005.12.002

1. Introduction

The Republic of Korea experienced an outbreak of the Type O_1 serotype (Pan-Asian topotype) of foot-and-mouth disease (FMD) during May and June of 2002. The index case was identified on 2 May 2002 in an 8302-sow piggery in Gyeonggi province, approximately 65 km south east of Seoul. By 23 June 2002 16 farms (15 piggeries and one dairy) had been confirmed with the disease and 162 farms had been pre-emptively depopulated as part of a stamping-out policy (without vaccination) that commenced on 3 May 2002. Although this outbreak was small compared with other recent outbreaks involving the Type O_1 serotype (for example, the 2001 British FMD epidemic where 2030 farm holdings were infected, Anderson, 2002) the post-epidemic phase is an opportune time to evaluate control policies, the procedures used, and their speed of implementation. This process firstly helps to identify which aspects of epidemic management could be improved in the event of future outbreaks and secondly identifies which aspects of management during the current outbreak were critical for rapid control and eradication of disease. To achieve these objectives, simulation modelling is a useful tool whereby alternative scenarios and control strategies can be simulated and predicted outcomes can be compared (Carpenter and Thieme, 1979; Carpenter and Dilgard, 1982; Habtemariam et al., 1983; Barlow, 1991; Beal, 1983; Bates et al., 2001). Stochastic simulation modelling offers further benefits in that repeated simulations of the same strategy allow the variability of predicted outcomes to be quantified (Taylor, 2003).

Our objective was to use a stochastic simulation model of between-farm spread of disease, InterSpread Plus, to replicate the temporal and spatial distribution of the 16 infected farms that comprised the 2002 outbreak of FMD in the Republic of Korea. This reference model was then modified to allow a series of alternative control strategies (such as those where the speed of commencement and extent of movement restrictions, extent of pre-emptive depopulation strategies, and vaccination usage) to be evaluated. The size and duration of predicted outbreaks under each of the alternative strategies were then compared with the reference model. Given that InterSpread Plus is a spatially referenced simulation model of disease spread (requiring explicit details about farm location, animal movement, incubation period and generation time) a secondary objective was to better define the approach that might be used to 'fit' model predictions to accumulated epidemic data, thereby producing a suitable reference model to be used as a starting point for further simulation work.

2. Materials and methods

2.1. Outbreak area and study population

The location of the outbreak area, relative to major Korean landmarks, is shown in Fig. 1. The outbreak area defined by the Korean Animal Hygiene Authority was in the counties of Anseong and Yongin covering an area of approximately 100 km × 100 km. The population of interest included the 3731 farms located within the boundaries of the outbreak area that contained any of the five FMD-susceptible domestic species (pigs,

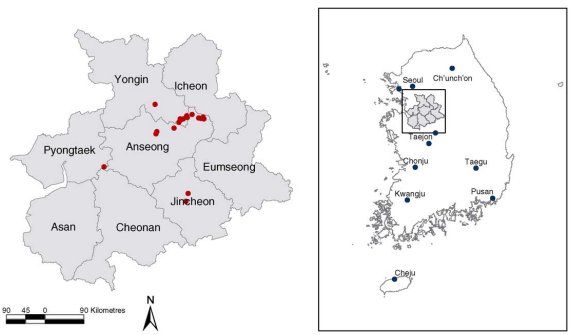


Fig. 1. Spatial and stochastic simulation of foot-and-mouth disease in the Republic of Korea, April–June 2002. Map of the eight counties included in the infected area. Centroids of the 16 infected farms are shown as points (#). Insert: map of the Republic of Korea showing major cities and the location of the infected area.

cattle, goats, deer, or sheep). Details for each farm in the outbreak area were obtained from regional government records that were collected on an ongoing basis for the purpose of administration. Farm-level details included a unique identifier, the name of the ri[1] in which the farm was located, and the number of adult domestic animal species present. Centroid locations for each ri allowed a series of Delaunay triangulations to be defined (de Berg et al., 2000) which were used to approximate the physical boundaries of each ri. A Geographic Information System was then used to randomly allocate each farm a location within the boundaries of its respective ri. On account of the approximations used to define farm location, we stress that the results presented in this paper are indicative of trend only and are unlikely to provide precise estimates of the direct losses associated with each of the alternative control strategies described.

Cases were those farms declared as FMD-infected under the Terrestrial Animal Health Code of the Office International des Épizooties (OIE, 2001). These were farms where the clinical signs of FMD were observed by a Korean Animal Hygiene Authority investigating officer or those farms where infection was confirmed by laboratory investigations made by the National Veterinary Research and Quarantine Service. Details of case farms were recorded at the time of diagnosis and included the farm identifier, easting and northing coordinates of the main farm building (measured using a global positioning device), the number of stock present of each of the five FMD-susceptible species, and the estimated date of infection (the date of examination minus the age, in days, of the oldest lesions identified minus an additional 5 days to represent an incubation period for the disease, after Gibbens and Wilesmith, 2002). Details of FMD case farms were merged with data obtained from the regional government records.

2.2. Model description

The simulations described in this study were conducted using a revised version of the InterSpread model of FMD (Sanson, 1993; Morris et al., 2001) InterSpread Plus, which we refer to as 'the model' in the remainder of this paper. Within the model—and in the absence of control measures—spread of disease among farms within an outbreak area depends on: (1) the frequency and distance of movement of animals, humans and fomites from farm to farm and market to farm (and in the reverse direction), (2) incubation period (defining the number of days from infection to onset of clinical signs) and virus production for each susceptible species, and (3) local-spread and airborne-spread probabilities. Once control measures are applied spread of disease is modified by: (1) surveillance (how quickly case farms are brought to the attention of authorities, if at all), (2) the nature and timing of pre-emptive depopulation strategies, and (3) the nature and timing of vaccination strategies (if used). Within the model the relative effectiveness of the application of each control measure can be varied over time and may, if required, be subject to resource constraints (for example, limitations on the number of farms processed per day and/or limitations on the number of animals processed by each activity per day).

Our first task was to define parameter settings such that, when simulation was initiated using the location details of the primary case (the first infected farm) an epidemic of similar

[1] The ri is the smallest administrative areal unit in South Korea, representing (on average) an area of 4 km^2.

size and temporal and spatial distribution to the observed epidemic was produced. In addition to replicating the details of infected farms, care was taken to ensure that the predicted number of depopulated farms was of the same order of magnitude to the number that were actually depopulated, as reported by the Korean Animal Hygiene Authority. This reference strategy, once defined, was then modified to reflect each of nine alternative control strategies that were of interest. The following section describes the approach used to derive parameter settings for the reference strategy.

2.3. Specification of the reference strategy

To fit the reference strategy three phases of the epidemic were defined: (1) the period between incursion and detection of the index case (from 22 April to 1 May 2002), (2) the 10 days following detection of the index case (from 2 May to 11 May 2002), and (3) beyond 10 days after detection of the index case (from 12 May 2002 to the end of the epidemic on 23 June 2002). Each phase of the epidemic was considered in turn and parameters applied so that the epidemic curve predicted by the model matched that observed.

For the first phase, spread of infection was considered to depend on the frequency and distance of movement among animal markets and farms, incubation period, and local- and airborne-spread probabilities. Given that this outbreak was due to the same serotype of FMD responsible for the 2001 epidemic in Great Britain we used incubation periods and local-spread parameters identical to those that were used for simulation analyses of the 2001 British FMD epidemic using InterSpread (Morris et al., 2001). Meteorological data for the area of investigation (mean daily wind direction and speed for the eight counties included in the outbreak area) were obtained from The Korean Meteorological Administration and used to parameterise airborne spread. With these influences regarded as known, our approach was then to adjust movement probabilities until the predicted epidemic for the first phase matched that which actually occurred. As a starting point, officers from the Regional Veterinary Service stationed in each of the affected counties were consulted regarding the likely number of off-farm movements that would occur in this population of farms each day and the likely range of distance over which each movement would occur. On the basis of this information we parameterised the number of movement events off farm per day as following a Poisson distribution with a mean of 0.25. In practical terms this specified the probability of making 0, 1, and 2 or more movements off farm per day at 47%, 36%, and 17%, respectively. A general distribution was used to parameterise movement distance ranges (Table 1).

For the second phase (the 10 days following detection of the index case) control measures were applied, in accordance with those specified by the Korean Animal Hygiene Authority. Restrictions were placed on animal movement in the outbreak area, surveillance for disease commenced, and pre-emptive depopulation initiated. The pre-emptive depopulation policy prescribed that all FMD-susceptible species within a 500-m radius and all FMD-susceptible species on swine enterprises within a 3000-m radius of infected farms were culled. Again, with these parameter settings regarded as known, adjustments were made to the movement and surveillance settings such that the simulated epidemic matched that which was observed. Korean Animal Hygiene Authority staffs involved in managing the epidemic were asked to rate the effectiveness of movement controls applied during the

Table 1
Input data and parameter values used as the reference strategy in a simulation of foot-and-mouth disease in the Republic of Korea, April–June 2002

Item	Details
Farm data	Easting and northing coordinates of farms in the outbreak area that contain at least one of the five FMD-susceptible species. Counts of cattle, pigs and other FMD-susceptible species on each farm in the outbreak area
Market data	Easting and northing coordinates of animal markets in the outbreak area
Epidemic history	Easting and northing coordinates and date of infection of the primary case farm
Zones—infected area	Easting and northing coordinates of the vertices of the polygon defining the boundaries of the outbreak area. Easting and northing coordinates of the vertices of the polygons defining the boundaries of Anseong, Yongin and Pyongtaek counties
Zones—radial	Defines four radial zones around detected farms. Radial zones: 0 to <500, 500 to <3000, 3000 to <5000, and 5000 to <10,000 m
Movement—general	Defines the background level of movement of animals and fomites throughout the infected area. Eligible states: all farms in the outbreak area. Number of movements per time period: ∼Poisson (0.25). Number of farm contacts generated from each movement: 1. Movement distance probabilities: 0.30 at 0 to <5 km; 0.55 at 5 to <10 km; 0.10 at 10 to <15 km, and 0.05 at 15 to <30 km. Probability of transmission relative to infection date of farm originating each movement. Probability of transmission, if originating farm infected: 0.65
Local spread	Defines the spread of disease between locations when there is no clear linkage other than geographical proximity. Eligible states: those farms not depopulated. Daily probability of transmission (constant from 2 days before date of infection to time of depopulation): lookup table
Airborne spread	Defines the spread of disease over distances greater than 5 km primarily due to prevailing meteorological conditions, particularly wind. Eligible states: those farms not depopulated. Separate airborne parameters defined for Anseong, Jincheon, Pyongtaek, and Yongin counties. For each county, spread probabilities defined for days 1–39 and days 40–69 after simulation start (incursion date). Probability of transmission (from date of onset of clinical signs): 0.0001 at 0 to <1000 m; 0.00002 at 1000 to <3000 m; 0.00001 at 3000 to <5000 m; 0.000025 at 5000 to <10,000 m. Relative susceptibility to infection from airborne spread: cattle 1.0; pigs 0.0078; other species 0.0550. Wind direction for each time period dependent on a probability lookup table based on meteorological data. Probability of airborne spread occurring on any given time period: 0.02. Directional weightings (used to modify wind 'dispersion' from a source farms): lookup table based on meteorological data. Relative infectivity from airborne spread: cattle 0.2; pigs 1.0; other species 0.2
Incubation period	Defines how quickly clinical signs appear after infection. Table defining the probability that clinical signs will appear on an infected farms relative to the date of infection: 0.01 at 2 days; 0.645 at 4 days; 0.23 at 6 days; 0.07 at 8 days; 0.025 at 10 days; 0.01 at 12 days; 0.01 at 14 days
Resource—depopulation	Defines the resources that are available for depopulation. Number of farms able to be processed per time unit: 100
Depopulation—0 to <500 m	Defines the nature of the depopulation strategy applied to farms that are within 0 to <500 m of detected farms. Species to be depopulated: cattle, pigs, all other FMD-susceptible species

Table 1 (*Continued*)

Item	Details
Depopulation—500 to <3000 m	Defines the nature of the depopulation strategy applied to farms that are within 500 to <3000 m of detected farms. Species to be depopulated: pigs
Surveillance—epidemic	Defines the intensity of surveillance once the index farm has been detected. Eligible states: all farms in the outbreak area. Detection probability: cattle 0.95; pigs 0.95; other species 0.95
Surveillance—contiguous	Defines the intensity of surveillance for disease on those farms selected for depopulation. Eligible states: all farms within 0 to <500 m of detected farms. Detection probability: cattle 0.95; pigs 0.95, other species 0.95
Movement restriction—detected	Defines restriction of movement off farms detected with disease. Eligible states: farms detected with disease. Movement type to be restricted: movement—general (see above). Source farm state: detected. Destination farm states: farms not detected with disease. From day 10 to day 20 after simulation start (incursion date) probability movement restricted: 0.85. From day 21 to day 1000 after simulation start probability movement restricted: 0.98.
Movement restriction—not detected	Defines restriction of movement off farms not detected with disease. Eligible states: farms not detected with disease. Movement type to be restricted: movement—general (see above). Source farm state: detected. Destination farm states: farms not detected with disease. From day 10 to day 20 after simulation start (incursion date) probability movement restricted: 0.45. From day 21 to day 1000 after simulation start probability movement restricted: 0.98.

course of the epidemic on a 0–10 scale (0 indicating no effect and 10 indicating complete effect). On the basis of this information we specified that movement off farms detected with disease was reduced by 90% and movement off all other farms was reduced by 55%. For the third phase (>10 days following detection of the index case) the effectiveness of movement controls was increased: movement off farms detected with disease was reduced by 95% and movement off all other farms was reduced by 85%. Surveillance parameters were set so that after the onset of controls 95% of infected farms were detected with disease immediately following the onset of clinical signs.

In summary, our approach for parameterising the reference strategy was to regard incubation period and local-spread parameters as fixed (being dependent on the viral serotype involved), apply local wind direction and speed data to define airborne-spread probabilities, and then to use local expert opinion to specify suitable distances and frequencies of animal movements. The reference strategy was simulated in 1-day time steps from the date of incursion for 60 days and the simulation repeated for 99 iterations to generate a distribution of predictions.

2.4. Alternative strategies

Four categories of alternative control strategies were considered: (1) those where the timing of commencement of control measures was varied, strategies 1–3; (2) those where ring vaccination was applied to a distance of <3000 or <5000 m around identified infected

Table 2
Details of the reference control strategy and each of the alternative control strategies for foot-and-mouth disease considered in this study (Republic of Korea, April–June 2002)

Strategy	Surveillance	Pre-emptive depopulation			Vaccination		
	Start	Start[a]	0 to <500 m[b]	500 to <3000 m[c]	Start	500 to <3000 m[c]	3000 to <5000 m[d]
Reference	2 May	2 May	C S O		–	–	–
Commencement of controls							
1. Five days earlier	27 April	27 April	C S O	S	–	–	–
2. Two days later	2 May	4 May	C S O	S	–	–	–
3. Five days later	2 May	7 May	C S O	S	–	–	–
Standard pre-emptive depopulation							
4. With ring vaccination to <3000 m	2 May	2 May	C S O	S	3 May	C O	–
5. With ring vaccination to <5000 m	2 May	2 May	C S O	S	3 May	C O	C S O
Limited pre-emptive depopulation							
6. With ring vaccination to <3000 m	2 May	2 May	C S O	–	3 May	C S O	–
7. With ring vaccination to <5000 m	2 May	2 May	C S O	–	3 May	C S O	C S O
Extended pre-emptive depopulation							
8. With ring vaccination to <5000 m	2 May	2 May	C S O	C S O	3 May	–	C S O
9. Without vaccination	2 May	2 May	C S O	C S O	3 May	–	–

Key: C = cattle farms, S = swine farms, O = other farms with FMD-susceptible species present.
[a] Start of pre-emptive depopulation control measures.
[b] 0 to < 500 m radius from centroid of infected farms.
[c] 500 to <3000 m radius from centroid of infected farms.
[d] 3000 to <5000 m radius from centroid of infected farms.

farms, strategies 4 and 5; (3) those using a combination of limited pre-emptive depopulation and ring vaccination, strategies 6 and 7; (4) those using a combination of extended pre-emptive depopulation with or without ring vaccination, strategies 8 and 9 (Table 2). Each strategy was simulated in 1-day time steps from the date of incursion for 60 days and repeated for a total of 99 iterations. Outcomes for each strategy are reported in terms of the distribution of the total number of infected, depopulated and vaccinated farms, and predicted epidemic duration (defined as the number of days from the infection date of the primary case farm to the infection date of the last farm infected in the epidemic).

Total numbers of infected, depopulated and vaccinated farms for each iteration were natural-log transformed and a two-sided, one-way ANOVA applied to test for differences in the 99 simulated outcomes for the reference strategy and the 99 simulated outcomes for each of the nine alternative control strategies. Dunnett's procedure was used to compare outcomes from each of the nine alternative control strategies with the reference strategy. Tests of significance are reported at the alpha level of 0.05.

3. Results

A line plot showing the actual cumulative number of infected farms as a function of calendar date and the 25th and 75th percentile of the cumulative number of farms predicted to become infected by the reference strategy is shown in Fig. 2. A contour plot identifying areas where, for the reference strategy, >80% of farms predicted to become infected where located is shown in Fig. 3. Descriptive statistics of the predicted number of infected farms and predicted epidemic duration are presented in Table 3. Descriptive statistics of the predicted number of depopulated and vaccinated farms are presented in Table 4.

For the reference strategy, the median number of farms predicted to be infected was 15. Starting the controls 5 days sooner or later (strategies 1 and 3) significantly changed the median predicted epidemic size to 6 and 20 farms, respectively (Table 3). Ring vaccination applied to a radius of <3000 and <5000 m around identified infected farms (strategies 4 and 5) reduced the predicted median number of infected farms to 14 and 11, respectively. The predicted number of infected farms and the predicted number of depopulated farms for strategies 4 and 5 did not significantly differ from the reference strategy (Tables 3 and 4).

Table 3
Predicted number of FMD-infected farms and duration of epidemic (Republic of Korea, April–June, 2002)

Strategy	Number of infected farms					Epidemic duration (days)				
	Minimum	*Q*1	Median	*Q*3	Maximum	Minimum	*Q*1	Median	*Q*3	Maximum
Reference	1	7	15	28	130	1	51	58	60	60
Commencement of controls										
1. Five days earlier[a]	1	3	6	12	43	1	36	53	59	60
2. Two days later	1	6	15	33	125	1	46	57	59	60
3. Five days later	1	11	20	52	202	1	52	59	60	60
Standard pre-emptive depopulation										
4. With ring vaccination to <3000 m	1	5	14	26	100	1	45	57	59	60
5. With ring vaccination to <5000 m	1	5	11	22	96	1	45	55	59	60
Limited pre-emptive depopulation										
6. With ring vaccination to <3000 m	1	6	14	24	109	1	51	58	59	60
7. With ring vaccination to <5000 m	1	6	12	24	103	1	45	56	59	60
Extended pre-emptive depopulation										
8. With ring vaccination to <5000 m[a]	1	3	8	16	71	1	17	46	57	60
9. Without vaccination[a]	1	3	10	20	115	1	19	54	58	60

The actual number of infected farms was 16. One infected swine enterprise was comprised of three geographically separate sites, thus the number of case locations was 18. The actual epidemic duration was 62 days (22 April–21 June 2002).

[a] Predicted number of infected farms significantly less than the reference strategy at the alpha = 0.05 level.

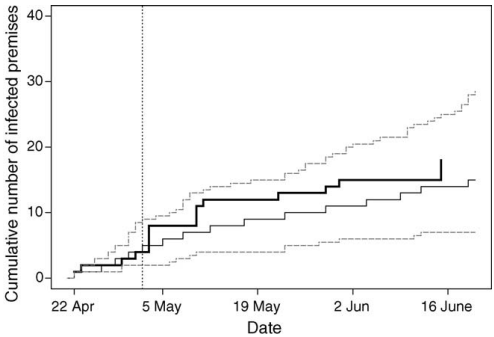


Fig. 2. Line plot showing the actual cumulative number of infected farms (thick solid line) and the median cumulative number of infected farms (thin solid line) predicted by the reference strategy described in Table 1. The lower and upper dashed lines show the 25th and 75th quantiles of the cumulative number of infected farms predicted by the reference strategy, respectively. The dashed vertical reference line indicates the date control measures commenced (2 May 2002).

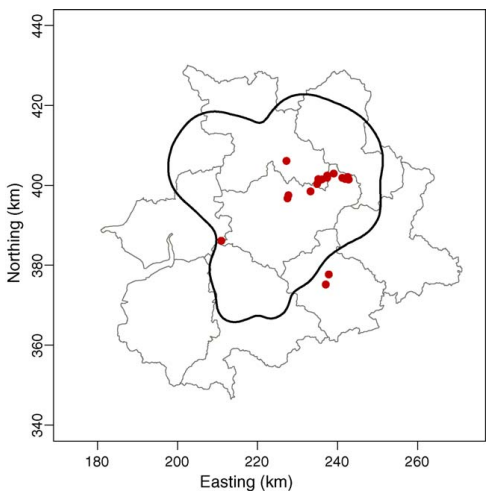


Fig. 3. Spatial and stochastic simulation of foot-and-mouth disease in the Republic of Korea, April–June 2002. Map of the eight counties that comprised the infected area. The contour line identifies areas where, for the reference strategy, >80% of farms predicted to become infected were located. Point locations of the 16 farms actually infected have been superimposed, for reference.

Table 4
Predicted number of depopulated and vaccinated farms (Republic of Korea, April–June, 2002)

Strategy	Number of depopulated farms					Number of vaccinated farms				
	Minimum	$Q1$	Median	$Q3$	Maximum	Minimum	$Q1$	Median	$Q3$	Maximum
Reference	60	171	306	430	1106	–	–	–	–	–
Commencement of controls										
1. Five days earlier[a]	60	116	177	258	572	–	–	–	–	–
2. Two days later	60	166	339	506	1150	–	–	–	–	–
3. Five days later	60	248	401	664	1366	–	–	–	–	–
Standard pre-emptive depopulation										
4. With ring vaccination to <3000 m	60	158	309	481	1101	57	166	323	508	1130
5. With ring vaccination to <5000 m[b]	60	158	283	465	1055	316	586	887	1294	2304
Limited pre-emptive depopulation										
6. With ring vaccination to <3000 m[a]	3	18	45	78	240	57	164	320	490	1123
7. With ring vaccination to <5000 m[a,b]	3	20	39	76	242	316	544	917	1236	2354
Extended pre-emptive depopulation										
8. With ring vaccination to <5000 m[b]	133	270	467	723	1452	186	392	624	1046	1800
9. Without vaccination	133	269	493	675	1396	–	–	–	–	–

The actual number of depopulated farms was 162.
[a] Predicted number of depopulated farms significantly less than the reference strategy at the alpha = 0.05 level.
[b] Predicted number of vaccinated farms significantly greater than strategy 4 at the alpha = 0.05 level.

Strategies involving a combination of limited depopulation and ring vaccination to a radius of <3000 and <5000 m around identified infected farms (strategies 6 and 7) reduced the predicted median number of infected farms to 14 and 12, respectively. The predicted number of depopulated farms for these strategies (45 and 39, respectively) was significantly less than the 306 depopulated farms predicted for the reference strategy (Table 4). Where pre-emptive depopulation of all susceptible species was extended to a radius of <3000 m (strategy 9) the median number of predicted infected farms was 10 (Table 3). Augmenting this strategy with ring vaccination to a radius of <5000 m (strategy 8) produced a median of eight infected farms (Table 3).

4. Discussion

InterSpread is a stochastic spatial simulation model of between-farm spread of disease suited to infectious agents transferred from farm-to-farm by a combination of mechanical, local and/or airborne-spread mechanisms (Sanson, 1993). Although the model has primarily been used to simulate the spread of FMD among animal populations (Sanson et al., 1991; Sanson, 1993; Morris et al., 2001, 2002) it has been adapted to other infectious

diseases of livestock such as Classical Swine Fever (Jalvingh et al., 1999; Nielen et al., 1999; Mangen et al., 2001) and Infectious Bovine Rhinotracheitis (Noordegraaf et al., 2000). In this study a revised version of the InterSpread model was used to simulate the temporal and spatial progression of a FMD epidemic following infection of the primary case farm in the 2002 epidemic of FMD in Korea.

Our judgement of what constituted an adequate 'match' between the actual epidemic and that predicted by the reference strategy was subjective and involved parameter adjustment so that: (1) the epidemic curve for the actual epidemic fell within the interquartile range of the epidemic simulated by the reference strategy (as shown in Fig. 2); (2) the spatial distribution of the 18 case locations fell largely within the boundaries of a contour line that delineated 80% of the predicted infected farm locations from 99 iterations of the reference strategy (Fig. 3); (3) the actual number of farms pre-emptively depopulated was of the same order of magnitude as that predicted by the reference strategy. In this case our requirement to precisely match numbers of pre-emptively depopulated farms was relaxed, given the approximations used to define farm location. On the basis of the data presented in Figs. 2 and 3 it is our belief that the parameters used to define the reference strategy provide an adequate representation of the 2002 Republic of Korea FMD epidemic, sufficient to serve as a comparison point for investigating alternative control strategies. As a result of the approximations to farm location (and therefore the numbers of farms depopulated and/or vaccinated as part of control efforts) we emphasise that the simulation results of alternative control strategies are indicative of trend only and are unlikely to precisely estimate the direct losses associated with each of the alternative control strategies described.

Of all the strategies evaluated, reducing the number of days between disease incursion and commencement of controls had the greatest effect on predicted epidemic size. Controls that were applied 5 days earlier resulted in epidemics that were shorter and had a significantly smaller number of infected and depopulated farms, compared with the reference strategy (Tables 3 and 4). Increasing the number of days between incursion and commencement of controls resulted in epidemics that were larger and more variable. These results indicate that as the delay in commencement of controls increases the propensity for a 'run away' epidemic increases. When the onset of control measures is delayed animal-health authorities would be advised to consider additional efforts aimed at increasing the efficacy of controls that are applied—for example, increasing the geographical extent of defined outbreak areas and enhancing the degree to which movement restrictions are enforced.

Ring vaccination to a radius of <3000 m around identified infected farms accompanied by standard or limited pre-emptive depopulation (strategies 4 and 6) had little effect on the predicted median number of infected farms but reduced the variability of predicted epidemic size (Table 3). Ring vaccination to a radius of <5000 m around identified infected farms accompanied by standard or limited pre-emptive depopulation (strategies 5 and 7) had little additional effect in decreasing predicted epidemic size, compared with strategies 4 and 6. The absence of additional benefits from a <5000-m ring vaccination strategy were most likely a result of the extent of local spread being limited to a distance of <3000 m in these simulations, resulting in a <3000 m vaccination ring providing a largely adequate protective barrier of immune animals

around identified infected farms. These results show that, on the basis of the assumptions made about local spread of virus outlined in Table 1, restricting pre-emptive depopulation accompanied by vaccination is a useful control option in some circumstances, for example the situation where an outbreak is still localised and commencement of controls has been delayed (as discussed above). In arriving at this conclusion it should be noted that the beneficial effects of this approach should be weighed carefully against the associated negative effects on trade and/or the cost of slaughtering vaccinated stock if prompt restoration of international trade is required.

Extending pre-emptive depopulation to include all species <3000 m of identified infected farms with or without ring vaccination (strategies 8 and 9, respectively) resulted in total numbers of depopulated farms that did not differ significantly from the reference strategy (Table 4). Extended depopulation accompanied by ring vaccination (strategy 8) resulted in significantly smaller numbers of infected farms, compared with the reference strategy (Table 3). Although strategy 8 produced a significant decrease in predicted numbers of infected farms, it was no more effective than strategy 1 where controls where started 5 days earlier.

5. Conclusions

The comparison of different alternatives to the reference strategy lead to some general conclusions concerning the management of future FMD epidemics involving the O_1 serotype in this area of Korea. Our first conclusion is that the prompt implementation of control measures (restriction of movement, enhanced surveillance, and pre-emptive depopulation) is effective in reducing both the size and variability of future outbreaks. Our second conclusion is that ring vaccination, when used with standard, limited, or extended pre-emptive depopulation strategies, reduces both the size and variability of predicted epidemics. Further analyses, more precisely defining local-spread probabilities of FMD virus, need to be undertaken to provide definitive recommendations on the optimal size of ring vaccination radii. In addition, economic analyses need to be undertaken to define the magnitude of savings accrued by limiting the number of farms requiring depopulation against the negative effects that vaccination holds in terms of adverse effects on international trade of animal product.

References

Anderson, I., 2002. Foot and Mouth Disease 2001: Lessons to be Learned Inquiry. HMSO, London.

Barlow, N., 1991. The role of modelling in policy and control decisions. In: Proceedings of a Symposium on Tuberculosis, Palmerston North, New Zealand, pp. 251–265.

Bates, T., Thurmond, M., Carpenter, T., 2001. Direct and indirect contact rates among beef, dairy, goat, sheep, and swine herds in three California counties, with reference to control of potential foot-and-mouth disease transmission. Am. J. Vet. Res. 62, 1121–1129.

Beal, V., 1983. The use of mathematical models in animal disease program evaluation. In: Proceedings of the 87th Annual Meeting of the United States Animal Health Association, Las Vegas, Nevada, pp. 386–402.

Carpenter, T., Dilgard, P., 1982. An application of computerized decision analysis in animal health economics. In: Proceedings of the Third International Symposium on Veterinary Epidemiology and Economics, Arlington, VA, USA, September 6–10, 1982, pp. 408–414.

Carpenter, T., Thieme, A., 1979. A simulation approach to measuring the economic effects of foot and mouth disease in beef and dairy cattle. In: Proceedings of the Second International Symposium on Veterinary Epidemiology and Economics, Canberra, Australia, pp. 511–516.

de Berg, M., van Kreveld, M., Overmars, M., Schwarzkopf, O., 2000. Computational Geometry. Springer-Verlag, London.

Gibbens, J., Wilesmith, J., 2002. Temporal and geographical distribution of cases of foot-and-mouth disease during the early weeks of the 2001 epidemic in Great Britain. Vet. Rec. 151, 407–412.

Habtemariam, T., Ruppanner, R., Riemann, H., Theis, J., 1983. Epidemic and endemic characteristics of trypanosomiasis in cattle: a simulation model. Prev. Vet. Med. 1, 137–145.

Jalvingh, A., Nielen, M., Maurice, H., Stegeman, A., Elbers, A., Dijkhuizen, A., 1999. Spatial and stochastic simulation to evaluate the impact of events and control measures on the 1997–1998 classical swine fever epidemic in The Netherlands. I. Description of simulation model. Prev. Vet. Med. 42, 271–295.

Mangen, M., Jalvingh, A., Nielen, M., Mourits, M., Klinkenberg, D., Dijkhuizen, A., 2001. Spatial and stochastic simulation to compare two emergency-vaccination strategies with a marker vaccine in the 1997/1998 Dutch classical swine fever epidemic. Prev. Vet. Med. 48, 177–200.

Morris, R., Sanson, R., Stern, M., Stevenson, M., Wilesmith, J., 2002. Decision-support tools for foot and mouth disease control. Rev. Sci. Tech. 21, 557–567.

Morris, R., Wilesmith, J., Stern, M., Sanson, R., Stevenson, M., 2001. Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain. Vet. Rec. 149, 137–144.

Nielen, M., Jalvingh, A., Meuwissen, M., Horst, S., Dijkhuizen, A., 1999. Spatial and stochastic simulation to evaluate the impact of events and control measures on the 1997–1998 classical swine fever epidemic in The Netherlands. II. Comparison of control strategies. Prev. Vet. Med. 42, 297–317.

Noordegraaf, A., Jalvingh, A., Jong, M., de Franken, P., Dijkhuizen, A., 2000. Evaluating control strategies for outbreaks in BHV1-free areas using stochastic and spatial simulation. Prev. Vet. Med. 44, 21–42.

OIE, 2001. Foot and mouth disease. In: International Animal Health Code, Office International des Épizooties, Paris, pp. 63–75 (Chapter 2.1.1).

Sanson, R., 1993. The development of a decision support system for an animal disease emergency. Unpublished Ph.D. Thesis. Massey University, Palmerston North, New Zealand.

Sanson, R., Liberona, H., Morris, R., 1991. The use of a geographical information system in the management of a foot-and-mouth disease epidemic. Prev. Vet. Med. 11, 309–313.

Taylor, N., 2003. Review of the Use of Models in Informing Disease Control Policy Development and Adjustment. Defra, London URL: http://www.defra.gov.uk/science/documents/publications/2003/UseofModelsinDisease-ControlPolicy.pdf, last accessed September 19, 2005.

Feature Series Article

A comparison of predictions made by three simulation models of foot-and-mouth disease

C Dubé[*], MA Stevenson[†§], MG Garner[‡], RL Sanson[#], BA Corso[¥], N Harvey[l], J Griffin[€], JW Wilesmith[Ω] and C Estrada[d]

Abstract

AIMS: To describe results of a relative validation exercise using the three simulation models of foot-and-mouth disease (FMD) in use by the quadrilateral countries (QUADS; Australia, Canada, New Zealand, and United States of America; USA).

METHODS: A hypothetical population of farms was constructed and, following the introduction of an FMD-like disease into a single farm, spread of disease was simulated using each of the three FMD simulation models used by the QUADS countries. A series of 11 scenarios was developed to systematically evaluate the key processes of disease transmission and control used by each of the three models. The predicted number of infected units and the size of predicted outbreak areas for each scenario and each model were compared using the Kruskal-Wallis test. Agreement among the three models in terms of geographical areas predicted to become infected were quantified using Fleiss' Kappa statistic.

RESULTS: Although there were statistically significant differences in model outputs in terms of the numbers of units predicted to become infected, the temporal onset of infection throughout the simulation period, and the spatial distribution of infected units, these differences were generally small and would have resulted in the same (or similar) management decisions being adopted in each case.

CONCLUSIONS: Agreement among the three models in terms of the numbers of premises predicted to become infected, the temporal onset of infection throughout the simulation period, and the spatial distribution of infected premises provides evidence that each of the model developers are consistent in their approach to simulating the spread of disease throughout a population of susceptible individuals. This consistency implies that the assumptions taken by each development team are appropriate, which in turn serves to increase end-user confidence in model predictions.

CLINICAL RELEVANCE: Relative validation is one of a number of steps that can be undertaken to increase end-user confidence in predictions made by infectious disease models.

KEY WORDS: *Foot-and-mouth disease, simulation, animal disease modelling, validation*

Introduction

Disease models are planning tools that can support decision-making by allowing various outbreak scenarios and control strategies to be evaluated and compared. They are useful for gaining insights into the conditions under which controversial control measures, such as when emergency vaccination might become economically viable in an FMD epidemic (Burrell 2002, non-peer-reviewed). Given the expense of controlling large-scale infectious disease epidemics in animal populations (Thompson et al 2002; Mangen et al 2004) and the short- and long-term consequences arising from decisions made in the early phase of such epidemics, decision-makers need to be confident in the reliability of model predictions when they are to be used as a tool to inform disease control policy. Models that are adequately verified and validated provide such confidence.

Model verification is the process that ensures that the explicit description of how disease is spread from one unit to another (by the subject matter expert responsible for model design) has been translated accurately into computer code (Taylor 2003; Sargent 2005; both non-peer-reviewed). Validation ensures that a model provides an adequate depiction of the process it is designed to represent (Schlesinger et al 1979; Taylor 2003). An infectious disease model is said to be internally valid when its outputs make epidemiological sense given the underlying population dataset and the set(s) of parameters used to initiate the simulation(s). External validity can only be assessed when model predictions are comparable with one or more real epidemics. Validation is a difficult issue for countries with limited or no recent experience with a disease of interest, as it cannot be assumed that experience from one outbreak can be used to infer the behaviour of another, particularly when it may be based on limited and incomplete data from another country.

FMD	Foot-and-mouth disease
MCH	Minimum convex hull
MRMCH	Modified reduced minimum convex hull
QUADS	Quadrilateral countries (Australia, Canada, New Zealand, and United States of America)

[*] Canadian Food Inspection Agency, 59 Camelot Street, Ottawa, Ontario, K1A 0Y9 Canada.
[†] EpiCentre, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Private Bag 11222, Palmerston North, New Zealand.
[‡] Office of the Chief Veterinary Officer, Department of Agriculture, Fisheries and Forestry, GPO Box 858, ACT 2601, Australia.
[#] AsureQuality Limited, PO Box 1654, Palmerston North, New Zealand.
[¥] USDA-APHIS, Veterinary Services, Centers for Epidemiology and Animal Health, Fort Collins, CO, USA.
[l] Department of Computing and Information Science, University of Guelph, Guelph, Ontario, N1G 2W1, Canada.
[€] Irish Department of Agriculture and Food, Kildare Street, Dublin 2, Ireland.
[Ω] Animal Health and Welfare Directorate General, 1A Page Street, London SW1P 1PQ, England.
[d] United States Department of Agriculture, 4700 River Road, Unit 41, Riverdale, MD 20737, USA.
[§] Author for correspondence. Email: m.stevenson@massey.ac.nz

Although acknowledged as a critical step in the model-building process, well-defined methods for validating and verifying disease models are lacking (Sargent 2005). Law and Kelton (2000) proposed a three-step approach: (1) develop a model with high face validity, i.e. a model which, on the surface, seems reasonable to those who are knowledgeable about the system under study; (2) test the assumptions of the model empirically; and (3) determine how representative the simulation output data are. The first two steps lead to internal validity, whereas the third step is required to establish external validity. An additional approach is to carry out what we term 'relative' validation. One or more test scenarios are defined and two or more independently developed models simulate the spread of disease using each test scenario. Agreement among the participant models in terms of the numbers of premises predicted to become infected, the temporal onset of infection throughout the simulation period, and in the case of spatial models, the spatial distribution of infected premises, provides evidence that each of the model developers are consistent in their approach to simulating the spread of disease throughout a population of susceptible individuals. This consistency implies that the assumptions taken by each development team make biological sense, which in turn serves to increase end-user confidence in model predictions. In addition, such comparison exercises are useful in terms of identifying and highlighting differences in model assumptions that need to be resolved, identifying areas for further research.

We describe the results of a relative validation exercise using the three simulation models of FMD in use by the QUADS countries. We provide a description of the models and data used for this comparison study, the scenarios tested, the statistical tests employed to measure differences, and a discussion of the key findings.

Materials and methods

A hypothetical population of farms was constructed and, following the introduction of an FMD-like disease into a single farm, spread of disease was simulated using each of the three FMD simulation models used by the QUADS countries. The models compared were AusSpread (Garner and Beckett 2005; Beckett and Garner 2007), InterSpread Plus (Sanson 1993; Stevenson et al 2003), and NAADSM (Schoenbaum and Disney 2003; Harvey et al 2007), referred to as the Australian, New Zealand, and North American models, respectively. A series of 11 outbreak scenarios was developed to systematically evaluate the key processes of disease transmission and control within the three models. Our justification for using a simulated farm population, rather than actual data, was to allow each disease transmission and control process to be individually evaluated on a population of farms that was unlike that in any of the participating countries. Our justification for using simple outbreak scenarios was to allow each mechanism of disease spread and control to be assessed independently. This would then provide a clearer picture of the similarities and differences among the three models, providing a starting point for understanding why the models might behave differently when applied to actual farm population data and outbreak scenarios. The study commenced in May 2005 and concluded in September 2006.

At the start of the study, each of the three modelling teams provided copies of their model design document to the Canadian team members. This allowed each model to be summarised in terms of the epidemiological unit of interest, options for differentiating units of interest, e.g. by production type and size, methods for representing the spatial attributes of each unit, disease states, mechanisms of disease spread, and disease control measures. A summary of the key features of each of the three models is shown in Table 1. A description of the capabilities of each model allowed a set of scenarios to be devised, such that each team could configure their model to represent the same set of epidemiological assumptions.

A hypothetical population of 3,960 farm units of varying size (median number of animals 163, range 2–990) was created, and the physical locations of units randomly distributed within a circular study area of 600 km diameter, with some clustering (Figure 1).

Scenarios

Five categories of scenarios were compared: (1) those where the mechanism of infection transmission was varied (Scenarios 1–3); (2) those where the frequency, distances moved and probabilities of infection associated with direct and indirect contacts (Bates et al 2001) were varied (Scenarios 4–6); (3) a single scenario where movement controls were applied (Scenario 7); (4) those where ring vaccination was applied (Scenarios 8 and 9); and (5) those where ring depopulation was applied (Scenarios 10 and 11). The key features of each of the 11 scenarios are outlined in Table 2. In some instances, extreme values were specified for transmission parameters so that model outputs could be assessed empirically.

For each scenario, epidemics were initiated from the same single infected unit located in the centre of the study area (Figure 1). Epidemics were simulated in 1-day time steps from incursion for a pre-determined number of days, and each simulation was repeated to generate a distribution of predictions. A preliminary evaluation had indicated that 40 replications would provide a reasonable representation of the distribution. Outputs from simulations were submitted to the Canadian team members who provided summaries to the rest of the group in terms of descriptive statistics of the predicted numbers of infected units and duration of the epidemics. Where the results of a scenario for one of the models differed substantially from the other two, clarification was

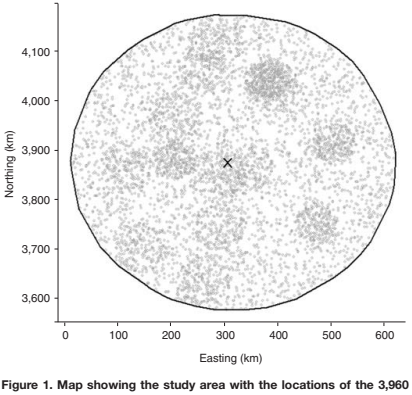


Figure 1. Map showing the study area with the locations of the 3,960 hypothetical livestock farm units (o) and the location of the infected unit (x) used to initiate each outbreak scenario.

Table 1. A comparison of the key features of three simulation models of foot-and-mouth disease used in this study.

	Country		
Item	**Australia**	**New Zealand**	**North America**
Type	Stochastic, simulation, spatial	Stochastic, simulation, spatial	Stochastic, simulation, spatial
Unit of interest	Group of animals	Group of animals	Group of animals
Spatial attributes of units	Point or polygon	Point or polygon	Point or polygon
Unit class	By production type	By production type	By production type
Unit size	Total stratified by animal type	Total stratified by animal type	Total
Within-unit prevalence[a]	Infectiousness curve	Infectiousness lookup table	Not available
Disease states	Susceptible	Susceptible	Susceptible
	Latent	Infected	Latent
	Infectious	Clinical	Infectious subclinical
	Immune	Immune	Infectious clinical
	Depopulated	Depopulated	Vaccinated immune
			Depopulated
Mechanisms of spread	Direct contact	Direct contact	Direct contact
	Indirect contact[b]	Indirect contact[b]	Indirect contact[b]
	Airborne spread	Airborne spread	Airborne spread
Control measures	Quarantine	Quarantine	Quarantine
	Movement restriction[c]	Movement restriction[c]	Movement restriction[d]
	Stamping-out	Stamping-out	Stamping-out
	Forward and backward tracing	Forward and backward tracing	Forward tracing
	Pre-emptive slaughter[e]	Pre-emptive slaughter[e]	Pre-emptive slaughter[e]
	Vaccination[f]	Vaccinationf	Vaccination[f]
	Surveillance[h]	Surveillance[h]	Surveillance[i]
Control zones	User-defined	User-defined	Not available
Disease detection	Passive	Passive	Passive
	Active	Active	
Resources	Overall capacity for surveillance, depopulation and vaccination, or specify teams for destruction, vaccination and surveillance	Overall capacity for surveillance, depopulation and vaccination	Overall capacity for depopulation and vaccination

[a] Accounting for increasing infectiousness over time
[b] Transfer of disease from one location to another via humans or fomites
[c] Entire study region or by specified control zones
[d] Entire study region
[e] Dangerous contacts and/or contiguous slaughter
[f] Emergency ring or area vaccination and/or targeted protective vaccination
[g] Emergency ring vaccination
[h] *Ad-hoc* reporting based on clinical signs and surveillance within a defined radius of infected units
[i] *Ad-hoc* reporting based on clinical signs

sought from the particular modelling team regarding the possibility of any misinterpretation of the specified input parameters for that scenario or whether fundamental differences in model design were responsible. When parameter-related issues were identified, the particular team was given the opportunity to re-simulate the scenario and submit the outputs from the second series of iterations for comparison. In the case of model design-related issues, differences in results were recorded and quantified. The purpose was to ensure that each model was simulating the same scenario (parameter set), and that only differences in model design could explain the differences in results, if any.

Statistical analysis

Number of units infected

For each of the 11 scenarios, the total numbers of units infected by the end of the specified simulation periods were determined, and a two-sided, Kruskal-Wallis test applied to test for differences in the distribution (rank) of the 40 outcomes for each of the three models.

Temporal analysis

Survival (time-to-event) analyses were used to describe the temporal onset of infection among the population of units, using the survival package (Therneau and Grambsch 2001) in R (R Development Core Team, 2007; R Foundation for Statistical Computing, Vienna, Austria). Here, the outcome of interest was the day of infection for units predicted to become infected. Units that were depopulated pre-emptively as part of specified control measures were removed from the population at risk (right-censored) on the day of depopulation. Units that remained free of infection throughout the simulation period were right-censored at the end of the simulation period. For each simulation day, the median number of infected units predicted by each model, across the entire set of 40 iterations, was determined, and these data were used to generate a Kaplan-Meier survival curve summarising the temporal onset of infection among units throughout the simulation period. Differences in the distribution of time-to-event among the three models were tested using the log rank statistic.

Table 2. Details of the key features of 11 outbreak scenarios of foot-and-mouth disease used in this study.

Scenario	Disease state[a]	Mechanisms of spread	Control	Duration (days)
1	1	**Direct contact**[b]:	None	300
		Shipment rate: 1 contact/day		
		Distance: triangular 10–20–30 km		
		Probability of infection: 1		
2	1	Airborne spread:	None	200
		Wind direction: 225°–315°		
		Probability of infection at 1km: 0.98		
		Maximum distance of spread: 50 km		
3	1	Parameters of Scenario 1 + 2	None	200
4	1	**Direct contact**[b]:	None	100
		Shipment rate: 1 per day		
		Distance: triangular 4–5–6 km		
		Probability of infection: 0.5		
		Indirect contact[c]:		
		Shipment rate: 2 per day		
		Distance: triangular 140–150–160 km		
		Probability of infection: 1		
5	1	Identical to Scenario 4	None	115
6	2	Identical to Scenario 1	None	150
7	2	Identical to Scenario 1	Movement restrictions[d]	200
8	2	Identical to Scenario 1	Movement restrictions[d]	200
			Vaccination in 5-km rings	200
9	2	Identical to Scenario 1	Movement restrictions[d]	200
			Vaccination in 35-km rings	200
10	2	Identical to Scenario 1	Movement restrictions[d]	75
			Depopulation:	75
			Stamping-out	75
			Pre-emptive culling in 10-km rings	75
11	2	Identical to Scenario 1	Movement restrictions[d]	75
			Depopulation:	75
			Stamping-out	75
			Pre-emptive culling in 35-km rings	75

[a] Disease states: 1 = latent (triangular 29–30–31 days), infectious (triangular 59–60–61 days), immune (triangular 99–100–101 days); 2 = latent (triangular 1–3–10 days), infectious (triangular 3–12–35 days), immune (triangular 180–240–360 days)

[b] Direct contact: The physical connection between animals from different locations. If the animal initiating the contact is in an infectious state a direct contact may result in the transfer of disease. Direct contacts usually occur as a result of animal movements

[c] Indirect contact: The physical connection between animals and physical objects (e.g. humans) or fomites (vehicles, equipment) from different locations. If the source of the indirect contact contains infectious particles, an indirect contact may result in the transfer of disease

[d] A progressive reduction in the number of permitted movements per day to 60% by 10 days after detection, and then to 80% by 60 days after detection

Spatial analysis

The spatial analyses included comparing the physical size of the simulated outbreak areas, as well as assessing spatial agreement in terms of the specific geographical locations of units predicted to become infected, recognising that outbreaks of similar size may not necessarily match well in terms of the location of units predicted to become infected.

To measure the size of the spatial extent of the main cluster(s) of infection for each simulation, polygon-fitting techniques developed for home-range analysis of wildlife (Harvey and Barbour 1965; Dixon and Chapman 1980; Anderson 1982; Wray et al 1992) were considered. These techniques define the central or core home ranges of individual animals based on sightings recorded over a period of time. A modified reduced minimum convex hull (MRMCH) method was developed as an adaptation of the minimum convex hull (MCH). For each iteration of each scenario, a 'standard' MCH, which creates a convex polygon by identifying and drawing a line through all of the outermost infected units, was constructed first. The actual infected units that comprised the vertices of this convex hull were then removed, and a new MCH computed based on the remaining infected units. This approach preserved the shape and extents of the main cluster(s) of infection, whilst removing outliers. The area of each MRMCH in square kilometres (km^2) was then computed. In iterations where there were insufficient points to generate an MRMCH, the standard MCH was used instead. In iterations with only one or two infected units, the area was set to zero. The resultant areas of these hulls were compared using the Kruskal-Wallis test.

To evaluate the level of spatial agreement in the location of predicted infected units, the study area was divided into a regular grid of cells 30 km x 30 km in size, producing a total of 314 cells. Each model was considered in turn, and for each iteration of a given scenario cells were labelled 1 if at least one unit within its boundaries was predicted to become infected, and 0 otherwise. The mean cell score over 40 iterations for each model, by scenario, was calculated and rounded to 1 or 0. Fleiss' Kappa was used as an index of agreement for the 314 cell scores for each of the three models. The analysis was repeated for the core zone of infection

identified by the MRMCH method. Almost perfect agreement is said to be present when Kappa is >0.8 (Landis and Koch 1977).

Results

Descriptive statistics of the predicted numbers of infected units, the median number of days of active spread of infection, and the sizes of the predicted outbreak areas for the 11 scenarios are shown in Tables 3, 4, and 5, respectively. Also shown are the test statistics and the p-values for the Kruskal-Wallis tests for significant differences in predictions made by each model, for each scenario. Table 6 lists the Fleiss' Kappa statistics for spatial agreement for each of the 11 scenarios.

Changes to specifications of each scenario produced biologically plausible changes in the outcomes of interest. Direct contact as the only means of spread from the index unit (Scenario 1) resulted in successive rings of infection moving outwards from infectious units; distances corresponded to the movement distances specified. Modelling airborne spread alone with a prevailing wind

Table 3. Descriptive statistics of the predicted number of infected units for 11 scenarios described in this study, and p-values for Kruskal-Wallis tests (K) for significant differences between the number of infected units predicted by each model, for each scenario.

Scenario	Model	Median (range)	K	P-value
1	AU	1,539 (1,386–1,720)	43.0	<0.01
	NZ	1,492 (1,377–1,697)		
	NA	1,444 (1,298–1,573)		
2	AU	741 (728–753)	86.0	<0.01
	NZ	749 (733–770)		
	NA	681 (662–695)		
3	AU	1,346 (1,315–1,384)	79.6	<0.01
	NZ	1,354 (1,305–1,422)		
	NA	1,279 (1,235–1,324)		
4	AU	97 (75–114)	66.0	<0.01
	NZ	82 (70–98)		
	NA	76 (64–99)		
5	AU	460 (341–607)	2.51	0.28
	NZ	468 (340–611)		
	NA	500 (319–689)		
6	AU	3,958 (3,956–3,959)	7.07	0.03
	NZ	3,959 (3,957–3,959)		
	NA	3,959 (3,957–3,959)		
7	AU	250 (0–521)	7.50	0.02
	NZ	202 (0–398)		
	NA	268 (0–601)		
8	AU	237 (0–420)	0.65	0.72
	NZ	227 (0–482)		
	NA	230 (0–369)		
9	AU	132 (0–217)	0.01	0.99
	NZ	129 (0–220)		
	NA	133 (0–205)		
10	AU	1,714 (1,385–2,052)	22.5	<0.01
	NZ	1,803 (1,656–2,091)		
	NA	1,846 (1,598–2,279)		
11	AU	796 (617–1,001)	0.78	0.68
	NZ	793 (575–1,087)		
	NA	795 (643–1,055)		

AU = Australia; NZ = New Zealand; NA = North America

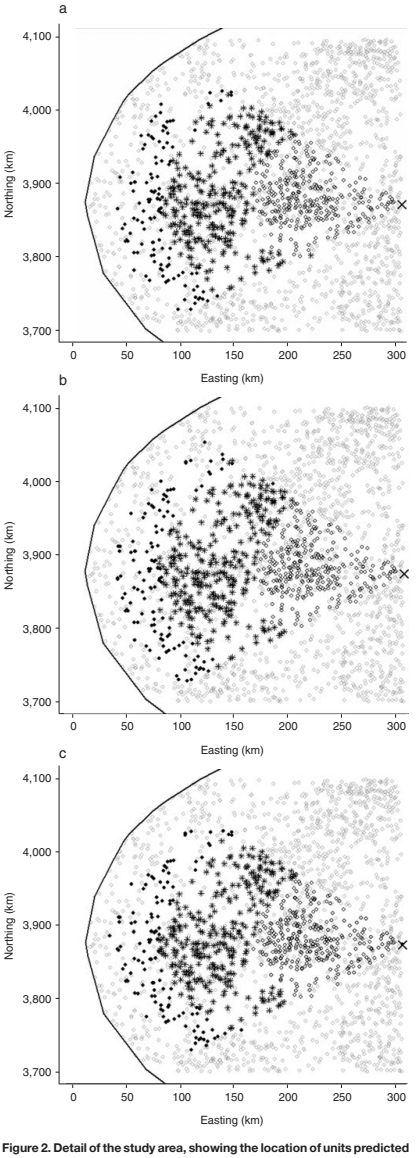


Figure 2. Detail of the study area, showing the location of units predicted to be in the susceptible (○), immune (▫), infected (*) and latent (●) state at Day 200 of Iteration 2 of Scenario 2 by the (a) Australian, (b) New Zealand, and (c) North American model.

direction from the east (Scenario 2) resulted in infected units occurring under the plume in a westerly direction from the index unit (Figure 2). Combining direct contact spread with airborne spread (Scenario 3) produced larger epidemics than either of these mechanisms on their own, and the spatial pattern of outbreaks was consistent with a mix of movement and airborne spread.

Increases in the length of the simulation period (Scenarios 4 and 5) produced a corresponding increase in the predicted numbers of infected units, and was attributed to a second wave of infection resulting from the reversion of previously immune units to a susceptible state. A simulation period of 100 days with no control measures resulted in 64–114 infected units (Table 3; Scenario 4); increasing the simulation period to 115 days increased the predicted numbers of infected units to 319–689 (Table 3; Scenario 5). It also increased the size of the predicted outbreak area from 70,000–112,000 km^2 in Scenario 4 to 209,000–269,000 km^2 in Scenario 5 (Table 5).

Table 4. Descriptive statistics of the median period (in days) that infection was active in the population (excluding the unit that initiated each epidemic) for 11 scenarios described in this study, and p-values for log rank tests for significant differences between the period of active infection predicted by each model, for each scenario.

Scenario	Model	Median (range)[a]	Log rank statistic	P-value
1	AU	213 (32-300)	6.80	0.03
	NZ	211 (31-300)		
	NA	208 (30-300)		
2	AU	127 (32-200)	4.00	0.14
	NZ	125 (31–200)		
	NA	124 (30–200)		
3	AU	129 (32–200)	5.30	0.07
	NZ	127 (31–200)		
	NA	127 (30–200)		
4	AU	73 (52–100)	3.60	0.17
	NZ	72 (51–100)		
	NA	71 (50–100)		
5	AU	110 (52–115)	1.10	0.59
	NZ	110 (51–115)		
	NA	109 (50–115)		
6	AU	87 (5–149)	43.8	<0.01
	NZ	80 (4–150)		
	NA	75 (2–142)		
7	AU	45 (4–200)	4.10	0.13
	NZ	39 (4–199)		
	NA	47 (3–200)		
8	AU	41 (4–200)	0.400	0.81
	NZ	47 (4–200)		
	NA	41 (3–200)		
9	AU	29 (4–96)	0.200	0.90
	NZ	33 (4–162)		
	NA	32 (3–87)		
10	AU	27 (4–75)	3.70	0.16
	NZ	31 (3–75)		
	NA	31 (2–75)		
11	AU	18 (4–75)	2.50	0.28
	NZ	20 (3–75)		
	NA	20 (2–75)		

[a] In Scenarios 1, 2, 3, 4, 5, 8, 10 and 11, the maximum day of infection for all models was equal to the length of the simulation period (Table 1)
AU = Australia; NZ = New Zealand; NA = North America

Table 5. Descriptive statistics of predicted outbreak areas (× 1,000 km^2) for 11 scenarios described in this study, and p-values for Kruskal-Wallis tests (K) for significant differences between the outbreak areas predicted by each model, for each scenario.

		Modified reduced minimum convex hull		
Scenario	Model	Median (range)	K	P-value
1	AU	98 (92–107)	54.1	<0.01
	NZ	95 (87–102)		
	NA	92 (87–97)		
2	AU	45 (43–47)	81.7	<0.01
	NZ	45 (43–48)		
	NA	38 (36–40)		
3	AU	87 (84–91)	76.9	<0.01
	NZ	86 (81–94)		
	NA	80 (76–84)		
4	AU	70 (67–72)	55.4	<0.01
	NZ	68 (62–70)		
	NA	67 (62–75)		
5	AU	240 (184–255)	14.1	<0.01
	NZ	230 (186–249)		
	NA	237 (193–250)		
6	AU	275 (275–275)	–	–
	NZ	275 (275–275)		
	NA	275 (275–275)		
7	AU	29 (0–58)	9.20	<0.01
	NZ	16 (0–56)		
	NA	23 (0–80)		
8	AU	24 (0–58)	0.54	0.76
	NZ	20 (0–68)		
	NA	20 (0–54)		
9	AU	14 (0–30)	6.33	0.04
	NZ	11 (0–24)		
	NA	11 (0–29)		
10	AU	129 (104–156)	26.3	<0.01
	NZ	137 (127–151)		
	NA	138 (120–163)		
11	AU	64 (42–86)	1.47	0.48
	NZ	67 (43–106)		
	NA	62 (41–91)		

AU = Australia; NZ = New Zealand; NA = North America

Table 6. Agreement of the Australian, New Zealand, and North American models for 11 scenarios described in this study, in terms of the spatial location of predicted infected areas.

	Fleiss' Kappa	
Scenario	All infected units	MRMCH
1	0.96	0.96
2	0.93	0.95
3	0.93	0.94
4	0.88	0.87
5	0.61	0.67
6	1.00[a]	1.00[a]
7	0.85	0.86
8	0.89	0.88
9	0.94	0.90
10	0.92	0.93
11	0.94	0.93

[a] All units predicted to become infected by each of the three models
MRMCH = modified reduced minimum convex hull

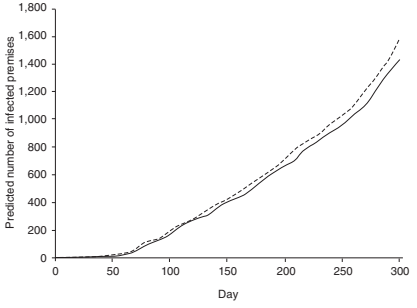


Figure 3. Simulation outputs from the North American model, using parameters from Scenario 1. Line plots showing the cumulative number of new infections as a function of simulation day when a unit changed state from susceptible to latent on the day contact occurred (...) and on the following day (–).

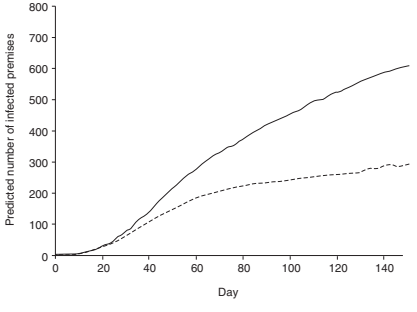


Figure 4. Simulation outputs from the North American model, using parameters from Scenario 7. Line plots showing the cumulative number of new infections as a function of simulation day when detected units could (...) and could not (–) receive direct contacts.

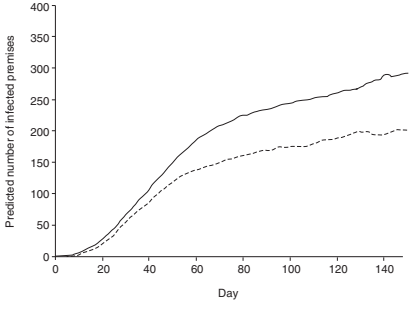


Figure 5. Simulation outputs from the North American model, using parameters from Scenario 7. Line plot showing the cumulative number of new infections as a function of simulation day when detection was allowed to occur before the simulation of disease spread (...), and when the simulation of disease spread occurred before the detection of disease (–), on any given day.

Using parameters that more closely reflected the behaviour of FMD and allowing direct contact to occur at shorter distances resulted in all susceptible units being infected (Table 3; Scenario 6). Vaccination that commenced when 50 units were detected (Scenario 8) in combination with spread by direct contact, detection, quarantine, and movement restrictions, resulted in fewer infected units (0–482 secondarily infected units) than in Scenario 7 where vaccination was not applied (0–601 secondarily infected units) (Table 3). Increasing the size of the vaccination area (Scenario 9) halved the predicted number of secondarily infected units (0–220) (Table 3). Depopulation as a control strategy (Scenarios 10 and 11) had a similar effect; for each of the three models, larger rings of depopulation led to smaller epidemics, i.e. fewer infected units and smaller outbreak areas.

The predicted numbers of infected units differed significantly ($p<0.05$) among the three models in 7/11 scenarios (Table 3). In four of these scenarios, the North American model predicted the fewest median outbreaks. The period of active infection differed significantly in 2/11 scenarios (Table 4). The predicted median size of each outbreak area differed significantly among models in 8/11 scenarios (Table 5). Apart from Scenario 5, there was close agreement in the predicted locations of infected units using an inferential grid cell size of 30 x 30 km (Table 6).

Discussion

The relative validation process described in this study is, we believe, one of a number of steps that can be undertaken to increase end-user confidence in infectious disease model predictions. In this study, the simulation of disease spread using a series of simple outbreak scenarios allowed specific mechanisms of the spread and control of disease in each of the three models to be evaluated and peer-reviewed. Given the greater understanding of factors influencing model predictions that has resulted from this study, we believe the QUADS team is well placed to carry out studies to evaluate the external validity of each model using actual population data and outbreak scenarios.

Although there were statistically significant differences among the numbers of infected units and the temporal and spatial spread predicted by the three models in each of the scenarios, the absolute differences were small and from a practical perspective would have resulted in the same (or similar) management decisions being adopted in each case. Differences in the spatial extents of simulated epidemics were expected, as the process of selecting direct and indirect contact units from each source unit involved randomly generating directions and distances from the prescribed probability distributions for each scenario. There were differences in the way each model conducted a search for recipient units. The New Zealand model randomly selects a distance band based on the predefined distance distribution, calculates the distance from the source unit to all potential recipient units, finds those within the relevant distance band, then randomly selects a unit in that distance band. The Australian model, in contrast, randomly selects a movement distance and direction, generates a point at that location and then searches around that point for a candidate recipient unit up to a specified distance.

By default, the Australian and New Zealand models allowed the transition of a unit from susceptible to latent (following successful exposure) to take place on the day of infection, while the transi-

tion to a latent state occurred on the day after infection in the North American model. This meant that the North American model produced consistently smaller outbreaks (Figure 3) than the other two models until this issue was identified and accounted for in the parameterisation of the Australian and New Zealand models. An additional important difference in model design was highlighted in scenarios that included detection of infected units (Scenarios 7–11). Once detected, units are normally placed under quarantine and are therefore ineligible to receive further contacts. In the Australian and New Zealand models, a direct contact with a detected unit was still permitted to occur, although it did not have any impact on that unit's disease status, i.e. it was a 'wasted' contact. The North American model, however, always selected recipients that were not under quarantine and so a new infected farm could result from those contacts to produce significantly larger outbreaks (Figure 4). Finally, the order in which events occurred in a simulation day had important impacts on the results of all scenarios. For example, implementing the spread of disease prior to detection on each simulation day produced larger epidemics compared with those where spread occurred after detection (Figure 5). A conclusion of this study was that all models should allow events such as spread and detection to occur in a random order throughout each simulation day, to mimic the fact that in a real-world outbreak, detection teams would be operative throughout each day and therefore could find disease at any time.

Developing parameters for each of the 11 scenarios forced each of the modelling teams to take an in-depth look at the way core functions were implemented in their models, and generated some useful insights. For example, in Scenario 1, the Australian model was initially run in its default mode, which was to allow the infectivity of a unit to increase with time (reflecting within-herd spread of FMD). This resulted in significantly fewer new infections than when infectivity was kept constant (assuming a 100% intra-unit prevalence from the first day of infection), indicating that this was an important issue to explore. Although not included in some of the mathematical models used in the FMD epidemic in the United Kingdom in 2001 (Ferguson et al 2001; Keeling et al 2001), it was accepted that there was within-herd transmission of FMD (Hutber and Kitching 2000). Accordingly, it is likely that farm-level infectiousness would increase over time as the number of animals infected increased (Taylor 2003; Haydon et al 2004; Honhold et al 2004; Kitching et al 2006). Future comparisons should assess the impact of within-herd spread in more complex, realistic scenarios.

The use of relatively simple population structures and outbreak scenarios was intentional as this was the only practical method for testing the core mechanisms of what are three relatively complex simulation models. The parameters for each scenario were developed to provide easy checks that models were performing as expected and adequately represented the features being tested. Although descriptions of the models used in this study have been published previously (Sanson 1993; Schoenbaum and Disney 2003; Garner and Beckett 2005; Stevenson et al 2006; Beckett and Garner 2007; Harvey et al 2007), it was not possible, from the information provided in those papers, to compare details of disease transmission and the impact these differences would have on model outputs. The differences identified in the model designs revealed the importance of documenting model-building assumptions, and testing alternative approaches to determine their impact on simulation results. Having demonstrated the utility of relative validation, future studies to compare model predictions in more complex populations and under more realistic outbreak conditions are planned.

Acknowledgements

MA Stevenson and RL Sanson were financially supported by the Ministry of Agriculture and Forestry Biosecurity New Zealand Contract BER-60-2004.

References

Anderson EJ. The home range: A new nonparametric estimation technique. *Ecology* 63, 103–12, 1982

Bates TW, Thurmond MC, Carpenter TE. Direct and indirect contact rates among beef, dairy, goat, sheep, and swine herds in three California counties, with reference to control or potential foot-and-mouth disease transmission. *American Journal of Veterinary Research* 62, 1121–9, 2001

Beckett S, Garner MG. Simulating disease spread within a geographic information system environment. *Veterinaria Italiana* 43, 595–604, 2007

Burrell A. *Outbreak Control and Prevention of Animal Diseases: Economic Aspects and Policy Issues*. AGR/CA/APM(2002)19. Working Party on Agricultural Policies and Markets, Directorate for Food, Agriculture and Fisheries, Committee for Agriculture, Organisation for Economic Co-operation and Development, Paris, France, 2002

Dixon KR, Chapman JA. Harmonic mean measure of animal activity areas. *Ecology* 61, 1040–4, 1980

Ferguson NM, Donnelly CA, Anderson RM. The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. *Science* 292, 1155–60, 2001

Garner MG, Beckett S. Modelling the spread of foot-and-mouth disease in Australia. *Australian Veterinary Journal* 83, 30–8, 2005

Harvey MJ, Barbour RW. Polygon fitting of *Microtus ochrogaster* as determined by a modified minimum area method. *Journal of Mammology* 46, 398–402, 1965

Harvey N, Reeves A, Schoenbaum MA, Zagmutt-Vergara FJ, Dubé C, Hill AE, Corso BA, McNab B, Cartwright CI, Salman MD. The North American Animal Disease Spread Model: A simulation model to assist decision making in evaluating animal disease incursions. *Preventive Veterinary Medicine* 82, 176–97, 2007

Haydon DT, Kao RR, Kitching RP. The UK foot-and-mouth disease outbreak – the aftermath. *Nature Reviews. Microbiology* 2, 675–81, 2004

Honhold N, Taylor NM, Mansley LM, Paterson AD. Relationship of speed of slaughter on infected premises and intensity of culling of other premises to the rate of spread of the foot-and-mouth disease epidemic in Great Britain, 2001. *Veterinary Record* 155, 287–94, 2004

Hutber AM, Kitching RP. The role of management segregations in controlling intra-herd foot-and-mouth disease. *Tropical Animal Health and Production* 32, 285–94, 2000

Keeling MJ, Woolhouse MEJ, Shaw DJ, Matthews L, Chase-Topping M, Haydon DT, Cornell SJ, Wilesmith J, Grenfell BT. Dynamics of the 2001 UK foot-and-mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* 294, 813–7, 2001

Kitching RP, Thrusfield MV, Taylor NM. Use and abuse of mathematical models: An illustration from the 2001 foot-and-mouth disease epidemic in the United Kingdom. *Revue Scientifique et Technique de l'Office Internationale des Épizooties* 25, 293–311, 2006

Landis G, Koch G. The measurement of observer agreement for categorical data. *Biometrics* 33, 159–74, 1977

Law AM, Kelton WD. *Simulation Modelling and Analysis*. McGraw-Hill Publishing Co, New York, USA, 2000

Mangen M-J, Burrell A, Mourits M. Epidemiological and economic modelling of classical swine fever: application to the 1997/1998 Dutch epidemic. *Agricultural Systems* 81, 37–54, 2004

Sanson RL. The development of a decision support system for an animal disease emergency. *PhD thesis*, Massey University, Palmerston North, NZ, 1993

Sargent RG. Verification and validation of simulation models. In: Kuhl ME, Steiger NM, Armstrong FB, Joines JA (eds). *Proceedings of the 2005 Winter Simulation Conference*. Pp 130–43. Orlando FL, USA, 2005

Schlesinger S, Crosbie R, Gagne R, Innis G, Lalwani C, Loch J, Sylvester R, Wright R, Kheir N, Bartos D. Terminology for model credibility. *Simulation* 32, 103–4, 1979

Schoenbaum M, Disney W. Modelling alternative mitigation strategies for a hypothetical outbreak of foot-and-mouth disease in the United States. *Preventive Veterinary Medicine* 58, 25–52, 2003

Stevenson MA, Morris RS, Wilesmith JW, Stern MW. Predicting when and where foot-and-mouth disease will occur – how well did InterSpread perform in 2001? http://www.sciquest.org.nz/crusher_download.asp?article=10002213 (accessed 06 November 2007). *Proceedings of 10th Symposium of the International Society for Veterinary Epidemiology and Economics*, Viña Del Mar, Chile, 2003

Stevenson M, Sanson R, Stern M, O'Leary B, Mackereth G, Sujau M, Moles-Benfall N, Morris R. *InterSpread Plus: a spatial and stochastic simulation model of disease in animal populations*. http://www.biosecurity.govt.nz/files/pests-diseases/surveillance-review/inter-spread-plus.pdf (accessed 06 November 2007). Biosecurity New Zealand, Wellington, NZ, 2006

Taylor N. *Review of the Use of Models in Informing Disease Control Policy Development and Adjustment*. http://www.defra.gov.uk/science/documents/publications/2003/UseofModelsinDiseaseControlPolicy.pdf (accessed 06 November 2007). DEFRA, London, UK, 2003

Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. Springer-Verlag, New York, USA, 2001

Thompson D, Muriel P, Russell D, Osborne P, Bromley A, Rowland M, Creigh-Tyte S, Brown C. Economic costs of the foot-and-mouth disease outbreak in the United Kingdom in 2001. *Revue Scientifique et Technique de l'Office International des Épizooties* 21, 675–87, 2002

Wray S, Cresswell WJ, Rogers D. Dirichlet tessellations: A new, non-parametric approach to polygon fitting analysis. In: Priede IG, Swift SM (eds). *Wildlife Telemetry: Remote Monitoring and Tracking of Animals*. Pp 247–55. Ellis Horwood, New York, USA, 1992

Submitted 28 August 2007

Accepted for publication 05 November 2007

frontiers in Environmental Science

ORIGINAL RESEARCH
published: 19 March 2015
doi: 10.3389/fenvs.2015.00017

A hybrid modeling approach to simulating foot-and-mouth disease outbreaks in Australian livestock

Richard A. Bradhurst[1]*, *Sharon E. Roche*[2], *Iain J. East*[2], *Paul Kwan*[1] and *M. Graeme Garner*[2]

[1] Discipline of Computer Science, School of Science and Technology, University of New England, Armidale, NSW, Australia,
[2] Epidemiology and One Health Program, Animal Health Policy Branch, Department of Agriculture, Canberra, ACT, Australia

Foot-and-mouth disease (FMD) is a highly contagious and economically important viral disease of cloven-hoofed animals. Australia's freedom from FMD underpins a valuable trade in live animals and animal products. An outbreak of FMD would result in the loss of export markets and cause severe disruption to domestic markets. The prevention of, and contingency planning for, FMD are of key importance to government, industry, producers and the community. The spread and control of FMD is complex and dynamic due to a highly contagious multi-host pathogen operating in a heterogeneous environment across multiple jurisdictions. Epidemiological modeling is increasingly being recognized as a valuable tool for investigating the spread of disease under different conditions and the effectiveness of control strategies. Models of infectious disease can be broadly classified as: population-based models that are formulated from the top-down and employ population-level relationships to describe individual-level behavior; individual-based models that are formulated from the bottom-up and aggregate individual-level behavior to reveal population-level relationships; and hybrid models which combine the two approaches into a single model. The Australian Animal Disease Spread (AADIS) hybrid model employs a deterministic equation-based model (EBM) to model within-herd spread of FMD, and a stochastic, spatially-explicit agent-based model (ABM) to model between-herd spread and control. The EBM provides concise and computationally efficient predictions of herd prevalence and clinical signs over time. The ABM captures the complex, stochastic and heterogeneous environment in which an FMD epidemic operates. The AADIS event-driven hybrid EBM/ABM architecture is a flexible, efficient and extensible framework for modeling the spread and control of disease in livestock on a national scale. We present an overview of the AADIS hybrid approach, a description of the model's epidemiological capabilities, and a sample case study comparing two strategies for the control of FMD that illustrates some of AADIS's functionality.

Keywords: AADIS, FMD, epidemiological model, hybrid model, spatiotemporal model

OPEN ACCESS

Edited by:
Christian E. Vincenot, Kyoto University, Japan

Reviewed by:
Jagdish Krishnaswamy, Ashoka Trust for Research in Ecology and the Environment, India
Fabrizio Carteni, University of Naples Federico II, Italy

***Correspondence:**
Richard A. Bradhurst, Discipline of Computer Science, School of Science and Technology, University of New England, Armidale, NSW 2351, Australia
rbradhur@myune.edu.au

Specialty section:
This article was submitted to Environmental Informatics, a section of the journal Frontiers in Environmental Science

Received: *05 December 2014*
Paper pending published: *14 January 2015*
Accepted: *24 February 2015*
Published: *19 March 2015*

Citation:
Bradhurst RA, Roche SE, East IJ, Kwan P and Garner MG (2015) A hybrid modeling approach to simulating foot-and-mouth disease outbreaks in Australian livestock. Front. Environ. Sci. 3:17. doi: 10.3389/fenvs.2015.00017

Introduction

An outbreak of foot-and-mouth disease (FMD) in Australia would have a major economic and social impact. This includes disruption of the domestic market for livestock and products, loss

of access to international markets, severe production and income losses in livestock and related industries, and the financial, political and social pressures of eradicating the disease (Carpenter et al., 2011; Matthews, 2011; Rushton et al., 2012). The present value of total direct economic losses from an outbreak of FMD in Australia are estimated at $5.6 to $52.2 billion AUD over 10 years, depending on the size of the outbreak and the effectiveness of control (Buetre et al., 2013).

Disease managers are faced with a number of challenges when responding to incursions of serious disease such as FMD. These include: what control measures to adopt; trade and economic implications of different control measures; how to manage resources such as personnel, equipment and vaccine; access to appropriate technology such as diagnostic tools; animal welfare issues; consumer concerns, and possible public health ramifications (Garner et al., 2007). The choice of control measures can be a compromise between the requirement for large-scale implementation and what is logistically and economically feasible (Tildesley et al., 2006). Disease models are increasingly being employed as decision support tools for outbreak planning and response (Garner and Hamilton, 2011). Models are especially useful when a country has not recently experienced the disease of concern (Bates et al., 2003b), for example, the last outbreak of FMD in Australia occurred in 1872 (Bunn et al., 1998).

Models of disease spread range from simple deterministic mathematical models (Haydon et al., 1997), through to complex spatially-explicit stochastic microsimulations (Garner and Beckett, 2005; Harvey et al., 2007; Stevenson et al., 2013). Models can be distinguished on the basis of how they handle time (discrete/continuous), space (spatially-explicit/non-spatial), and chance and uncertainty (deterministic/stochastic) (Taylor, 2003). Another way of classifying models is whether they are population-based, individual-based or a combination of both. A population-based model is formulated from the top-down and employs population-level relationships to describe individual-level behavior. An example is a traditional equation-based model (EBM) which uses a system of ordinary differential equations (ODEs) to prescribe ratios of infection states in a population over time (Keeling and Rohani, 2008). The model concisely and efficiently describes how a population 'flows' between Susceptible, Exposed, Infectious and Recovered (SEIR) compartments. Compartmental EBMs carry a general assumption of homogeneous contact rates and susceptibility, i.e., individuals mix uniformly and randomly, and have an equal likelihood of contracting a disease.

While simple mathematical models can provide useful insights into disease dynamics and epidemic behavior they tend to ignore the spatial, environmental, and social dimensions of epidemiology (Perez and Dragicevic, 2009). Assumptions of homogeneous mixing of the population and model parameters not varying over the solution interval understate the complexity of an epidemic. From a disease manager's perspective, outbreaks occur in a physical, economic, technological, management, and socio-political context (Garner and Hamilton, 2011). An epidemic environment is irregular and subject to probabilistic events that dynamically reshape the spread of disease (Bansal et al., 2007; Garner and Hamilton, 2011). Spatial effects, population heterogeneity, contact structures and social behavior all influence the course of an outbreak (Caraco et al., 2001; Hagenaars et al., 2004; Galvani and May, 2005; Lloyd-Smith et al., 2005; Bansal et al., 2007; James et al., 2007).

An individual-based model is formulated from the bottom-up and aggregates individual-level behavior to reveal population-level dynamics. Relationships between individuals emerge over time, as opposed to a population-based model where the relationships are prescribed as inputs. An example is a spatially-explicit agent-based model (ABM) where autonomous individuals with independent infection states interact within an environment. In this case, the emergent behavior of the model is the spatio-temporal spread of disease across a population. Individual-based models are well-suited to complex environmental systems due to their affinity for capturing heterogeneity, stochasticity, spatiality, social systems, and policy (Hare and Deadman, 2004), and subtle interactions between individuals that are especially important during the initial and final stages of an outbreak (Germann et al., 2006; Bansal et al., 2007). A data-driven, individual-based, modeling approach has proven popular in the field of animal health policy development with stochastic, spatially-explicit, state-transition microsimulations such as AusSpread (Garner and Beckett, 2005), InterSpread Plus (ISP) (Stevenson et al., 2013), and the North American Animal Disease Spread Model (NAADSM) (Harvey et al., 2007).

In this paper, we describe the Australian Animal Disease Spread (AADIS) model. AADIS is a national-scale hybrid model of livestock disease spread and control designed to support emergency animal disease planning in Australia. For this context, we narrow the definition of a hybrid model to one that employs both population-based and individual-based modeling techniques. AADIS models within-herd spread with a deterministic EBM and between-herd spread with a spatially-explicit stochastic ABM. The model architecture and software architecture were specifically developed for efficient handling of the national livestock population. Computational efficiency is especially important for large-scale stochastic models. It is often desirable to re-run a particular scenario hundreds, possibly thousands, of times to

Abbreviations: AADIS, Australian Animal Disease Spread model; ABARES, Australian Bureau of Agricultural and Resource Economics and Sciences; ABM, Agent-based model; ABS, Australian Bureau of Statistics; AUD, Australian dollar; AUSVETPLAN, Australian Veterinary Emergency Plan (Animal Health Australia, 2014a); CA, Control Area—a controlled area enclosing an RA and subject to lower levels of movement restrictions than those applied in RAs; CSV, Comma-Separated Values; DADS, Davis Animal Disease Simulation model (Bates et al., 2003a); DCP, Dangerous Contact Premises—a premises that, based on a risk assessment, is considered highly likely to contain an FMD-infected animal(s) or contaminated animal products, equipment or other material.; DTU-DADS, Technical University of Denmark—Davis Animal Disease Simulation model (Boklund et al., 2013); EBM, Equation-based model; FMD, Foot-and-mouth disease; GIS, Geographic Information System; GSAM, Global-Scale Agent Model (Parker and Epstein, 2011); HPAI, Highly Pathogenic Avian Influenza; HPC, High-Performance Computing; ISP, InterSpread Plus (Stevenson et al., 2013); IP, Infected Premises—a premises where infection has been confirmed.; NAADSM, North American Animal Disease Spread Model (Harvey et al., 2007).; NLIS, National Livestock Identification System; ODE, Ordinary Differential Equation; RA, Restricted Area—a controlled area surrounding an IP and subject to the highest level of movement restrictions; SEIR, Susceptible Exposed Infectious Recovered; SO, Stamping Out; SORV, Stamping Out plus suppressive Ring Vaccination; SQL, Structured Query Language.

see if patterns emerge from the underlying stochastic processes. Although the AADIS architecture supports any pathogen, FMD is the development test-case.

Modeling Context

Foot-and-Mouth Disease

FMD is an acute, highly contagious viral disease of domestic and wild cloven-hoofed animals. The disease is clinically characterized by the formation of vesicles and erosions in the mouth and nostrils, on the teats, and on the skin between and above the hoofs (Meyer and Knudsen, 2001; Animal Health Australia, 2014a). The FMD virus spreads between hosts through direct contact (e.g., movement of live animals between farms, and between farms and markets), indirect contact (e.g., livestock products, byproducts, and fomites), and aerosol (Meyer and Knudsen, 2001). Australia is a significant livestock producer and a major exporter of livestock, livestock products, and livestock genetic material. An outbreak of FMD would have severe economic consequences for the economy, in particular the loss of export markets (Buetre et al., 2013). Because of the serious consequences of an FMD outbreak, Australia invests considerable resources in prevention and planning.

Australia's approach to managing an incursion of FMD is described in the Australian Veterinary Emergency Plan—AUSVETPLAN (Animal Health Australia, 2014a). In brief, the policy is to eradicate the disease as quickly as possible using stamping out, which involves culling and disposal of infected and exposed animals. Standard zoo-sanitary measures and movement restrictions are also applied, with a minimum 3-day national livestock stand-still and the establishment of control zones around infected premises (IPs) and dangerous contact premises (DCPs). Vaccination is identified as an option under some circumstances in AUSVETPLAN.

Livestock Production Systems

Livestock production in Australia is largely based on extensive grazing and is dominated by wool, sheepmeat, beef, and dairy. Australia also has smaller intensive pig and poultry industries (Animal Health Australia, 2014b). The livestock industry is diverse and extends from the beef cattle areas of tropical north Queensland to the sheep areas of temperate southern Tasmania, and from the dairying areas of coastal New South Wales to the merino wool producing areas of Western Australia (Garner et al., 2002). The main industries that would be directly affected by FMD are beef, dairy, wool, sheepmeat, and pigs. Australia has approximately 74 million sheep, 28 million cattle and 2 million pigs on approximately 78,000 commercial farms (Australian Bureau of Statistics, 2012), with a further estimated 104,000 smallholder/lifestyle farms. From a disease transmission perspective, the key unit of interest is a herd, defined as a group of animals of the same species that is managed as a single group. Commercial farms in Australia can be large and may consist of more than one herd of the same or different species, e.g., sheep-beef farms.

Australia is a federation made up of six states and two mainland territories. The Australian Government is responsible for quarantine, disease reporting, export certification, and trade government. State and territory governments are responsible for animal health services within their respective jurisdictions. This means that while there are national policies for managing diseases like FMD, the actual control measures are administered by the jurisdictions under their own legislation. For disease control purposes, it is the farming enterprise rather than the herd that is the key unit.

AADIS Hybrid Approach

To study FMD in Australia on a national scale, a model needs to handle approximately 240,000 herds across a variety of species and production systems, as well as incorporating regional heterogeneity in disease transmission and jurisdictional variations in control measures and resourcing. To address this complexity, AADIS employs a hybrid model architecture that combines population-based modeling with individual-based modeling. This approach provides computationally efficient within-herd spread and captures the rich heterogeneous environment in which between-herd spread operates. For modeling purposes, the Australian livestock population has been categorized into 11 herd types and 10 farm types (**Table 1**). A herd has static attributes such as type, size, location, jurisdiction, and local government area, and dynamic attributes such as infection status. A farm is made up of one or more herds. Spatially, a farm and its constituent herds are defined as a point identified by latitude and longitude. The herd population is synthesized from agricultural census data (Australian Bureau of Statistics, 2012) and industry reports and data.

Equation-Based Modeling of Within-Herd Disease Spread

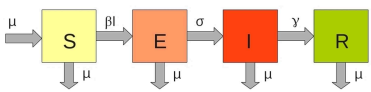
AADIS considers a herd to be well-mixed from a disease transmission point of view, i.e., all members of the herd are equally likely to contract a disease. This is a reasonable simplification for modeling the spread of disease at a national-scale, and one that lends itself to a population-based approach (Bradhurst et al., 2013). AADIS employs a non-spatial, deterministic SEIR compartmental EBM to represent within-herd spread of FMD (**Figure 1**). The approach is similar to that described by Keeling and Rohani (2008).

Each herd has its own ODE system customized for the herd type and the pathogen under study (**Figure 2**). AADIS simplifies a herd's size by considering it to be constant in the absence of culling. When a susceptible herd becomes infected the ODE system is solved numerically via a fourth-order Runge Kutta method (Cash and Karp, 1990), to yield the SEIR compartmental ratios over time. The EBM generates curves describing the prevalence and clinical signs of the infected herd. The EBM approach is computationally efficient as the solution remains in place up until an external asynchronous event acts upon the herd. If a herd is vaccinated and immunity levels increase, the EBM reacts by resolving the ODE system to yield updated SEIR compartment ratios from that point in time onwards (**Figure 3**). The EBM thus adapts and provides a dynamic representation of the within-herd infection state and presence of clinical signs.

TABLE 1 | Herd and farm types used in AADIS.

Farm type	Number of farms	Mean farm population size (min–max)	Herd type	Number of herds
Extensive beef	1331	1909 (1200–46, 575)	Extensive beef	3993
Intensive beef	51,383	280 (30 – 7436)	Intensive beef	51,383
Feedlot	508	1825 (100–39, 963)	Feedlot	508
Mixed beef/sheep	21,556	242 (30 – 5700)	Mixed beef	21,556
			Mixed sheep	21,556
Dairy	8675	298 (40 – 2742)	Dairy	8675
Small pigs	1873	244 (40 – 4850)	Small pigs	1873
Large pigs	333	4922 (1000–17, 896)	Large pigs	333
Sheep	22,150	1649 (20–44, 000)	Sheep	22,150
Small holder	103,641	5 (1 – 14)	Small holder	103,641
Total	202,775			235,668

$$\frac{dS}{dt} = \mu - \beta I S - \mu S$$
$$\frac{dE}{dt} = \beta I S - \mu E - \sigma E$$
$$\frac{dI}{dt} = \sigma E - \mu I - \gamma I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$



where S = proportion of the herd that are susceptible
E = proportion of the herd that are exposed
I = proportion of the herd that are infectious
R = proportion of the herd that are recovered
$\frac{1}{\mu}$ = average natural lifespan of the host, (μ = birth rate = natural mortality rate)
β = effective contact rate (contact rate × transmission probability)
$\frac{1}{\sigma}$ = average duration of the latent period, (σ = progression rate from exposed to infectious)
$\frac{1}{\gamma}$ = average duration of the infectious period, (γ = recovery rate)

FIGURE 1 | ODE system used by AADIS to model within-herd spread of FMD.

Agent-Based Modeling of Between-Herd Disease Spread and Control

Whilst a herd is viewed as a population for within-herd disease spread, it is somewhat paradoxically also viewed as an individual for between-herd spread (**Figure 2**). Aggregated herd-level infectious, latent (exposed), and clinical prevalence generated by the EBM, are inputs for modeling disease spread between herds. This is a sensible simplification for a model of national-scale, especially for a highly contagious disease such as FMD that when introduced into a susceptible herd will typically progress unchecked (Meyer and Knudsen, 2001; Carpenter et al., 2003). A herd is thus viewed as an atomic agent participating in an ABM for the purposes of between-herd spread.

While within-herd disease spread is deterministic and non-spatial, between-herd disease spread is highly stochastic and spatially-explicit. This is achieved through a rich ABM environment comprising disease spread pathways and control measures. The spread of disease is modeled with the following pathways:

- *Direct contact* – movement of live animals between premises,
- *Market/saleyard spread* – movement of live animals in and out of markets/saleyards,
- *Indirect contact* – movement of animal products, byproducts or fomites between herds,
- *Local spread* – proximity-based contact, e.g., over a boundary fence shared by adjoining premises,
- *Airborne transmission* – virus excreted by animals in aerosol form that remains viable in the air.

Each spread pathway has an algorithm that determines on any given simulation day whether disease transfers from an infectious herd to susceptible herd(s). AADIS introduces stochasticity through Monte Carlo sampling of probability distribution

functions (Vose, 2008). The spread of disease between heterogeneous herds is well-suited to an individual-based model such as an ABM.

The control of disease is also part of the ABM environment. This includes movement restrictions, surveillance and tracing, IP operations, resource management and vaccination. The emergent behavior of the ABM is the spatiotemporal spread of disease across the population and the subsequent activities to control and eradicate the disease. The disease spread pathways and control measures can be thought of as *components* of the ABM environment. A component has autonomous logic, its own thread of execution and a blocking queue for receiving asynchronous events. Each component of the AADIS ABM environment operates independently and concurrently.

AADIS Functional Description

Transmission Pathways

AADIS models five independent means by which FMD can be transmitted between herds:

Direct Contact Spread

Direct contact spread is driven by the movements of live animals between herds. The expected number, size and destination of daily movements into and out of herds, stratified by month, is derived from various reports and industry sources (AusVet Animal Health Services, 2005, 2006; Hassall and Associates, 2006; Kokic and Mues, 2006; East and Foreman, 2011; East et al., 2014). AADIS only models movements from infected herds since it

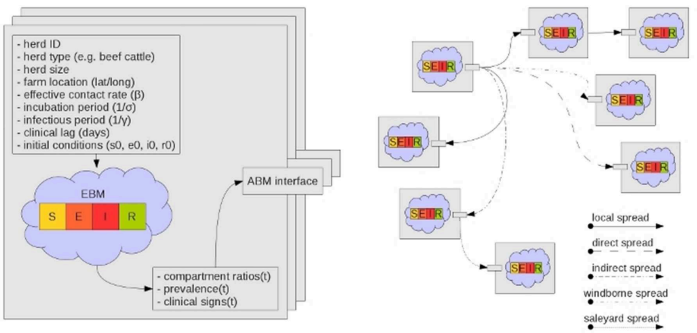


FIGURE 2 | Each herd instance has a customized SEIR ODE-based EBM. The ABM stochastically establishes infection connection paths between herds (Bradhurst et al., 2013).

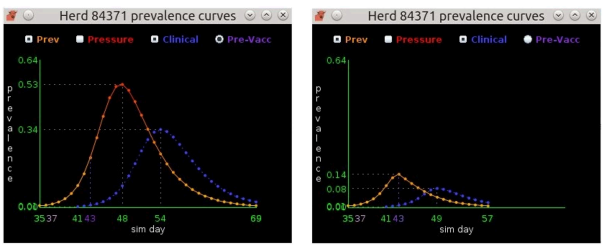


FIGURE 3 | The prevalence curves on the left depict the EBM solution for a non-vaccinated beef herd. Infection starts on day 35, peaks at 53% prevalence on day 48, and ends on day 69. The prevalence curves on the right show the same herd, but with vaccination occurring on day 37. Susceptible animals in the herd achieve immunity on day 43 resulting in a greatly diminished peak prevalence of 14% and an earlier end to infection on day 57.

would be computationally prohibitive to consider all movements from all herds. For each infected herd, the daily likelihood of a movement, the type of herd the movement is directed to, and the movement distance and direction is determined stochastically. This is based on configuration data that includes movement frequencies, distance distributions and contact matrices.

Transmission depends on the prevalence of infection in the source herd and the consignment size. The probability that a consignment contains at least one exposed or infectious animal is given by:

$$p_i = 1 - \left[1 - p(t)\right]^n \quad (1)$$

where, p_i = probability of infection, $p(t)$ = prevalence of infection in the source herd at time *t*, where prevalence is defined as the proportion of infectious and exposed animals in the herd (per the EBM), n = consignment size.

When a susceptible herd becomes infected an EBM is created and solved with initial conditions based on the proportion of infectious and exposed animals in the consignment, and the size of the destination herd.

Saleyard/Market Spread

Markets and saleyards have the potential to greatly amplify an outbreak prior to the disease being recognized and controls implemented (Gibbens et al., 2001; Mansley et al., 2003). This is because disease transmission is greatly facilitated by the large number of susceptible animals, and the degree of mixing and partitioning of animals into consignments. Outgoing consignments may then be moved to multiple, widely dispersed locations.

AADIS provides two options for simulating saleyard spread, depending on the availability of data. A simplified module takes into account the frequency and destination of consignments from different herd types. On any given day the likelihood that an infected herd sends animals to a saleyard is determined stochastically. Each infected consignment to a saleyard generates multiple infected outgoing consignments based on beta pert distributions. A more explicit representation of saleyard spread is available which takes into account the type, frequency and timing of livestock sales. This approach is driven by specific buying and selling patterns at individual livestock sales (Hassall and Associates, 2007). AADIS models plausible sale events during a simulation. If a sale happens to involve an infected herd, then a series of stochastic decisions are made to determine the number of outgoing infected consignments, the consignment destination types (herd, feedlot or abattoir), and destination locations. Infection is transmitted to the destination herds with a force relative to the viral load in the consignment.

Indirect Contact Spread

Indirect contact transmission arises from the movement between herds of contaminated animal products, byproducts, and fomites such as equipment, people and vehicles. Potential sources include veterinarians, shearing contractors, artificial insemination technicians, milk tankers, and feed delivery vehicles. Indirect contacts can be categorized as high, medium or low according to their potential for transmitting infection (Nielen et al., 1996; Bates et al., 2001; Sanson, 2005; Noremark et al., 2013). In the interests of computational efficiency, AADIS only uses a single category of indirect contacts with a specified average (baseline) probability of transmission. The user can parameterize this to represent different risk profiles. Compared to direct contacts, there is limited data on indirect contacts. The type and location of exposed herds is determined stochastically using a contact matrix and distance distributions by herd type.

If a herd is exposed through indirect contact, the probability of transmission depends on the viral load of the source herd, the relative infectiousness of the source herd (based on species and herd size), environmental conditions that influence virus survival, biosecurity practices, and relative susceptibility of the exposed herd (based on species and herd size).

$$p_i = P_b\, p(t)\; w_i\, w_s\, w_b\, w_x \quad (2)$$

where, p_i = probability that an indirect contact results in an infection, P_b = baseline probability that any indirect contact results in infection, $p(t)$ = normalized prevalence of the source herd at time *t*, w_i = infectivity weight of the source herd, w_s = susceptibility weight of the destination herd, w_b = biosecurity weight of the destination herd, w_x = seasonal weight.

Local Spread

Local spread covers the transmission of disease from an infected herd to susceptible herds in close proximity (default within 3 km). The actual means of transmission is poorly understood and could involve local aerosol spread across fences, straying of stock, vehicles, people, run off, sharing of equipment between neighbors, etc. (Gibbens et al., 2001). AADIS uses a spatial kernel approach to represent local spread, with all susceptible herds inside the local spread radius at risk. The probability of transmission for at-risk herds is decided stochastically taking into account infectious prevalence in the source herd, infectivity of the source herd (based on species and size), susceptibility of the destination herd, biosecurity measures in place at the destination premises, and distance between the source and destination herds. The influence of distance between the source herd and target herds is described by a linear decay function—the closer a herd is to the source, the greater the probability of transmission. Local spread can also occur between herds that are co-resident on the same farm, with the probability of transmission increased to reflect the higher potential for local contact between herds managed on the same farm.

$$p_i = P_b\, p(t)\; w_i\, w_s\, w_b\, w_x\, w_d\, w_n \quad (3)$$

where p_i = probability that a local contact results in an infection, P_b = baseline probability that a local contact between farms results in infection, $p(t)$ = normalized prevalence of the source herd at time *t*, w_i = infectivity weight of the source herd, w_s = susceptibility weight of the destination herd, w_b = biosecurity weight of the destination herd, w_x = seasonal weight, w_d = distance weight, w_n = detection weight.

Airborne Spread

Airborne spread is the infection of susceptible animals by virus conveyed on the wind. Pigs pose the greatest threat for airborne

spread because of their potential to excrete large quantities of virus relative to other species. Airborne spread requires a concentrated source of virus, appropriate weather conditions and susceptible animals downwind (Donaldson and Alexandersen, 2002). AADIS assumes that only pig herds are capable of transmitting FMD by airborne spread beyond a distance of 3 km. Aerosol transmissions within 3 km are captured by the local spread pathway. For each simulation day, the weather station closest to each infected pig herd is queried for conditions conducive to airborne spread (Garner et al., 2006). If suitable, a sector is constructed at the infected herd's location in the prevailing wind direction, subtended by a configurable angle (**Figure 4**). The sector radius represents the extent of the viral plume on that day and is determined by the number of infectious pigs in the source herd (Donaldson et al., 2001). Susceptible herds within the sector are identified, excluding those within 3 km. The probability of transmission takes into account the susceptible herd species, the size of the herd, and the distance of the susceptible herd from the infected herd.

$$p_i = \left[1 - \left(1 - P_{sp}\right)^n\right] w_d \quad (4)$$

where, p_i = probability that a susceptible herd will become infected, P_{sp} = probability that a single animal of the susceptible species will become infected, n = size of the susceptible herd, w_d = distance weight.

The distance weight models the diffusion of the plume over distance from the source herds, and hence the diminishing risk of transmission. Distance weight is configurable as either a linear or exponential decay function.

Disease Control

Australia's FMD policy is to eradicate the disease in the shortest possible time using a combination of strategies, while minimizing economic impact, (Animal Health Australia, 2014a). Mandatory control strategies include:

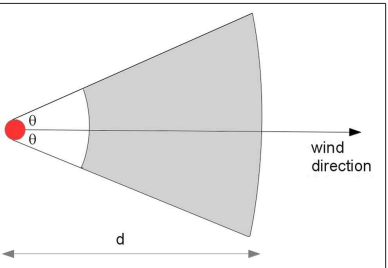


FIGURE 4 | Downwind extent of airborne spread for an infected pig herd.

- quarantine and movement controls of animals, animal products and fomites in declared areas in order to minimize the spread of infection
- tracing and surveillance to determine the source and extent of infection
- valuation and destruction of animals on infected premises and potentially on dangerous contact premises
- disposal of destroyed animals and infected animal products, and decontamination of depopulated premises.

Optional control strategies include:

- vaccination to reduce susceptibility of animals to infection and clinical disease, and potentially reduce virus excretion
- pre-emptive destruction of susceptible animals in order to minimize the spread of infection
- zoning and/or compartmentalization (to support trade)
- risk-based movement controls.

The farm is the population unit of interest for disease control. An AADIS farm has static attributes such as type and constituent herds, and dynamic attributes such as premises classification and declared area. The main simulated control strategies are movement restrictions, surveillance, tracing, IP operations and vaccination. The control and eradication phase of an outbreak commences after the declaration of the first infected premises. The day of first detection is either determined stochastically (using pre-configured probabilities of reporting by herd type, and clinical prevalence), or occurs on a fixed day at a specific or randomly selected farm.

Movement Restrictions

A national livestock standstill (minimum of 3 days), is implemented immediately following detection of the first IP. AADIS models livestock standstill by restricting the direct and saleyard spread pathways. The level of restriction depends on standstill status, type of control area, and the spread pathway being throttled. A compliance percentage for each pathway is defined in the AADIS configuration data to allow for the possibility of illegal movements during the standstill. The AADIS configuration data defines the length of the national standstill by jurisdiction. This reflects how individual jurisdictions may extend a standstill beyond the initial 3-day national period.

Controlled areas are established around each infected premises in order to restrict the movement of livestock, products and other material. The controlled areas are defined and enforced per-jurisdiction, and may be designated areas (local government, state/territory), or radius-based per IP. There are two levels of control: Restricted Areas (RAs) that immediately enclose IPs, and Control Areas (CAs) that enclose RAs. RAs have the highest level of control while CAs have a lower level of control (Animal Health Australia, 2014a). AADIS models the imposition of controlled areas in a staged manner. Larger controlled areas are enforced at the start of an outbreak. As the control program progresses, the dimensions of the controlled areas are reduced according to per-jurisdictional preferences. A radius-based controlled area is clipped to fall within the jurisdictional boundaries of the subject

IP. When IPs are clustered a meta-RA and meta-CA are formed from the union of the constituent RAs and CAs.

Surveillance and Tracing

Surveillance is the process by which new infections are identified and declared. During an FMD outbreak, surveillance is used to detect new outbreaks, define the extent of infection, and demonstrate freedom in uninfected areas (Animal Health Australia, 2014a).

AADIS allows for reporting of suspect cases on an *ad hoc* basis by owners/inspectors or others. This represents one of the most important mechanisms for finding new IPs (McLaws et al., 2007). AADIS commences suspect case reporting the day after the first IP has been declared, and allows for both true positive and false positive reports. False positive reports identify herds that are exhibiting symptoms but are not actually infected with FMD. True positive reports are generated stochastically based on an infected herd's clinical prevalence, the probability of reporting and the expected time to report. The latter two parameters are defined per herd-type in the AADIS configuration data. The number of false positive reports generated is proportional to an *n*-day (default 3), moving average number of true positive reports. The default ratio of false to true reports is 2.34 based on McLaws et al. (2007). The modeling of both true and false reports facilitates more realistic modeling of surveillance, i.e., team resources are consumed regardless of whether a surveillance visit yields a positive assessment or not. AADIS also models the active inspection of premises within RAs. All farms within a designated distance of IPs are subject to a configurable inspection schedule (number and frequency of inspections).

Tracing is the identification of movements onto and off IPs in order to ascertain where infection may have come from, or gone to. AUSVETPLAN provides minimum periods over which tracing should be carried out (Animal Health Australia, 2014a). Tracing includes animals, products, equipment, vehicles and people. Traced premises may be true cases (and thus infected), or false (not infected). AADIS can readily identify true traces by following infection chains during a simulation, allowing for variable tracing effectiveness by herd type and pathway (direct contact vs. indirect contact), and tracing duration. False forward traces are obtained by applying the direct and indirect spread pathways to a premises of interest within the forward tracing window. False backward traces are obtained by reversing the direct and indirect spread pathways over the backwards tracing window (i.e., modeling movements onto the premises of interest). This approach results in a set of plausible false traces, i.e., premises of a suitable type and location that could well have been sources or destinations of movements of concern.

Premises that require visits by surveillance teams are identified through tracing, active inspection of premises within RAs, and reporting of suspect premises. Laboratory samples are taken when needed. Surveillance visits are prioritized according to risk (Animal Health Australia, 2014a). AADIS maintains a resource-constrained dynamic queue of premises awaiting a surveillance visit. Visits are prioritized according to a configurable scheme that takes into account premises classification, declared area and herd type. If multiple premises have the same priority, then arbitration is based on how long a premises has been waiting for a visit. The visit duration (based on herd type), visit frequency (based on priority), and overall surveillance period are configurable.

IP Operations

IP Operations is comprised of the valuation, destruction and disposal of animals (stamping out), and decontamination of premises. Stamping out is Australia's default initial policy for controlling an outbreak of FMD (Animal Health Australia, 2014a). It is considered the fastest way to reduce viral excretions on IPs and thus dampen spread. Stamping out is implemented on all IPs, and potentially on DCPs, subject to risk assessment.

Premises undergoing IP Operations transition through the following states: cull pending, cull in progress, disposal pending, disposal in progress, decontamination pending, decontamination in progress, and resolved. Each jurisdiction has separate pools of teams for culling, disposal and decontamination. When a pool is exhausted (i.e., all of the teams are on assignment), pending jobs are held in a queue. Visits to premises are prioritized based on premises classification, herd/species priority, herd size, time in queue, and proximity to an IP. The times required for a premises to undergo culling, disposal and decontamination are defined by herd type in the AADIS configuration data.

Vaccination

Vaccination is one of the available options to support stamping out of an FMD outbreak. The decision to vaccinate and the specific role of vaccination in an FMD response varies according to the specific outbreak scenario (Animal Health Australia, 2014a). Vaccination strategies include:

- *Suppressive* – vaccination is carried out inside known infected areas (RAs) in order to suppress virus production in at-risk and exposed herds to reduce further spread.
- *Protective* – vaccination is carried out outside known infected areas in order to protect susceptible animals from infection.
- *Mass* – vaccination is carried out across a broad area to large numbers of animals. This strategy could be applied if an outbreak is not under control and there is a risk of spread escalating.

AADIS provides two triggers for commencing a vaccination program: on a configurable day into the control program, or once a configurable number of IPs has been declared. AADIS models all vaccination policies with an annulus of configurable inner and outer radii. The inner radius is set to zero for suppressive and mass vaccination. A vaccination annulus is established around each target IP, and eligible premises inside the annulus are scheduled for vaccination. The user can select to only vaccinate around IPs found on or after the day the vaccination program begins, or around all new and previously identified IPs. The vaccination candidates inside each annulus are prioritized according to herd type, herd size, and proximity to the nearest IP. It is also possible to omit certain herd types from vaccination. The direction of vaccination (from the outside in, or from the inside out), is set in the AADIS configuration data.

The effect of vaccination is to increase herd immunity (i.e., reduce a herd's susceptibility to infection) over time. When a partially immune herd is exposed to infection, the virus production profile generated by the EBM reflects that some of the animals have protective immunity.

As with surveillance and IP operations, the ability to implement a vaccination program depends on the availability of resources. Each jurisdiction has a separate pool of vaccination teams. When a pool is exhausted (i.e., all of the teams are on assignment), pending jobs are held in a queue. Visits to premises are prioritized according to herd type, herd size, time in queue, and proximity to an IP. The time required for a premises to undergo vaccination is defined by herd type in the AADIS configuration data.

Resourcing

The resources required to manage an emergency animal disease outbreak include personnel (e.g., veterinarians, animal health officers, control center staff), equipment (e.g., vehicles), facilities (e.g., laboratories) and consumables (e.g., vaccine, disinfectant). Some aspects of disease control and eradication are resource-intensive and the lack of resources can severely hamper the response to an outbreak (Matthews, 2011; Roche et al., 2014). AADIS models the personnel resources required for key operational activities: surveillance, culling, disposal, decontamination, and vaccination. As state and territory governments are responsible for emergency animal disease management within their own boundaries (Animal Health Australia, 2014a), the teams are organized into pools by jurisdiction, i.e., each jurisdiction has five pools. It is anticipated that resource levels ramp up over time, so initially the pools are small and increase in a linear manner up to the maximum size. The starting point, duration of the ramp-up and maximum pool size are defined in the AADIS configuration data by resource type and by jurisdiction. AADIS tracks the availability and allocation of resources to provide immediate feedback as to whether/where the control program is resource constrained (**Figure 5**).

Model Implementation

AADIS is implemented in Java (Oracle, 2014) and employs open-source products such as PostgreSQL (PostgreSQL, 2014) and OpenMap (BBN, 2014). AADIS runs under either Linux™ or Windows™ and has an asynchronous software architecture with concurrency achieved through Java threads. This takes good advantage of the inexpensive parallelism available on the quad-core x64 target machine. Although C and C++ are perhaps more typical language choices for computationally intense applications, Java offers the advantage of platform-independence and a rich collection of utility libraries. Parker and Epstein (2011) describe how the Java-based GSAM pandemic model scales up to 6.5 billion agents distributed across a 32-node high-performance computing (HPC) cluster.

AADIS is able to run complex disease spread and control scenarios across the entire Australian population of FMD-susceptible herds efficiently on a single desktop platform. For example, a 100-day national outbreak with all disease spread pathways enabled, all control measures deployed, dynamic resourcing, report writing, and real-time visualization takes around 10 s to complete on a quad-core laptop with 16 GB RAM.

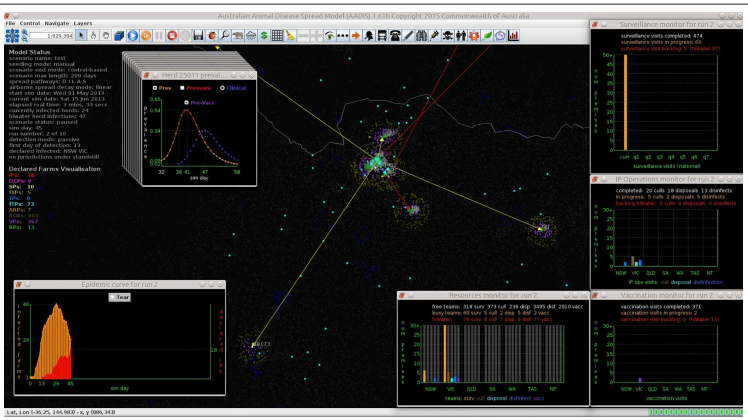


FIGURE 5 | Dynamic visualization of outbreak dynamics.

This is achieved through several strategies including the hybrid model architecture, asynchronous software architecture, a grid-based spatial indexing system (in lieu of geospatial Structured Query Language (SQL) exchanges with the database server), and lightweight agents. Implementation and performance details of interest will feature in a future paper. **Figure 6** provides a summary of the AADIS subsystems and the main relationships between them.

Simulation Flow

AADIS operates in discrete time steps of a day. At the start of a simulation day, the disease spread components and the control components access the herd/farm initial conditions for the day. All components then independently and concurrently proceed with their daily processing, making various stochastic decisions on the spread and control of disease. As each component finishes its daily processing, a set of herd/farm update requests are sent

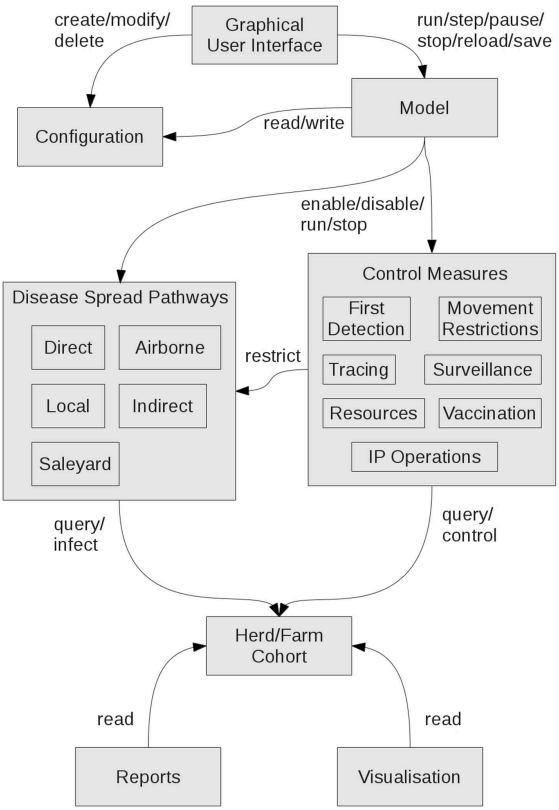


FIGURE 6 | AADIS subsystems.

asynchronously to the ABM component scheduler where they are queued. When all updates have been received, they are collated and submitted to the cohort of herd/farm agents. The new herd/farm reality is then available for all components at the start of the next simulation day. This concurrent approach is computationally efficient and reflects the reality that spread and control proceed independently and in parallel during an outbreak. The scheduler arbitrates whenever one or more components attempt to act upon the same herd/farm on the same day. The arbitration may be random or rule-based. For example, if the direct and indirect spread pathways both attempt to infect the same herd on the same day, then the scheduler randomly selects one pathway to succeed. On the other hand, if for example, the IP Operations component and the Vaccination component both attempt to control the same farm on the same day, then the scheduler always gives priority to IP Operations.

Configuration Data

AADIS has three levels of configuration:

- Project data for the study at hand includes the herd population, weather data, movement patterns and pathogen specific parameters. This data typically does not change often and may be large with cross-dependencies. The project data is stored in a relational database (PostgreSQL, 2014), and any changes require a database rebuild (which ensures referential integrity).
- Scenario-specific data is stored in a Java properties file that is persistent across multiple invocations of the model. The data is stored outside the database and so changes do not trigger a database rebuild.
- The graphical user interface can be used to make short-term adjustments of selected configuration data. The changes only last for the current invocation of the model.

Outputs

As AADIS is a stochastic model, it generates a range of possible outcomes when run with the same starting parameters. When modeling a specific scenario, multiple model runs (iterations) are used to generate a probability distribution of potential outcomes. Results of individual runs and summaries of groups of runs are produced. AADIS provides both tabular and graphical outputs.

Tabular

The formal outputs of an AADIS scenario run are comma-separated values (CSV) files. These contain a range of metrics at the herd, farm and scenario level, and are used for subsequent epidemiological analysis.

Graphical

AADIS provides three modes for visualizing an outbreak in progress:

- *Within-herd spread (EBM)* – infected herds are represented as heat-colored dots reflecting the viral load.
- *Between-herd spread (ABM)* – infected herds are represented as color-coded dots reflecting the particular pathway that triggered the infection. There is an option of displaying each pathway connection as a vector – thus depicting the entire infection network.
- *Control (ABM)* – farms are represented as color-coded dots reflecting the current premises classification.

AADIS provides a range of graphical utilities for the dynamic display of herd prevalence curves, epidemic curves, convex hull of infection, controlled areas, traces, resource usage, resource backlog, and peak resource levels (**Figure 5**).

Sample Case Study

The following simple epidemiological case study is provided to illustrate how AADIS can be used to address policy issues.

Outbreak Scenario

The south-east of Australia is an agriculturally intensive area that has previously been identified as vulnerable to an FMD outbreak (East et al., 2013). The Goulburn Valley is a 14,287 km^2 sub-region of Victoria with significant cattle and horticultural sectors (Regional Development Victoria, 2010). The dairy industry in this region comprises around 3000 farms and accounts for approximately 13% of Australia's milk production (Department of Environment and Primary Industries, 2015). Other livestock-based sectors in the region include beef, wool, sheepmeat, and pigs.

We assume FMD is introduced into the Goulburn Valley with the primary case occurring on a pig farm with a population of 3209 pigs. The farm has 20 neighboring farms within a 3 km radius. The outbreak occurs in May when the usual cool weather favors the survival of FMD virus outside a host. Detection of the index case occurs 21 days after the primary infection. **Table 2** lists some of the key EBM parameter values.

Two strategies for controlling the outbreak were assessed:

(1) Stamping out of infected premises (SO),
(2) Stamping out of infected premises plus suppressive ring vaccination (SORV).

TABLE 2 | Selected EBM ODE parameters.

Herd type	Effective contact rate	Latent period (days)	Infectious period (days)
Extensive beef	0.7	2	4
Intensive beef	2	2	4
Feedlot	8	2	4
Mixed beef	2	2	4
Mixed sheep	0.8	2	7
Dairy	6	2	4
Small pigs	6	1	4
Large pigs	8	1	4
Sheep	0.8	2	7
Small holder	2	2	5

Selected parameter settings for the control strategies are provided in **Table 3**. Note that this is a simplification of the model setup as only a subset of key parameters are described.

Method

The simulation was run 500 times for each control strategy and the following outputs compared:

- duration of the outbreak (defined as the number of days from when the index case was declared to when the last infected premises was resolved)
- cumulative number of infected premises
- cumulative number of culled premises
- cumulative number of culled animals
- cumulative number of vaccinated premises
- cumulative number of vaccinated animals

TABLE 3 | Selected control program parameter settings.

Control parameter	Value
National livestock standstill	3 days
Restricted area (RA)	Circle of 3 km radius enclosing each IP
Controlled area (CA)	Circle of 10 km radius enclosing each IP
Num days to report suspect premises after clinical signs	0–19 days (herd type-dependent)
Probability of reporting suspect premises	70–100% (herd type-dependent)
Ratio of false suspect premises reports to true reports	2.34:1
Forward tracing window	14 days
Backward tracing window	14 days
Time needed for a direct trace	0–4 days (species-dependent)
Time needed for an indirect trace	1–5 days (species-dependent)
Effectiveness of direct tracing	70–100% (species-dependent)
Effectiveness of indirect tracing	70–90% (species-dependent)
Non-compliance with direct movement controls inside RA	2%
Non-compliance with direct movement controls inside CA	2%
Reduction of indirect movements inside RA	15%
Reduction of indirect movements inside CA	50%
Surveillance visit duration	0.5 day (herd type-dependent)
Max number of surveillance teams	20 Per jurisdiction
Max number of culling teams	20 Per jurisdiction
Max number of disposal teams	20 Per jurisdiction
Max number of decontamination teams	20 Per jurisdiction
Max number of vaccination teams	200 Per jurisdiction
Days to cull a herd	0.5–14 (herd type-dependent)
Days to dispose a herd	0.5–18 (herd type-dependent)
Days to decontaminate a premises	1–28 (herd type-dependent)
Start of vaccination program	Seventh day of the control program
Days to vaccinate a herd	0.5–7 (herd type-dependent)
Vaccination annulus radii (km)	1, 3
Vaccination direction	Outside-in

In addition, a simple sensitivity analysis was carried out on selected parameters under strategy SO.

- time to first detection (7, 14, 21, 28 days)
- duration of the national standstill (0, 3, 7, 10 days)

The test hardware platform was a quad-core laptop with 16 GB RAM running 64-bit Kubuntu Linux™.

The Stata/IC statistical package (Stata, 2014) was used to analyse the distributions of the key model outputs. Data sets were imported into Stata and checked for normality. Non-parametric statistical methods were used throughout this analysis as some data sets were non-normal and could not be transformed to normality by standard transformation techniques. The number of infected premises, outbreak duration, number of culled animals, number of vaccinated premises and number of vaccinated animals were analyzed using the Kruskal-Wallis test for comparison of multiple independent groups of data. *Post hoc* analysis to identify differences between strategies was conducted using the Kruskal-Wallis test with the significance level adjusted per the Bonferroni correction for multiple pairwise comparisons. Model outcomes were expressed as medians with 90% confidence intervals.

Results

Figures 7–9 provide visualization snapshots at day 21 of run number 1 (of 500) of the baseline stamping out scenario. **Figure 7** shows how within-herd spread is represented as heat-colors reflecting prevalence levels generated by the EBM of each infected herd. **Figure 7** also illustrates the optional display of the convex hull area of infection, in this case 33 km^2. **Figure 8** shows the infection network generated by the ABM, with color-coded vectors reflecting the particular spread pathway that triggered. At this stage in the outbreak there is only local (green) and airborne (cyan) spread emanating from the primary case pig herd. **Figure 9** shows the outbreak from a disease management point of view. Despite there being 13 infected herds on day 21, there is only one known infected premises (red). **Figure 9** also shows two optional popup windows: the prevalence curves for a herd (in this case the index case), and the epidemic curve depicting declared infected premises vs. actual infected premises. These outputs demonstrate the potential of AADIS as a training tool that provides various visualizations of disease transmission, and also contrasts a disease manager's incomplete view of an outbreak (what is known), with the physical reality (infected herds in the population).

In this study we investigated the effect of incorporating suppressive ring vaccination into the control program for an FMD outbreak. Strategy SORV was effective in reducing both the size and duration of an outbreak when compared to the baseline SO strategy. There were significantly less IPs, significantly shorter outbreaks, and significantly less culled animals than stamping out alone ($p < 0.05$) (**Figure 10** and **Table 4**). SORV was particularly effective in reducing the likelihood of a very large outbreak, which could be an important consideration for a disease manager.

The sensitivity analyses showed that findings are significantly influenced by the time to first detection. Varying the time to detection for strategy SO produced strongly correlated changes

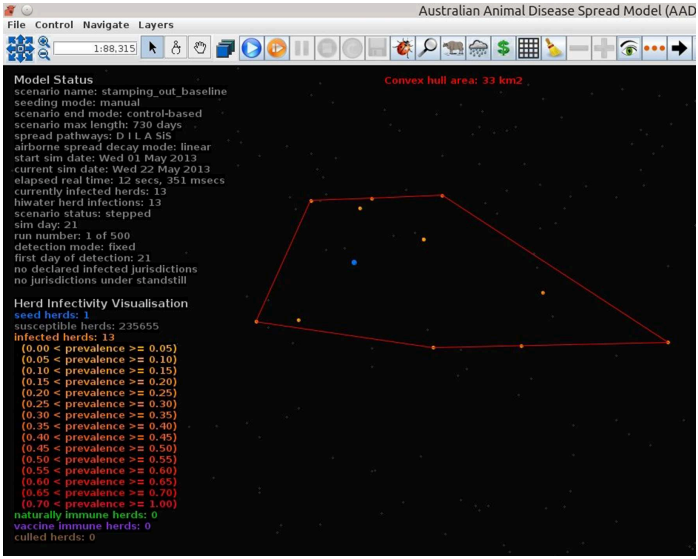


FIGURE 7 | Visualization of within-herd prevalence as heat-colors.

to the number of IPs, outbreak duration, and number of culled animals ($p < 0.05$) (**Table 4**). The findings were less sensitive to the duration of the national livestock standstill with only a 0-day standstill and a 10-day standstill producing significantly different outcomes ($p < 0.05$). This suggests that for the outbreak scenario, there is perhaps not a significant advantage in extending the default 3-day standstill.

Discussion

An incursion of FMD into Australia would have severe economic consequences and Australia thus invests heavily in prevention and contingency planning. The control and eradication of FMD is challenging due to the complexities of a highly contagious and multi-host pathogen operating in a heterogeneous environment across multiple jurisdictions. Models of disease spread and control are increasingly recognized as valuable tools for informing policy. Population-based approaches and individual-based approaches have both been used to model the spread and control of FMD and inform policy makers and disease managers. The hybrid approach of AADIS combines the advantages of population-based and individual-based approaches in order to efficiently model the spread and control of FMD on a national scale.

Advantages and Disadvantages of Population-Based Modeling

Livestock epidemics can occur in highly heterogeneous environments. Take for example, an outbreak of FMD within an extensive beef production system in a northern Australian jurisdiction, compared to one in an intensive dairy production system in a southern Australian jurisdiction. Despite the same pathogen and the same host species, there are significant differences in livestock density, farming practices, market systems and climate. The probability of disease detection and reporting varies with the level of contact between owners/inspectors and livestock. State/territory jurisdictions are responsible for their own disease control policies and resourcing. This results in distinct disease spread dynamics and control environments between the two regions.

Population-based models carry a general assumption of homogeneous contact rates and susceptibility. In the case of a compartmental SEIR EBM, individuals within any given compartment are indiscernible. The subtle contributions of specific

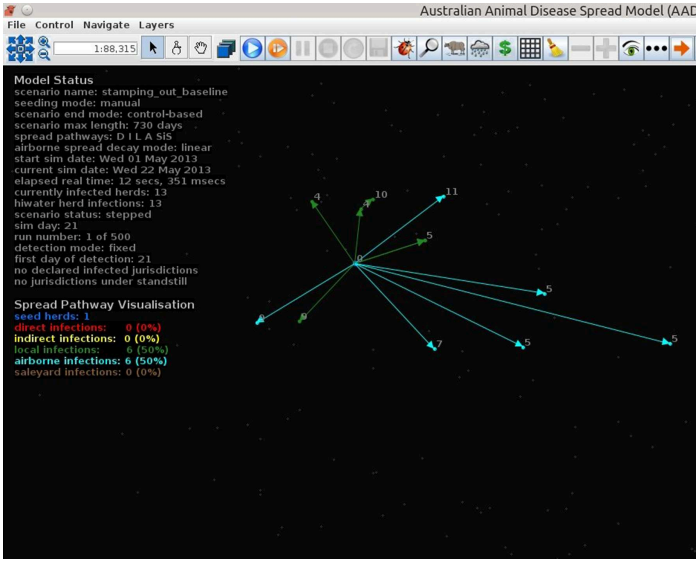


FIGURE 8 | Visualization of between-herd spread as an infection network.

individuals to the dynamics of an outbreak are thus lost in a population-based model. This is a limitation if the population and environment being modeled is heterogeneous. Complex environmental systems are typically multi-scale, non-linear and heterogeneous—characteristics that are ill-suited to an aggregated population-based modeling approach (Bansal et al., 2007; D'Souza et al., 2009; Parker and Epstein, 2011; Vincenot et al., 2011a). Although computationally efficient, an EBM can become complex and less tractable as more variables are factored into the mathematical abstraction (Miller, 1976; Parunak et al., 1998; Bobashev et al., 2007).

Advantages and Disadvantages of Individual-Based Modeling

Individual-based models are better suited to complex environmental systems due to their natural affinity for capturing heterogeneity, stochasticity, spatial relationships, social systems and policy (Hare and Deadman, 2004). The ability to distinguish between individuals in a population is especially important during the initial and final stages of an outbreak (Germann et al., 2006; Bansal et al., 2007). A data-driven, individual-based modeling approach has proven popular in the field of veterinary epidemiology with stochastic, spatially-explicit, state-transition models such as AusSpread, ISP and NAADSM. Individual-based models tend to be complex with a large number of parameters for which data may not always be available. Individual-based models may not scale well for large populations. Consider individual-based models of human pandemics in populations of millions or even billions. Such models have considerable computational requirements and typically require highly parallel platforms such as HPC clusters (Carley et al., 2006; Germann et al., 2006) or general purpose computing on graphics processing units (D'Souza et al., 2009) and custom software implementations (Parker and Epstein, 2011).

Advantages of Hybrid Models

Hybrid epidemiological models incorporate a population-based approach and an individual-based approach into a single model. Epidemics across a meta-population are multi-scale in the sense that the mechanisms and rates of within-site spread are distinct from those of between-site spread. In the case of a livestock epidemic, once infection is introduced into a farm the rate of within-farm propagation is dependent on the specifics of the pathogen and the farm. Factors include the host species, livestock

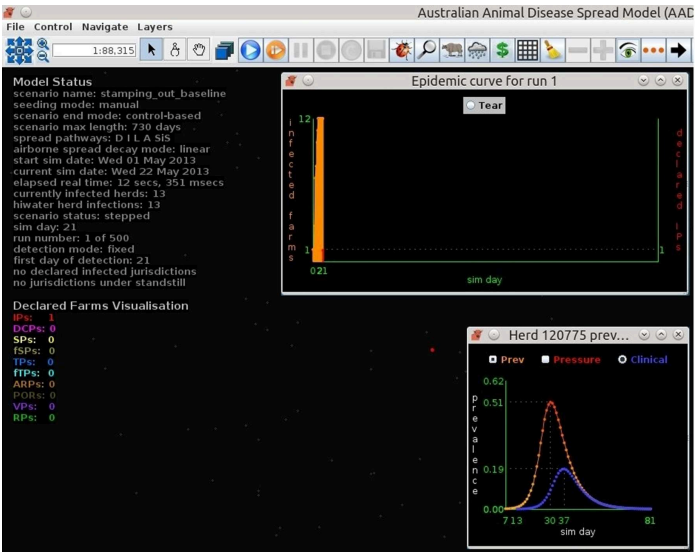


FIGURE 9 | Visualization of controlled premises.

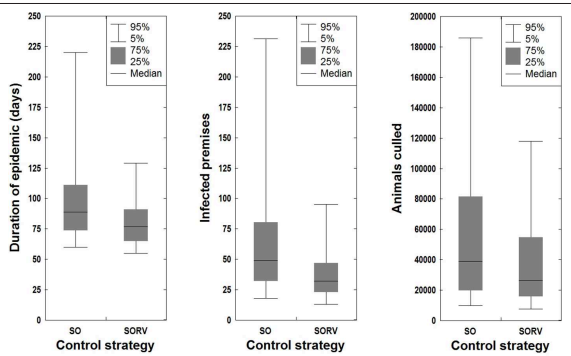


FIGURE 10 | Effect of control strategy on outbreak duration, outbreak size, and number of culled animals.

TABLE 4 | Case study results.

Control strategy	Detection day	Standstill duration (days)	Outbreak duration (days)[3,4,5]	Number of IPs[4,5]	Number of culled animals[4,5]	Number of vaccinated farms[4]	Number of vaccinated animals[4]	Scenario runtime (s)[4]
SO[1]	21	3	89 (60–220)[a]	49 (18–231)[a]	38, 875 (9838–185, 996)[a]	0	0	5.5 (3.3–16.1)
SORV[2]	21	3	77 (55–129)[b]	32 (13–95)[b]	26, 388 (7688–118, 036)[b,c]	192 (70–561)	51, 102 (15, 442–153, 972)	4.8 (3.1–9.6)
SENSITIVITY ANALYSIS OF THE TIME TO DETECTION								
SO	7	3	73 (51–107)[b]	20 (9–48)[b]	13, 385 (7201–61, 081)[b]	0	0	3.0 (2.0–4.8)
SO	14	3	78 (57–146)[b]	32 (14–98)[b]	19, 323 (7448–92, 393)[b]	0	0	4.3 (2.9–8.6)
SO[1]	21	3	89 (60–220)[a]	49 (18–231)[a]	38, 875 (9838–185, 996)[a]	0	0	5.5 (3.3–16.1)
SO	28	3	103 (63–380)[c]	78 (23–732)[c]	72, 275 (13, 314–738, 018)[d]	0	0	7.5 (4.0–46.6)
SENSITIVITY ANALYSIS OF THE DURATION OF THE NATIONAL LIVESTOCK STANDSTILL								
SO	21	0	90 (61–215)[a]	53 (19–241)[a]	45, 683 (10, 163–208, 485)[a]	0	0	5.6 (3.3–17.0)
SO[1]	21	3	89 (60–220)[a]	49 (18–231)[a]	38, 875 (9838–185, 996)[a]	0	0	5.5 (3.3–16.1)
SO	21	7	86 (59–184)[a]	48 (17–184)[a]	37, 111 (9919–165, 532)[a]	0	0	6.1 (3.9–15.1)
SO	21	10	85 (60–189)[a]	46 (19–176)[a]	39, 130 (10, 754–148, 028)[a]	0	0	5.2 (3.4–13.7)

[1] *Baseline stamping out policy.*
[2] *Baseline vaccination policy (stamping out plus suppressive ring vaccination).*
[3] *Time from detection of index case to resolution of final IP.*
[4] *Median (90% confidence interval).*
[5] *Within each column, values with a different superscript are significantly different.*

density, livestock numbers, production system, and biosecurity measures. The spread of disease between farms is influenced by more irregular factors such as contact networks between farms (direct and indirect), market practices, distance between farms and environmental conditions (including weather).

Bobashev et al. (2007) describe a stage-based hybrid model of global human influenza that dynamically switches between an ABM and an EBM based on the number of cases. Within-city spread is initially simulated by an ABM in order to capture subtle interactions between individuals early in an epidemic. When a cases threshold is reached, the ABM is halted and a snapshot of agent states is used as initial conditions for an EBM. Although the granularity of modeling decreases to population-level, it occurs at a point in the outbreak when the number of cases is sufficient to support a population-averaged approach. Moreover, the overall performance of the model is maintained due to the computationally efficient EBM. When the number of cases in a city falls below a threshold value, the model switches back to an ABM in order to capture subtle interactions between individuals as the epidemic wanes.

Network-based hybrid models employ a multi-scale approach to modeling the spread of disease across a meta-population. A population-based model handles the spread of disease within each meta-population site while an individual-based model handles the spread of disease between sites. An example is provided by Vincenot and Moriya (2011b) where a system dynamics-based EBM is used for within-site spread and a contact network is used for between-site spread. A compartment-based EBM is a good match for a closed homogeneous site while a data-driven spatially-explicit individual-based model captures heterogeneity in the epidemic environment. The edges of a contact network topology are formed from the potential conduits of disease across the meta-population. Network-based hybrid models have proven tractable in the study of human pandemics—driven by local and international mobility patterns derived from such sources as census data, surveys and the International Air Transport Association (IATA) database (Bansal et al., 2007; Balcan et al., 2009; Yu et al., 2010; Parker and Epstein, 2011; Van den Broeck et al., 2011; Yoneyama et al., 2012). Hybrid models used in the field of veterinary epidemiology include:

- The Davis Animal Disease Simulation Model (DADS) (Bates et al., 2003a) and DTU-DADS (Boklund et al., 2013) where within-herd spread of FMD is modeled with a Reed-Frost EBM (Fine, 1977), and between-herd spread modeled with a stochastic spatially-explicit contact network.
- The Netherlands FMD model (Backer et al., 2012) where within-herd spread is handled by an SEIR-based EBM and between-herd spread is modeled with a spatial kernel driven by probabilities derived from the 2001 outbreak in the Netherlands.
- Nickbakhsh et al. (2013) where within-flock spread of highly pathogenic avian influenza (HPAI) is modeled with a SEIR-based EBM and between-flock spread with a stochastic contact network.
- LaBute et al. (2014) where within-herd spread of FMD and HPAI are modeled with a compartmental SIR EBM and between-herd spread with a spatially-explicit contact network.

How AADIS Differs from other Hybrid Models

AADIS extends the network-based hybrid approach by employing an event-driven ABM in lieu of a contact network. The meta-population under study is heterogeneous, reflecting the multiple species of domestic cloven-hoofed animals that are susceptible to FMD. The network by which meta-population sites (i.e., herds) can 'connect' is multi-layer, reflecting how FMD

spreads via direct contact (animal movements between herds and between herds and markets), indirect contact (livestock products, by-products and fomites) and aerosols.

The AADIS ABM also models the control and eradication of FMD. Each disease spread pathway and control measure operates as an autonomous concurrent 'component' of the ABM environment. The decoupled component approach is robust, flexible and extensible. Components can be added/removed/modified with minimal impact on other components.

How AADIS Differs from Other Major Models of FMD Spread and Control

The AADIS EBM predicts a herd's prevalence and clinical signs over time based on the pathogen, herd type and herd size. These values dynamically feed into ABM decisions on the spread of disease between herds, the probability of detection, and the control of disease. In its role as an agent in the ABM, a herd reacts to environmental events such as culling and vaccination by resolving the EBM ODE system which in turn yields updated predictions for prevalence and clinical signs (**Figure 3**). The decoupling of within-herd spread and between-herd spread reflects the multi-scale nature of livestock epidemics (Carpenter et al., 2003; Keeling, 2005). Stochastic state-transition microsimulations such as AusSpread, ISP and NAADSM simplify intra-farm transmission as transitions through atomic infection states according to durations sampled from probability distributions. A state-transition approach to within-herd spread doesn't naturally capture the dynamics of intra-herd transmission. A simple herd state of 'infectious' doesn't distinguish between the infectiousness of a herd with 1% of the animals infected and that of a herd with 100% of the animals infected. This leads to a loss of prevalence information that is relevant to between-herd spread, and a loss of information on clinical signs that influences the detection and control of disease (Carpenter et al., 2003). It is possible to augment infection states with transmission probabilities that vary over time (Stevenson et al., 2013). However, this is less intuitive than the AADIS organic EBM approach. An architectural advantage of decoupling within-herd spread and between-herd spread is that alternative EBMs can be readily employed as required for the specific pathogen under study. This is awkward to accomplish when intra-herd spread and inter-herd spread are tightly coupled in a pure individual-based model such as a state-transition microsimulation.

Other distinguishing functional features of AADIS include:

- The configuration and deployment of control measures are decentralized to the separate state/territory jurisdictions. This permits realistic modeling of an epidemic that may spread across borders and require control at the jurisdictional level.
- The resources available for disease control and eradication are configurable by jurisdiction. This improves model realism as resource levels and priorities may vary considerably between jurisdictions. The AADIS ABM also allows resource requirements to emerge from a scenario as opposed to a top-down modeling approach that prescribes resourcing levels ahead of time. The inclusion of false positive suspect premises reports and traces provides more realistic modeling of surveillance as it reflects how resources are consumed regardless of the result of a surveillance visit.
- AADIS provides detailed graphical visualization modes that allow a user to dynamically view an outbreak unfolding in 'real' time. The graphical user interface allows a user to interact with an epidemic, for example to pause a scenario and view details of any herd/farm in the population. It is also possible to manually adjust the declared state of any farm. AADIS has potential as not only a predictive tool that informs policy, but also as a vivid training tool for disease managers.
- The multi-threaded asynchronous AADIS architecture offers significant performance improvements over a single-threaded state-transition approach. As all AADIS spread and control tasks proceed concurrently the length of a simulation day is only limited by the longest individual task. Computational efficiency is an important consideration for a stochastic model of national-scale as complex scenarios are re-run hundreds if not thousands of times to allow trends to emerge.
- Most of the current microsimulation models use a farm as the epidemiological unit of interest. AADIS's use of the herd captures heterogeneity in the spread of disease involving farms with co-located but separately managed herds, for example mixed beef/sheep farms.
- The national set of herds can be viewed abstractly as nodes in a network (Dube et al., 2011; Noremark et al., 2011). A network topology forms over time when spread pathways trigger and create edges (**Figures 2**, **8**). The topology takes the form of a directed acyclic graph, until such time as recovered herds lose their immunity. Network paths can subsequently be traversed forward to determine the downstream impact of an infected herd, and backward to trace the historical infection route. The network topology thus captures the spatiotemporal history of the simulated epidemic. The infection network can be mathematically analyzed to identify topological features of interest such as sinks and spreaders.

It should be noted that specific functional advantages of one model over another can be short-lived. Models such as AusSpread, ISP, NAADSM, DADS, DTU-DADS, and the Netherlands model (Backer et al., 2012) are active and continue to evolve. The principle innovation of AADIS is perhaps architectural, i.e., the movement away from the state-transition microsimulation approach of AusSpread, ISP and NAADSM to a hybrid EBM/ABM model. Network-based hybrid models tend to have single species meta-population and single layer contact network. AADIS expands this genre of models to a multi-species meta-population and a multi-layer contact network.

Limitations

The realism of data-driven models of disease spread hinges on the quality of the underlying data. This includes population data, contact structures, environmental data and pathogen data. Inadequate data can be replaced with assumptions/expert opinion but this has the potential to introduce bias into a model. In countries such as Australia where agriculture is of great importance to the economy, there is increasing availability

of spatially-based data on livestock and livestock products. An example is the National Livestock Identification System (NLIS) which tracks livestock from property of birth to place of slaughter/export (Meat and Livestock Australia, 2011). The NLIS database is a rich source of livestock movement data and takes into account species, production system and region. For AADIS to be used in a jurisdiction with a paucity of data, the spread and control components would need to be simplified. For example, a complex spread pathway based on animal movement data could be replaced with a simple distance kernel-based spread module.

AADIS has extensive configuration data spread across 40 tables in a relational database and three ASCII configuration files. This allows for detailed configuration of a heterogeneous environment and population, and pathogen under study. A result of this complexity is that the parameterization of the model requires a good understanding of the epidemiological system being modeled.

An artifact of the concurrent architecture adopted by AADIS is that thread scheduling arbitrarily influences the order that components request random numbers. This means that it is not possible to replay scenarios by specifying the pseudo-random number generator seed (and thus control the stream of random numbers used to sample from probability distributions). The ability to control the random number stream makes a stochastic model temporarily deterministic, and allows specific aspects of a scenario to be isolated. For example, a specific control measure such as vaccination can be varied and the impact on the scenario outcome directly observed (in the absence of variability introduced through stochasticity). The implication of this for AADIS is that a greater number of scenario runs may be required before results converge.

Concluding Remarks

Disease managers have to take into account technical, socio-political, economic and logistical issues when developing policies for disease control. Often there are conflicting objectives to balance, for example, to eradicate the disease as soon as possible and regain export markets, while minimizing the costs of control and compensation, and reducing impacts on other industries. Epidemiological modeling is emerging as an important contributor to the complex task of policy development.

Population-based models represent the spread of disease in a closed homogeneous population in a concise and computationally efficient manner. Individual-based models have a natural affinity for incorporating stochasticity, population heterogeneity, spatial effects, social factors and jurisdictional differences. This flexibility and realism has led to a strong interest in microsimulations for the purposes of informing official policy on disease control. Hybrid models have the modeling advantages of an individual-based approach but are also computationally efficient, which is particularly important when dealing with large livestock populations. The AADIS assumption that a herd is homogeneous is reasonable given that livestock are typically managed as single species cohorts that share a single contact network whilst on a farm. The AADIS SEIR-based EBM provides computationally efficient and adaptive predictions of herd prevalence and clinical signs over time. The AADIS ABM is well-suited to the complex, stochastic and heterogeneous environment in which an FMD epidemic operates.

There is an increasing availability of livestock movement and marketing data (including spatially-referenced data), through livestock identification, and tracing systems. This allows data-driven disease models such as AADIS to realistically simulate production system dynamics and contact structures.

The AADIS asynchronous hybrid EBM/ABM architecture has thus far shown itself as a flexible, efficient and extensible framework for modeling the spread and control of FMD in livestock on a national scale.

Acknowledgments

AADIS is a joint research venture between the Australian Department of Agriculture and the University of New England (UNE). The authors acknowledge both organizations for their support of the project. The authors would like to thank Dr. A.S.M. Sajeev who was a strong supporter of the project whilst Professor of Computer Science at UNE. The authors would also like to thank Dr. Rachel Iglesias of the Department of Agriculture for providing helpful comments on the manuscript. This work is funded under the Australian Government's Animal Biosecurity Response and Reform Program.

References

Animal Health Australia. (2014a). *Disease Strategy: Foot-and-Mouth Disease (Version 3.4). Australian Veterinarian Emergency Plan (AUSVETPLAN), 3rd Edn.* Canberra, ACT: Standing Council on Primary Industries.

Animal Health Australia. (2014b). *Animal Health in Australia 2013*. Canberra, ACT: Animal Health Australia.

Australian Bureau of Statistics. (2012). Agricultural Commodities, Australia. Available online at: http://www.abs.gov.au/ausstats/abs@.nsf/mf/7121.0

AusVet Animal Health Services. (2005). *A Review of the Structure and Dynamics of the Australian Dairy Cattle Industry*. Report prepared for the Department of Agriculture, Fisheries and Forestry, Canberra, ACT, Australia.

AusVet Animal Health Services. (2006). *A Review of the Structure and Dynamics of the Australian Beef Cattle Industry*. Report prepared for the Department of Agriculture, Fisheries and Forestry, Canberra, ACT, Australia.

Backer, J. A., Hagenaars, T. J., Nodelijk, G., and van Roermund, H. J. W. (2012). Vaccination against foot-and-mouth disease I: epidemiological consequences. *Prev. Vet. Med.* 107, 27–40. doi: 10.1016/j.prevetmed.2012.05.012

Balcan, D., Colizza, V., Goncalves, B., Hu, J., Ramasco, J. J., and Vespignani, A. (2009). Multiscale mobility networks and the spatial spreading of infectious diseases. *Proc. Natl. Acad. Sci. U.S.A.* 106, 21484–21489. doi: 10.1073/pnas.0906910106

Bansal, S., Grenfell, B. T., and Ancel Meyers, L. (2007). When individual behaviour matters: homogeneous and network models in epidemiology. *J. R. Soc. Interface* 4, 879–891. doi: 10.1098/rsif.2007.1100

Bates, T. W., Thurmond, M. C., and Carpenter, T. E. (2001). Direct and indirect contact rates among beef, dairy, goat, sheep and swine herds in three California counties, with reference to control of potential foot-and-mouth disease transmission. *Am. J. Vet. Res.* 62, 1121–1129. doi: 10.2460/ajvr.2001.62.1121

Bates, T. W., Thurmond, M. C., and And Carpenter, T. E. (2003a). Description of an epidemic simulation model for use in evaluating strategies to control an outbreak of foot-and-mouth disease. *Am. J. Vet. Res.* 64, 195–204. doi: 10.2460/ajvr.2003.64.195

Bates, T. W., Thurmond, M. C., and And Carpenter, T. E. (2003b). Results of epidemic simulation modeling to evaluate strategies to control an outbreak of foot-and-mouth disease. *Am. J. Vet. Res.* 64, 205–210. doi: 10.2460/ajvr.2003.64.205

BBN. (2014). *OpenMap*. BBN Technologies. Available online at: http://openmap.bbn.com/

Bobashev, G. V., Goedecke, D. M., Yu, F., and Epstein, J. M. (2007). "A hybrid epidemic model: combining the advantages of agent-based and equation-based approaches," in *Proceedings of the 2007 Winter Simulation Conference* (Washington, DC), 1532–1537.

Boklund, A., Halasa, T., Christiansen, L. E., and And Enoe, C. (2013). Comparing control strategies against foot-and-mouth disease: will vaccination be cost-effective in Denmark? *Prevent. Vet. Med.* 111, 206–219. doi: 10.1016/j.prevetmed.2013.05.008

Bradhurst, R. A., Roche, S. E., Garner, M. G., Sajeev, A. S. M., and Kwan, P. (2013). "Modelling the spread of livestock disease on a national scale: the case for a hybrid approach," in *Proceedings of the 20th International Congress on Modelling and Simulation (MODSIM2013), Modelling and Simulation Society of Australia and New Zealand* (Adelaide, SA), 345–351.

Buetre, B., Wicks, S., Kruger, H., Millist, N., Yainshet, A., Garner, G., et al. (2013). *Potential Socio-Economic Impacts of an Outbreak of Foot-and-Mouth Disease in Australia*. Research Report 13.11, October 2013, Australian Bureau of Agricultural and Resource Economics and Sciences (ABARES).

Bunn, C. M., Garner, M. G., and Cannon, R. M. (1998). The 1872 outbreak of foot-and-mouth disease in Australia – why didn't it become established? *Aust. Vet. J.* 76, 262–269. doi: 10.1111/j.1751-0813.1998.tb10157.x

Caraco, T., Duryea, M. C., and Glavavakov, S. (2001). Host spatial heterogeneity and the spread of vector-borne infection. *Theor. Popul. Biol.* 59, 185–206. doi: 10.1006/tpbi.2000.1517

Carley, K. M., Fridsma, D. B., Casman, E., Yahja, A., Altman, N., Chen, L., et al. (2006). BioWar: Scalable agent-based model of bioattacks. *IEEE Trans. Syst. Man Cybern. A Syst. Hum.* 36, 252–265. doi: 10.1109/TSMCA.2005.851291

Carpenter, T. E., Bates, T. W., and Thurmond, M. C. (2003). "The importance of including intra-herd transmission in a foot-and-mouth disease model," in *Proceedings of the 10th Symposium of the International Society for Veterinary Epidemiology and Economics, Vina del Mar, Chile, November 2003, New Concepts – Modelling Session*," 249–251.

Carpenter, T. E., O'Brien, J. M., Hagerman, A. D., and McCarl, B. A. (2011). Epidemic and economic impacts of delayed detection of foot-and-mouth disease: a case study of a simulated outbreak in California. *J. Vet. Diagn. Invest.* 23, 26–33. doi: 10.1177/104063871102300104

Cash, J. R., and Karp, A. R. (1990). A variable order Runge-Kutta method for initial value problems with rapidly varying right-hand sides. *ACM Trans. Math. Softw.* 16, 201–222. doi: 10.1145/79505.79507

Department of Environment and Primary Industries. (2015). *Goulburn Valley Regional Overview*. State Government of Victoria. Available online at: http://www.depi.vic.gov.au/agriculture-and-food/food-and-fibre-industries/region-overviews/goulburn

Donaldson, A. I., Alexandersen, A., Sorensen, J. H., and Mikkelsen, T. (2001). Relative risks of the uncontrollable (airborne) spread of FMD by different species. *Vet. Rec.* 148, 602–604. doi: 10.1136/vr.148.19.602

Donaldson, A. I., and Alexandersen, A. (2002). Predicting the spread of foot and mouth disease by airborne spread. *Rev. Sci. Tech.* 21, 569–575.

D'Souza, R. M., Marino, S., and Kirschner, D. (2009). "Data-parallel algorithms for agent-based model simulation of tuberculosis on graphics processing units," in *Proceedings of the 2009 Spring Simulation Multiconference (SpringSim '09), Society for Computer Simulation International* (San Diego, CA), 1–12.

Dube, C., Ribble, C., Kelton, D., and McNab, B. (2011). Introduction to network analysis and its implications for animal disease modelling. *Rev. Sci. Tech.* 30, 425–436.

East, I. J., and Foreman, I. (2011). The structure, dynamics and movement patterns of the Australian sheep industry. *Aust. Vet. J.* 89, 477–489. doi: 10.1111/j.1751-0813.2011.00852.x

East, I. J., Wicks, R. M., Martin, P. A. J., Sergeant, E. S. G., Randall, L. A., and Garner, M. G. (2013). Use of a multi-criteria analysis framework to inform the design of risk based general surveillance systems for animal disease in Australia. *Prev. Vet. Med.* 112, 230–247. doi: 10.1016/j.prevetmed.2013.09.012

East, I. J., Davis, J., Sergeant, E. S. G., and Garner, M. G. (2014). Structure, dynamics and movement patterns of the Australian pig industry. *Aust. Vet. J.* 92, 52–57. doi: 10.1111/avj.12141

Fine, P. E. M. (1977). A commentary on the mechanical analogue to the Reed-Frost epidemic model. *Am. J. Epidemiol.* 106, 87–100.

Galvani, A. P., and May, R. M. (2005). Dimensions of superspreading. *Nature* 438, 293–294. doi: 10.1038/438293a

Garner, M. G., and Beckett, S. D. (2005). Modelling the spread of foot-and-mouth disease in Australia. *Aust. Vet. J.* 83, 758–766. doi: 10.1111/j.1751-0813.2005.tb11589.x

Garner, M. G., Dube, C., Stevenson, M. A., Sanson, R. L., Estrada, C., and Griffen, J. (2007). Evaluating alternative approaches to managing animal disease outbreaks – the role of modelling in policy formulation. *Vet. Ital.* 43, 285–298.

Garner, M. G., and Hamilton, S. A. (2011). Principles of epidemiological modelling. *Rev. Sci. Tech.* 30, 407–416.

Garner, M. G., Hess, G. D., and Yang, X. (2006). An integrated modelling approach to assess the risk of wind-borne spread of foot-and-mouth disease virus from infected premises. *Environ. Model. Assess.* 11, 195–207. doi: 10.1007/s10666-005-9023-5

Garner, M. G., Murray, J. G., and Fisher, B. S. (2002). Economic aspects of foot and mouth disease: perspectives of a free country, Australia. *Rev. Off. Int. Epizoot.* 21, 625–635. doi: 10.1016/j.prevetmed.2013.07.013

Germann, T. C., Kadau, K., Longini, I. M., and And Macken, C. A. (2006). Mitigation strategies for pandemic influenza in the United States. *Proc. Natl. Acad. Sci. U.S.A.* 103, 5935–5940. doi: 10.1073/pnas.0601266103

Gibbens, J. C., Sharpe, C. E., Wilesmith, J. W., Mansley, L. M., Michalopoulou, E., Ryan, J. B., et al. (2001). Descriptive epidemiology of the 2001 foot-and-mouth disease epidemic in Great Britain: the first five months. *Vet. Rec.* 149, 729–743.

Hagenaars, T. J., Donnelly, C. A., and Ferguson, N. M. (2004). Spatial heterogeneity and the persistence of infectious diseases. *J. Theor. Biol.* 229, 349–359. doi: 10.1016/j.jtbi.2004.04.002

Hare, M., and Deadman, P. (2004). Further towards a taxonomy of agent-based simulation models in environmental management. *Math. Comput. Simul.* 64, 25–40. doi: 10.1016/S0378-4754(03)00118-6

Harvey, N., Reeves, A., Schoenbaum, M. A., Zagmutt-Vergara, F. J., Dubé, C., Hill, A. E., et al. (2007). The North American Animal Disease Spread Model: a simulation model to assist decision making in evaluating animal disease incursions, *Prevent. Vet. Med.* 82, 176–97. doi: 10.1016/j.prevetmed.2007.05.019

Hassall and Associates. (2006). *The Structure and Dynamics of Australia's Sheep Population*. Report prepared for the Department of Agriculture, Fisheries and Forestry, Canberra, ACT, Australia.

Hassall and Associates. (2007). *A Review and Analysis of Saleyard Marketing in Australia*. Report prepared for the Department of Agriculture, Fisheries and Forestry, Canberra, ACT, Australia.

Haydon, D. T., Woolhouse, M. E., and Kitching, R. P. (1997). An analysis of foot-and-mouth-disease epidemics in the UK. *IMAJ. Math. Appl. Med. Biol.* 14, 1–9. doi: 10.1093/imammb/14.1.1

James, A., Pitchford, J. W., and Plank, M. J. (2007). An event-based model of superspreading in epidemics. *Proc. R. Soc. B Biol. Sci.* 274, 741–747. doi: 10.1098/rspb.2006.0219

Keeling, M. J. (2005). Models of foot-and-mouth disease. *Proc. R. Soc. B Biol. Sci.* 272, 1195–1202. doi: 10.1098/rspb.2004.3046

Keeling, M. J., and Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton; Oxford. Princeton University Press.

Kokic, P., and Mues, C. (2006). *Cattle Movements*. Research Report. Australian Bureau of Agricultural and Resource Economics and Sciences (ABARES).

LaBute, M. X., McMahon, B. H., Brown, M., Manore, C., and Fair, J. M. (2014). A flexible spatial framework for modeling spread of pathogens in animals with biosurveillance and disease control applications. *ISPRS Int. J. Geo-Inform.* 3, 638–661. doi: 10.3390/ijgi3020638

Lloyd-Smith, J. O., Schreiber, S. J., Hopp, P. E., and Getz, W. M. (2005). Super-spreading and the effect of individual variation on disease emergence. *Nature* 438, 355–359. doi: 10.1038/nature04153

Mansley, L. M., Dunlop, P. J., Whiteside, S. M., and Smith, R. G. H. (2003). Early dissemination of FMD virus through sheep marketing in February 2001. *Vet. Rec.* 153, 43–50. doi: 10.1136/vr.153.2.43

Matthews, K. (2011). *A Review of Australia's Preparedness for the Threat of Foot-and-Mouth Disease*. Australian Government Department of Agriculture, Fisheries and Forestry, Canberra, ACT. Available online at: http://www.agriculture.gov.au/animal-plant-health/pests-diseases-weeds/animal/fmd/review-foot-and-mouth-disease

McLaws, M., Ribble, C., Stephen, C., McNab, B., and Barrios, P. R. (2007). Reporting of suspect cases of foot-and-mouth disease during the 2001 epidemic in the UK, and the herd sensitivity and herd specificity of clinical diagnosis. *Prevent. Vet. Med.* 78, 12–23. doi: 10.1016/j.prevetmed.2006.09.001

Meat and Livestock Australia. (2011). *National Livestock Identification Scheme Database*. Available online at: http://www.mla.com.au/Meat-safety-and-traceability/National-Livestock-Identification-System

Meyer, R. F., and Knudsen, R. C. (2001). Foot-and-mouth disease: a review of the virus and the symptoms. *J. Environ. Health* 64, 21–23.

Miller, W. M. (1976). "A state-transition model of epidemic foot-and-mouth disease," in *Proceedings of the International Symposia on Veterinary Epidemiology and Economics (ISVEE 1), New Techniques in Veterinary Epidemiology and Economics*. Reading: University of Reading, Descriptive Modelling Session, 56–72.

Nickbakhsh, S., Matthews, L., Dent, J. E., Innocent, G. T., Arnold, M. E., Reid, S. W. J., et al. (2013). Implications of within-farm transmission for network dynamics: consequences for the spread of avian influenza. *Epidemics* 5, 67–76. doi: 10.1016/j.epidem.2013.03.001

Nielen, M., Jalvingh, A. W., Horst, H. S., Dijkhisen, A. A., Maurice, H., Schut, B. H., et al. (1996). Quantification of contacts between Dutch farms to assess the potential risk of foot-and-mouth disease spread. *Prevent. Vet. Med.* 28, 143–158. doi: 10.1016/0167-5877(96)01042-2

Noremark, M., Hakansson, N., Sternberg Lewerin, S., Lindberg, A., and Jonsson, A. (2011). Network analysis of cattle and pig movements in Sweden: measures relevant for disease control and risk based surveillance. *Prevent. Vet. Med.* 99, 78–90. doi: 10.1016/j.prevetmed.2010.12.009

Noremark, M., Frossling, J., and Sternberg Lewerin, S. (2013). A survey of visitors on Swedish livestock farms with reference to the spread of animal diseases. *BMC Vet. Res.* 9:184. doi: 10.1186/1746-6148-9-184

Oracle. (2014). *Java*. Oracle Corporation. Available online at: http://www.java.com/en/

Parker, J., and Epstein, J. M. (2011). A distributed platform for global-scale agent-based models of disease transmission. *ACM Trans. Model. Comput. Simul.* 22:2. doi: 10.1145/2043635.2043637

Parunak, H. V. D., Savit, R., and Riolo, R. L. (1998). "Agent-based modeling vs. equation-based modeling: a case study and users' guide," in *Proceedings of Multi-Agent Systems and Agent-Based Simulation* (MABS'98), 10–25.

Perez, L., and Dragicevic, S. (2009). An agent-based approach for modeling dynamics of contagious disease spread. *Int. J. Health Geogr.* 8:50. doi: 10.1186/1476-072X-8-50

PostgreSQL. (2014). *PostgreSQL*. The PostgreSQL Global Development Group. Available online at: http://www.postgresql.org/

Regional Development Victoria. (2010). Goulburn Valley sub-regional plan – The Hume Strategy for sustainable communities 2010-2010. State Government of Victoria. Available online at: http://www.rdv.vic.gov.au/victorian-regions/hume

Roche, S. E., Garner, M. G., Wicks, R. M., East, I. J., and de Witte, K. (2014). How do resources influence control measures during a simulated outbreak of foot and mouth disease in Australia? *Prevent. Vet. Med.* 113, 436–446. doi: 10.1016/j.prevetmed.2013.12.003

Rushton, J., Knight Jones, T. J. D., Donaldson, A. I., de Leeuw, P. W., Ferrari, G., and Domenech, J. (2012). *The Impact of Foot and Mouth Disease – Supporting Document N° 1*. Paper prepared for the FAO/OIE Global Conference on Foot and Mouth Disease Control, Bangkok (Thailand), 27 to 29 June 2012.

Sanson, R. L. (2005). A survey to investigate movements off sheep and cattle farms in New Zealand, with reference to the potential transmission of foot-and-mouth disease. *N. Z. Vet. J.* 53, 223–233. doi: 10.1080/00480169.2005.36550

Stata. (2014). *STATA Intercooled Software v11.0*. Stata Corporation. Available online at: http://www.stata.com/products/which-stata-is-right-for-me/#IC

Stevenson, M. A., Sanson, R. L., Stern, M. W., O'Leary, B. D., Sujau, M., Moles-Benfell, N., et al. (2013). InterSpread Plus: a spatial and stochastic simulation model of disease in animal populations. *Prevent. Vet. Med.* 109, 10–24. doi: 10.1016/j.prevetmed.2012.08.015

Taylor, N. (2003). *Review of the Use of Models in Informing Disease Control Policy Development and Adjustment*. School of Agriculture, Policy and Development, The University of Reading.

Tildesley, M. J., Savill, N. J., Shaw, D. J., Deardon, R., Brooks, S. P., Woolhouse, M. E. J., et al. (2006). Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. *Nature* 440, 83–86. doi: 10.1038/nature04324

Van den Broeck, W., Gioannini, C., Gonçalves, B., Quaggiotto, M., Colizza, V., and Vespignani, A. (2011). The GLEaMviz computational tool, a publicly available software to explore realistic epidemic spreading scenarios at the global scale. *BMC Infect. Dis.* 11:37. doi: 10.1186/1471-2334-11-37

Vincenot, C. E., Giannino, F., Rietkerk, M., Moriya, K., and Mazzoleni, S. (2011a). Theoretical considerations on the combined use of System Dynamics and individual-based modeling in ecology. *Ecol. Modell.* 222, 210–218. doi: 10.1016/j.ecolmodel.2010.09.029

Vincenot, C. E., and Moriya, K. (2011b). Impact of the topology of metapopulations on the resurgence of epidemics rendered by a new multiscale hybrid modeling approach. *Ecol. Inform.*, 6, 177–186. doi: 10.1016/j.ecoinf.2011.04.002

Vose, D. (2008). *Risk Analysis: A Quantitative Guide, 3rd Edn*. Chichester: John Wiley and Sons, Ltd.

Yoneyama, T., Das, S., and Krishnamoorthy, M. (2012). A hybrid model for disease spread and an application to SARS pandemic. *J. Artif. Soc. Soc. Simul.* 15, 5.

Yu, B., Wang, J., McGowan, M., Vaidyanathan, G., and Younger, K. (2010). "Gryphon: A hybrid agent-based modeling and simulation platform for infectious diseases. Advances in Social Computing," in *Third International Conference on Social Computing, Behavioural Modeling and Prediction, SBP 2010, Proceedings, LNCS 6007* (Bethesda, MD), 199–207.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Environmental Modelling & Software 77 (2016) 1–12

Contents lists available at ScienceDirect

Environmental Modelling & Software

journal homepage: www.elsevier.com/locate/envsoft

Improving the computational efficiency of an agent-based spatiotemporal model of livestock disease spread and control

R.A. Bradhurst [a, *], S.E. Roche [b], I.J. East [b], P. Kwan [a], M.G. Garner [b]

[a] School of Science and Technology, University of New England, Armidale, NSW, Australia
[b] Epidemiology and One Health Program, Animal Health Policy Branch, Department of Agriculture and Water Resources, Canberra, ACT, Australia

ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form
10 November 2015
Accepted 23 November 2015
Available online 11 December 2015

Keywords:
AADIS
ABM
FMD
Spatial indexing
Spatiotemporal model

ABSTRACT

Agent-based models (ABMs) are well suited to representing the spatiotemporal spread and control of disease in a population. The explicit modelling of individuals in a large population, however, can be computationally intensive, especially when models are stochastic and/or spatially-explicit. Large-scale ABMs often require a highly parallel platform such as a high-performance computing cluster, which tends to confine their utility to university, defence and scientific research environments. This poses a challenge for those interested in modelling the spread of disease on a large scale with access only to modest hardware platforms.

The Australian Animal DISease (AADIS) model is a spatiotemporal ABM of livestock disease spread and control. The AADIS ABM is able to complete complex national-scale simulations of disease spread and control on a personal computer. Computational efficiency is achieved through a hybrid model architecture that embeds equation-based models inside herd agents, an asynchronous software architecture, and a grid-based spatial indexing scheme.

1. Introduction

Mathematical models of disease spread have been in use since at least the 18th century (Dietz and Heesterbeek, 2002). An example is a Susceptible, Exposed, Infectious and Recovered (SEIR) compartmental equation-based model (EBM) that uses a system of ordinary differential equations (ODEs) to predict infection state proportions in a population over time (Keeling and Rohani, 2008). The population is dynamically disaggregated into the SEIR compartments; however, individuals within any particular compartment are indistinguishable. Models such as this are termed population-based, in that top-down population-level relationships provide insight into individual-level states. Population-based models can be concise and computationally efficient, but generally assume homogeneous contact rates and susceptibility, i.e., individuals mix uniformly and randomly, and have an equal likelihood of contracting a disease. The homogeneous 'well-mixed' assumption of an aggregated population-based model is a limitation if the population is heterogeneous and mixes heterogeneously (Hethcote, 2000; Keeling et al., 2001; Kitching et al., 2006; Bansal et al., 2007; Grassly and Fraser, 2008).

Agent-based models of disease spread are formulated from the bottom-up, whereby population-level relationships emerge organically from the aggregation of individual-level behaviours. Agent-based models are well suited to capturing population heterogeneity, stochasticity, spatial relationships, adaptivity, social systems and policy elements (Parunak et al., 1998; Davidsson, 2001; Hare and Deadman, 2004; Crooks and Heppenstall, 2012). The explicit modelling of individuals in a population, however, can be computationally intensive, especially for large populations. Computational efficiency is important for models that employ Markov chain Monte-Carlo (MCMC) methods (Hamra et al., 2013). A stochastic model may be called upon to re-run a scenario with the same initial conditions thousands of times to allow trends to emerge from the underlying probabilistic mechanisms (Driels and Shin, 2004). Spatiotemporal models have additional computational challenges of efficiently managing spatial objects, spatial relationships and spatial queries (Kennedy et al., 2009). Large-scale agent-based models can require custom software implementations (Parker and Epstein, 2011), and highly parallel platforms such as high-performance computing (HPC) clusters (Carley et al., 2006; Germann et al., 2006) or general purpose computing on graphics

* Corresponding author. School of Science and Technology, University of New England, Armidale NSW 2351, Australia.
E-mail address: rbradhur@myune.edu.au (R.A. Bradhurst).

http://dx.doi.org/10.1016/j.envsoft.2015.11.015
1364-8152/

processing units (Lysenko and D'Souza, 2008; D'Souza et al., 2009; Welch et al., 2014). Access to HPC clusters is largely in the hands of university, defence and scientific research organisations. This poses a challenge for those interested in modelling the spread of disease efficiently on a large scale with access to only standard hardware platforms.

Epidemiological models are used in Australia to support planning and policy development for exotic animal diseases such as foot-and-mouth disease (FMD) (Garner et al., 2007, 2014; Roche et al., 2014). FMD is a highly contagious disease of cloven-hoofed animals that significantly impacts livestock production and trade in livestock and livestock products (Buetre et al., 2013). Modelling the spread and control of FMD is complex as the virus has multiple serotypes, and spreads via multiple pathways (direct contacts, indirect contacts and aerosol plumes), to multiple host species (including cattle, sheep, goats and pigs). The environment of a potential outbreak is also complex as there is considerable heterogeneity in Australian livestock production systems, market systems, geography and climate (Animal Health Australia, 2014a). Further, disease control in Australia is managed by the individual states and territories (Animal Health Australia, 2014b), so for national planning purposes, a model needs to handle jurisdictional differences in the implementation of control programs. AusSpread is a spatially-explicit, farm-based state-transition microsimulation developed by the Australian Department of Agriculture and Water Resources to study FMD (Garner and Beckett, 2005). It is based on the MapBasic/MapInfo geographic information system (GIS) platform (Pitney Bowes, 2015). Runtime constraints limit AusSpread's practical use to studying disease at a regional level.

The Australian Animal DISease (AADIS) model is a national-scale epidemiological model developed by the Australian Department of Agriculture and Water Resources (Bradhurst et al., 2013, 2015). The AADIS model is written in Java (Oracle, 2015), and employs open-source products such as OpenMap (BBN, 2015), PostgreSQL (PostgreSQL, 2015) and SQL Power Architect (SQL Power Group, 2015). A national-scale epidemiological model must be computationally efficient while addressing the needs of disease managers in terms of capturing the disease epidemiology, regional variability in transmission (for example, due to different livestock movement patterns, production systems and climates), and jurisdictional approaches to control. In this paper we present the key design features that allow the AADIS model to run complex national-scale simulations efficiently on a personal computer: a hybrid agent-based model (ABM) architecture that embeds EBMs inside herd agents; an asynchronous software architecture that features lightweight agents in an active concurrent environment; and grid-based spatial indexing. We describe the performance gains achieved through the use of uniform grid-based spatial indexing instead of R-Tree-over-GiST spatial indexing provided in the PostGIS (OSGeo, 2015) extension to PostgreSQL. We also compare the runtime performance of the AADIS ABM with the AusSpread microsimulation and discuss some advantages and disadvantages of concurrent processing over the sequential approach taken by many microsimulations such as AusSpread.

2. Material and methods

2.1. Hybrid model architecture

The main Australian industries vulnerable to an FMD outbreak are beef, dairy, wool, sheep meat, and pigs. This implies an FMD-susceptible national population in excess of 100 million animals (Australian Bureau of Statistics, 2014). It is possible to derive realistic individual-based contact networks from identification and tracing systems such as the Australian National Livestock Identification System (Meat and Livestock Australia, 2014). Australian cattle, for example, undergo mandatory tagging with a radio frequency identification ear tag or rumen bolus that facilitates per-animal tracking from property of birth to place of slaughter/export. It is, however, computationally infeasible for a personal computer to accommodate an ABM with 100 million agents. The AADIS ABM, instead, employs the herd as the modelling unit of interest, yielding a national population of approximately 236,000 FMD-susceptible herds. This is a reasonable simplification as livestock are typically managed as single-species herds that effectively share a single contact network whilst on a farm (Kostova-Vassilevska, 2004). A herd is assumed to be homogeneous with respect to species and farming practices, and well-mixed from a disease transmission point of view. This implies that any one member of a herd has the same likelihood of contracting a disease as any other member. The number of animals in a herd is simplified to be constant over time, that is, births and incoming consignments are assumed equivalent to natural deaths and outgoing consignments. Modelling the spread of disease on a per-herd basis captures heterogeneity within multi-species farms. For example, farms that manage both sheep and cattle can be modelled as comprising multiple independent herds with distinct disease dynamics and animal management practices. An example national dataset of FMD-susceptible herd and farm types is presented in Table 1.

Each herd agent has an embedded ODE-based SEIR EBM that deterministically predicts the infected, infectious and clinical prevalence of the herd over time. The parameterisation of the EBM ODE system is dependent on the strain of FMD, the relative infectiousness and susceptibility of the species, and the production system (which influences the degree of contact between animals). Modelling the spread of disease within a herd deterministically is reasonable for such a highly contagious disease as FMD, that once introduced into a susceptible herd will typically progress

Table 1
Farm and herd types used in the AADIS ABM.

Farm type	Number of farms	Number of animals mean (min – max)	Herd type	Number of herds
Extensive beef	1331	1909 (1200–46,575)	Extensive beef	3993
Intensive beef	51,383	280 (30–7436)	Intensive beef	51,383
Feedlot	508	1825 (100–39,963)	Feedlot	508
Mixed beef/sheep	21,556	242 (30–5700)	Mixed beef	21,556
			Mixed sheep	21,556
Dairy	8675	298 (40–2742)	Dairy	8675
Small pigs	1873	244 (40–4850)	Small pigs	1873
Large pigs	333	4922 (1000–17,896)	Large pigs	333
Sheep	22,150	1649 (20–44,000)	Sheep	22,150
Small holder	103,641	5 (1–14)	Small holder	103,641
Total	**202,775**			**235,668**

unchecked (Meyer and Knudsen, 2001; Carpenter et al., 2003). The SEIR ODE-based EBM was chosen as it is well-understood and easily solved using standard numerical techniques (Cash and Karp, 1990). An ODE-based EBM is computationally efficient as the system is solved once to yield compartmental proportions over the entire solution interval. The solution remains in place up until an external ABM event (such as culling or vaccination), acts upon the herd agent. For example, if a herd is vaccinated the EBM reacts by resolving the ODE system to reflect increasing levels of immunity from the day of inoculation through to effective immunity. The EBM thus adapts and provides a dynamic representation of within-herd prevalence.

A herd is both a population for the purposes of within-herd disease spread and an individual agent for the purposes of between-herd disease spread. The EBM-generated predictions of infected, infectious and clinical prevalence over time, feed into ABM decisions on the spread of disease between herds and the control of disease. The AADIS ABM environment is comprised of disease spread pathways (direct, indirect, local, airborne, saleyard), and control measures (detection of the first infected premises, movement restrictions, surveillance, tracing of direct/indirect movements on/off an infected premises, reporting of suspect premises, culling, disposal and disinfection of infected premises, and vaccination) (Bradhurst et al., 2015). The spread pathways and control measures can be thought of as *components* of the ABM environment. Each component operates independently which in turn provides flexibility for the modeller. Individual components can be disabled/enabled/modified with minimal impact on other components. For example, the five discrete spread pathways can be seamlessly replaced with a single jump diffusion spread pathway.

Epidemics are multi-scale when the mechanisms and rates of disease spread within a sub-population are distinct from those between sub-populations (Carpenter et al., 2003; Balcan et al., 2010). Whereas the spread of disease within a homogeneous herd is governed by species, pathogen and production system, the spread of disease between farms is influenced by more heterogeneous and irregular factors such as contact networks, market practices, distances between farms, geography and weather. The AADIS hybrid model architecture captures this by decoupling the EBM and ABM spread mechanisms. The ABM simply requires a herd agent's EBM to predict infected, infectious and clinical prevalence over time. This means that alternate EBMs such as the Reed-Frost approach (Bates et al., 2003), can be employed with minimal impact on the ABM.

2.2. Asynchronous software architecture

An ABM is comprised of autonomous agents that interact with each other, and with an environment. The relative complexity of the agents and the environment depends on the modelling domain. An ABM environment can be as simple as a two-dimensional lattice or as complex as a nation. An agent can be as simple as a cell, or as complex as the resident of a large city. A livestock epidemic exists in a complex, heterogeneous and irregular environment with respect to climate, geography, biosecurity levels on individual farms, production systems, market systems, jurisdiction-dependent disease control policies and resourcing. In a similar spirit to Claude Bernard's counter to Louis Pasteur's germ theory, that the 'pathogen is nothing, the terrain is everything' (Longmore et al., 2014), an agent outside the context of an environment is 'effectively useless' (Odell et al., 2003). If the environment is 'removed' from an outbreak all that is left is a disconnected meta-population of susceptible herds that will never interact with virus carrying animals, plumes or fomites, and thus never become infected. The importance of the outbreak environment is reflected in the AADIS ABM design with a detailed environment that is spatial, stochastic, active and concurrent, and herd agents that are simplified and lightweight. The components of the AADIS ABM environment have independent threads of execution and operate concurrently. The AADIS ABM simulates the spread and control of disease in discrete time steps of a day.

The need for agent autonomy in an ABM often leads to a software implementation where each agent has a separate thread of execution. This approach, however, does not scale well for large populations as platform thread/process limits are quickly reached (Bellifemine et al., 2001; Shi et al., 2014). In the absence of a specialised parallel hardware platform it is simply not feasible for a model to have large numbers of threads/processes. Strategies for handling large populations include lightweight agents that share pools of threads (Kim et al., 2007), custom memory management (Parker and Epstein, 2011), and aggregated 'super-individuals' (Parry and Evans, 2008). Each herd agent in the AADIS ABM has autonomous state and logic but is not threaded. At the start of a simulation day the ABM environment components independently and concurrently proceed with their daily processing, making various stochastic decisions on the spread and control of disease amongst the herd population. During this phase the cohort of herd agents is read-only. As each component finishes its daily processing a set of herd/farm update events are sent asynchronously to the ABM 'scheduler' where they are queued. When all updates for the day have been received they are collated and submitted to the cohort of herd agents. All herd agent updates are processed on the ABM scheduler's thread of execution. If, for example, a herd agent receives a vaccination message it reacts by resolving its EBM ODE system which yields updated within-herd prevalence predictions. Once all the queued herd/farm updates have been processed the new herd/farm reality is released back into the environment for the start of the next simulation day.

As the environment components are independent and concurrent it is inevitable that at some stage one or more components will attempt to act upon the same herd/farm on the same day. In such cases it is the job of the ABM scheduler to arbitrate and choose a particular update to succeed. The arbitration may be random or rule-based. For example, if the direct and indirect spread pathways both attempt to infect the same herd on the same day then the scheduler randomly selects one pathway to succeed. On the other hand, if for example, the culling component and the vaccination component both attempt to control the same farm on the same day, then the scheduler always gives priority to culling.

There are parallels between the AADIS ABM architecture and the blackboard design pattern that is sometimes employed in artificial intelligence applications (Corkhill, 1991; Buschmann et al., 1996). The blackboard pattern stems from the analogy of multiple professors (knowledge sources), working on a complex problem and sharing a single chalkboard. Each professor works independently on a sub-problem specific to their individual specialisation. Whilst individual professors cannot solve the greater problem alone, the iterative sharing of partial solutions on the blackboard contributes to the group's overall understanding of the problem. In a similar vein, each ABM component is an independent source of knowledge for a specific aspect of an epidemic. The cohort of herds/farms is the 'blackboard' from which the ABM knowledge sources obtain their view of the epidemic 'problem'. ABM components work independently and concurrently on a sub-problem of the epidemic with no knowledge of, or assistance from, other components, and iteratively contribute daily 'partial solutions' onto the blackboard. The ABM scheduler is the blackboard 'controller' and arbitrates when components submit conflicting partial solutions. Over time, a solution to the greater problem emerges on the blackboard. In the case of a livestock epidemic, the emergent solution is the spatiotemporal

spread and control of disease in the population of herds/farms.

2.3. Grid-based spatial indexing

The AADIS ABM is data-driven and makes constant and intensive use of the underlying data. This includes the national herd population of FMD-susceptible livestock, livestock movements, weather data, pathogen specific transmission characteristics, control measures, and resources (Bradhurst et al., 2015). The components of the AADIS ABM environment issue a range of spatial queries involving herds, farms, weather stations, saleyards and jurisdiction-based regions. Examples of spatial queries are: 'locate all susceptible herds within 3 km of a specific infected herd', and 'calculate the distance and bearing between an infected herd and a specific susceptible herd'. Incorporating spatially-referenced data enhances the realism of a model, but this comes with increased computational complexity. Efficiently managing spatial objects, spatial relationships and spatial queries in a large-scale simulation model can be challenging. One-dimensional indexing techniques such as primary and secondary keys do not extend naturally to higher-dimensional geographic data (Guttman, 1984). A spatial query may involve data not explicitly stored in the database, for example, the intersection of spatial objects (Samet, 1995). In the absence of some form of spatial indexing, spatial queries can result in the sequential scanning of database records. The performance of spatially-based models then becomes heavily dependent on the size of the underlying population.

The AADIS ABM employs an in-memory database in conjunction with a custom grid-based spatial index scheme to efficiently handle spatial queries over the national population of FMD-susceptible herds. During model initialisation all data are retrieved from a disk-based relational database (PostgreSQL, 2015), and cached in a simple custom in-memory database. Records can be fetched from the cache based on primary and secondary keys. This provides indexed data access in terms of microseconds rather than in terms of milliseconds through Structured Query Language (SQL) exchanges with the PostgreSQL server. Also during model initialisation, a national grid is created based on configurable latitude and longitude boundaries, and cell dimensions (default 10 km × 10 km). In effect, a cellular automata-style lattice is superimposed over the continuous geographical environment (Fig. 1).

The grid cells are numbered in row-major order and each herd is assigned a home grid cell according to its latitude and longitude. Fig. 2 depicts the Moore neighbourhood with radius $r = 1$ (Weisstein, 2015) of cell ID 13. The red (in the web version) dots represent herds located in the cells.

A grid lookup table (Fig. 3) is constructed that maps the ID of each populated cell to a list of the constituent herd IDs. The empty cells contain Java null references and are effectively just placemarkers in the addressing scheme described herein.

As the cells are uniformly sized and the IDs contiguous, the Moore neighbourhood for any cell is derived through simple arithmetic on the cell ID. For any cell ID i, the cell IDs of the immediate Moore neighbourhood ($r = 1$) are given by:

$$\text{west}(i) = i - 1 \quad (1 < i \le \text{n},\ i\text{mod}(\text{c}) \neq 1) \tag{1}$$

$$\text{east}(i) = i + 1 \quad (1 \le i < \text{n},\ i\text{mod}(\text{c}) \neq 0) \tag{2}$$

$$\text{north}(i) = i - \text{c} \quad (\text{c} < i \le \text{n}) \tag{3}$$

$$\text{south}(i) = i + \text{c} \quad (1 \le i \le \text{n} - \text{c}) \tag{4}$$

$$\text{northwest}(i) = i - \text{c} - 1 \quad (\text{c} < i \le \text{n},\ i\text{mod}(\text{c}) \neq 1) \tag{5}$$

$$\text{northeast}(i) = i - \text{c} + 1 \quad (\text{c} < i \le \text{n},\ i\text{mod}(\text{c}) \neq 0) \tag{6}$$

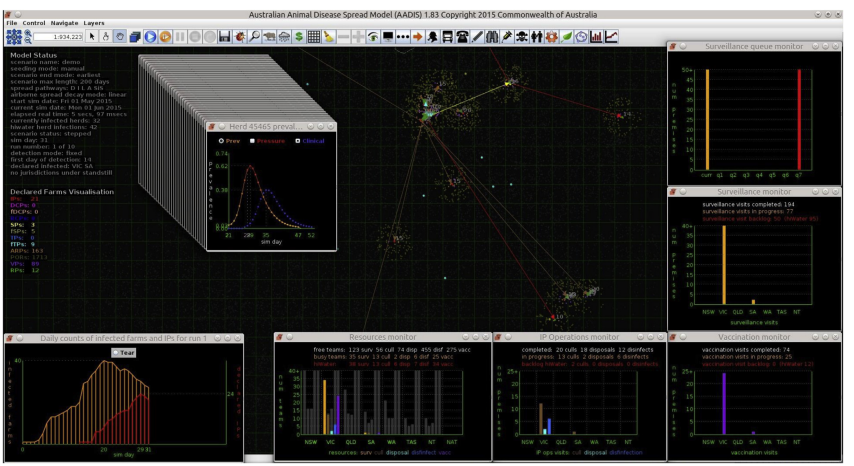


Fig. 1. AADIS dynamic outbreak visualisation with optional display of the grid used for spatial indexing.

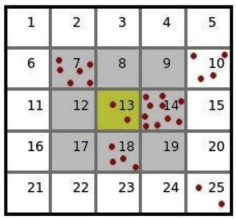


Fig. 2. Visualisation of the Moore neighbourhood for a cell.

$$\text{southwest}(i) = i + \text{c} - 1 \quad (1 \le i \le \text{n} - \text{c},\ i\text{mod}(\text{c}) \ne 1) \tag{7}$$

$$\text{southeast}(i) = i + \text{c} + 1 \quad (1 \le i \le \text{n} - \text{c},\ i\text{mod}(\text{c}) \ne 0) \tag{8}$$

where

n = number of cells in the grid
c = number of columns in the grid

Equations (1)–(8) are used as primitives to obtain the IDs of cells in the extended Moore neighbourhood ($r > 0$). For example, the northerly neighbours of cell i within radius r are determined by simply iterating over r in a northerly direction:

```
create a list to hold the neighbouring cell IDs;
int neighbour = i;
for (int row = 0; row < r; row++) {
    neighbour = north(neighbour);
    add neighbour to the list;
}
```

Consider, for example, the spatial query 'find all herds within x km of a particular infected herd'. The grid-based spatial indexing scheme addresses this with a blend of table lookups and simple arithmetic:

1) An extended Moore neighbourhood is defined for the home cell of the infected herd that fully encloses the circular search area (Fig. 4). The required radius r of the neighbourhood is easily determined as the cells are uniform.
2) The herd IDs corresponding to all cells in the Moore neighbourhood of radius r are retrieved from the grid lookup table.
3) The herds that lie outside the circle but inside the Moore neighbourhood are discarded from the set. Distances between herds are dynamically calculated using the Haversine formula on the points of latitude and longitude (Williams, 2011).
4) The set of candidate herd IDs is returned to the client. The client then uses the herd IDs to retrieve herd data as required from the herd table in the-memory database.

2.4. Evaluation of performance gains

Two studies were conducted to assess the computational efficiency of the AADIS ABM. Firstly, the spatial query response time of the grid-based spatial indexing scheme was compared with an R-Tree-based spatial indexing scheme. Secondly, the scenario runtime performance of the AADIS ABM was compared with the AusSpread microsimulation in the context of a regional simulation of FMD spread and control.

2.4.1. Comparison of grid-based and R-Tree-over-GiST spatial indexing

The response time of spatial queries using grid-based spatial indexing was compared to that of the R-Tree-over-GiST (Generalised Search Tree) spatial indexing provided in the PostGIS extension to PostgreSQL. When the AADIS ABM (optionally) employs R-Tree-

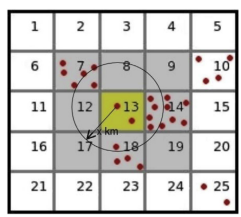


Fig. 4. Moore neighbourhood enclosing a spatial query search radius.

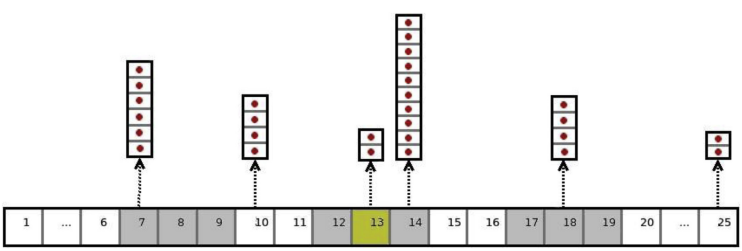


Fig. 3. The grid lookup table maps grid cell IDs to lists of herd IDs.

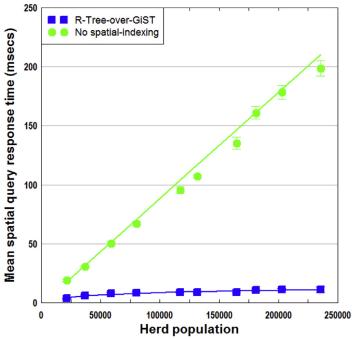


Fig. 5. Spatial indexing vs. no spatial indexing.

over-GiST spatial indexing, PostGIS geometric *point* objects are precomputed for each herd and spatial queries are carried out via SQL exchanges with the PostgreSQL server. When the AADIS ABM employs grid-based spatial indexing, the location of a herd is defined by a point of latitude and longitude, and the PostgreSQL database is not involved in spatial queries. R-Tree-over-GiST spatial indexing was used as a baseline for assessing the performance and scalability of the grid-based spatial indexing system. To illustrate the importance of spatial indexing, the response time of PostGIS spatial queries with no spatial indexing was also recorded.

The test scenario was a 21-day uncontrolled outbreak of FMD starting in a medium-sized pig herd. The scenario was run 100 times for each of the three spatial query approaches (no spatial indexing, R-Tree-over-GiST and grid-based). This was repeated across 10 herd populations ranging from 21,617 up to 235,668 FMD-susceptible herds. The test hardware platform was a quad-core laptop with 16 GB RAM, running 64-bit Kubuntu Linux™. The

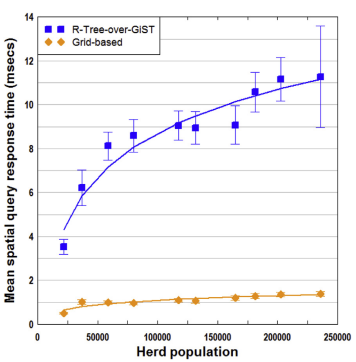


Fig. 6. R-Tree-over-GiST vs. grid-based spatial indexing.

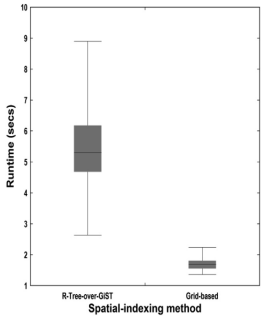


Fig. 7. Mean scenario run times for R-Tree-over-GiST vs. grid-based spatial-indexing.

Stata/IC statistical package (Stata, 2015) was used to check for significant differences between the following model outputs for each of the three spatial indexing methods:

- total number of infected premises,
- number of infections by disease spread pathway (direct, indirect, local, saleyard, airborne),
- size of the infected area based on the convex hull of all infected premises.

Data sets were imported into Stata and checked for normality. Non-parametric statistical methods were used throughout this analysis as some data sets were non-normal and could not be

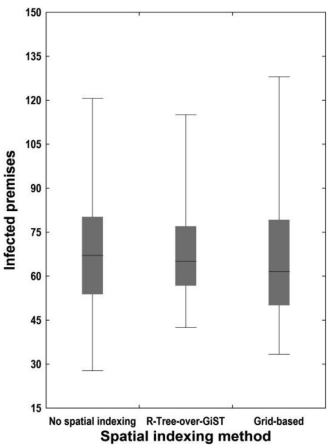


Fig. 8. Effect of spatial indexing method on the number of infected premises.

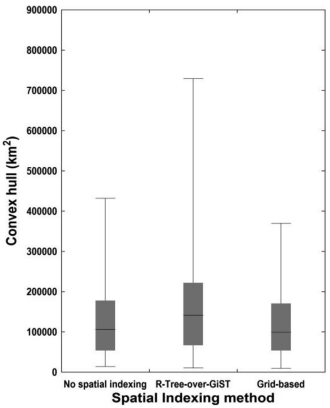


Fig. 9. Effect of spatial indexing method on the area of infection.

transformed to normality by standard transformation techniques. The number of infected premises, convex hull area, spatial query response time, and scenario run time were analysed using the Kruskal–Wallis test for comparison of multiple independent groups of data. Post hoc analysis to identify differences between strategies was conducted using the Kruskal–Wallis test with the significance level adjusted per the Bonferroni correction for multiple pairwise comparisons. The proportions of disease spread by each of the five spread pathways were compared using Pearson's chi-squared test. Results are presented as box plots (Figs. 7–9), where a box represents the interquartile range, the horizontal line inside the box represents the median value, and the whiskers represent the extents of the 95% probability interval.

2.4.2. Comparison of the AADIS ABM with the AusSpread microsimulation

The AADIS ABM herd dataset was temporarily reduced from 235,668 to 42,217, corresponding to the livestock population of the state of Victoria. FMD was introduced into five herds of different types (small pig, medium pig, dairy, sheep and beef), and allowed to spread up until fixed detection on the 21st day. At this point the standard Australian control measures for an FMD outbreak were applied per the Australian Veterinarian Emergency Plan (AUSVETPLAN) (Animal Health Australia, 2014b). These include:

- The establishment of a national livestock standstill that imposes total movement controls on all species susceptible to FMD for a minimum of three days.
- Quarantine and movement controls of animals, animal products and fomites in declared areas in order to minimise the spread of infection. A 'restricted area' (RA) of minimum radius 3 km is established around each 'infected premises' (IP) and 'dangerous contact premises' (DCP). An RA imposes the highest levels of surveillance and movement controls. A 'control area' (CA) of minimum radius 10 km is also established around each IP and DCP. A CA is intended to be a disease-free buffer between the (known-to-be infected) RAs and (the believed to be uninfected) areas outside the controlled areas. A CA imposes lower levels of surveillance and movement controls than an RA.
- Tracing and surveillance to determine the source and extent of infection. A 'trace premises' (TP) is a temporary classification for a premises that has been identified through tracing has having been potentially exposed to the FMD virus, and is awaiting surveillance. A 'suspect premises' (SP) is a temporary classification for a premises that has been reported as containing susceptible animal(s) that are exhibiting clinical signs consistent with FMD, and is awaiting surveillance.
- Valuation and destruction of animals on IPs and potentially on DCPs.
- Disposal of destroyed animals and infected animal products, and decontamination of depopulated premises. An IP is re-classified as a 'resolved premises' (RP) when all IP operations have been completed.

Each of the five scenarios was run 1000 times under the AADIS ABM and 100 times under AusSpread, and the following outputs

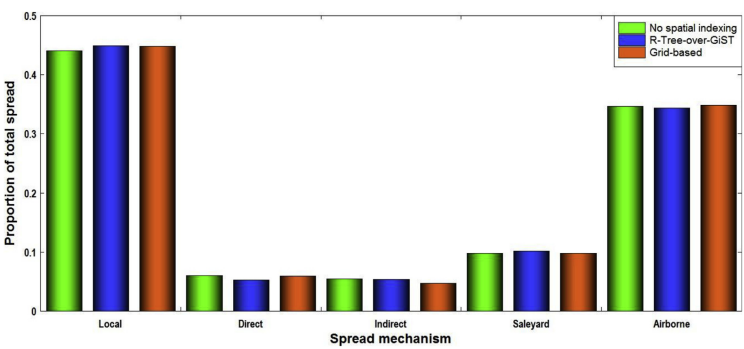


Fig. 10. Effect of spatial indexing method on disease spread mechanism.

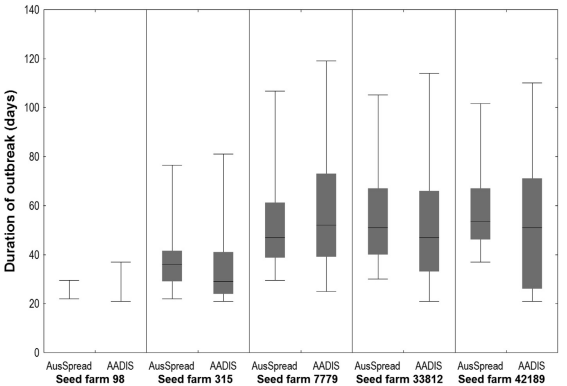


Fig. 11. AADIS ABM vs. AusSpread microsimulation: outbreak duration.

compared:

- average runtime per iteration,
- duration of the outbreak (defined as the simulation day when the last infected premises was declared),
- cumulative number of infected premises,
- cumulative number of culled premises.

The test hardware platform was a quad-core desktop with 16 GB RAM, running 64-bit Microsoft Windows 7™. Results are presented as box plots (Figs. 11 and 12), where a box represents the inter-quartile range, the horizontal line inside the box represents the median value, and the whiskers represent the extents of the 95% probability interval.

3. Results

3.1. Spatial indexing comparison

Fig. 5 illustrates that the mean response time of spatial queries in the absence of spatial indexing was O(n), i.e., linearly dependent on the size n of the population. This is because each spatial query triggered a sequential scan over all herd records. Fig. 5 also shows how R-Tree-over-GiST spatial indexing improved the mean response time of spatial queries to O(log n). Fig. 6 illustrates how the AADIS ABM grid-based spatial indexing scheme provided approximately an eight-fold improvement in the mean spatial query response time over R-Tree-over-GiST spatial indexing, and was less sensitive to the size of the herd population. The whiskers

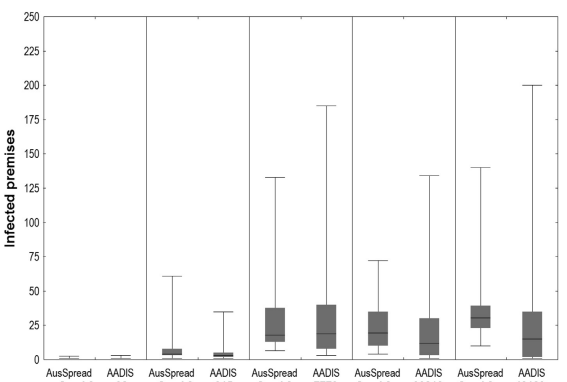


Fig. 12. AADIS ABM vs. AusSpread microsimulation: number of infected premises.

in Figs. 5 and 6 are error bars and represent ±one standard deviation of the mean value.

Fig. 7 illustrates how grid-based spatial indexing provided a three-fold improvement in the mean runtime of a 21-day outbreak across all population sizes, compared with R-Tree-over-GiST spatial indexing. Over the course of 100 iterations of a 21-day outbreak across the national herd population, approximately 80,000 spatial queries were made. The runtime performance of the AADIS ABM was highly dependent on the response time of spatial queries. The simulation took 3 h to run when spatial indexing was not employed, 10 min when R-Tree-over-GiST spatial indexing was used, and 3 min when grid-based spatial indexing was used.

The effects of spatial indexing method on outbreak metrics are shown in Figs. 8–10. There were no significant differences ($p > 0.05$) in total number of infected premises, spread pathway mix, and size of the infected area.

3.2. AusSpread comparison

The AADIS ABM and the AusSpread microsimulation produced broadly similar outbreaks for each of the five scenarios (Table 2, Figs. 11 and 12). Minor outcome variations between the two models were to be expected given the differences in the way the spread of disease within a herd/farm is handled. The AADIS ABM explicitly models within-herd spread with an SEIR mass-action EBM that takes into account herd type and size. The probability of transmission for an infectious consignment depends on the prevalence of the source herd and the consignment size. AusSpread on the other hand does not explicitly model the spread of disease within a farm. An infected farm transitions through atomic infection states according to durations sampled from probability distributions. Relative infectivity varies over time according to a simple step function that applies to all farm types, and does not take outgoing consignment size into account. There was greater statistical error in the AusSpread results, with the sampled mean number of IPs within 18%, 126%, 15%, 12% and 34% respectively of the theoretical population means (with 95% confidence). The AADIS ABM on the other hand generated sample means that were within 12%, 9%, 9%, 14% and 12% respectively of the theoretical population means. This can be explained in terms of the number of runs completed per scenario for each of the models − 100 for AusSpread and 1000 for the AADIS ABM. The convergence of the AusSpread results would have improved with increased runs; however, the slow runtime effectively precluded this.

The key result (from a computational perspective), was that the AADIS ABM conducted comparable simulations on the same computing platform up to 750 times faster than the AusSpread microsimulation. To put this into perspective, the AADIS ABM was able to complete 1000 iterations of the small pig herd scenario in 23 min whereas AusSpread would have taken approximately five days to complete the same number of iterations.

4. Discussion

4.1. Concurrent vs. sequential processing

As the AADIS ABM components operate concurrently, the execution time of a simulation day is effectively limited by the longest time taken by any one component. The AADIS ABM concurrent approach takes advantage of the inexpensive parallelism available on a multi-core hardware platform. Concurrency also reflects the epidemiological reality that spread and control proceed independently and in parallel during an outbreak. In contrast, the constituent tasks of a simulation day in the AusSpread microsimulation are carried out sequentially, i.e., disease is given the opportunity to spread in turn over each pathway followed by the various control measures in turn. The execution time of a simulation day is largely the sum of the times needed for each constituent task. As each AADIS ABM component has its own independent thread of execution it is easy to identify computational bottlenecks. To this end, computationally intensive components can be optimised and/or assigned higher runtime thread priorities. The approach of lightweight agents in an active concurrent environment scales well with population size. Increasing the number of herds does not increase the number of threads in the system. Although not yet explored, it is likely that the AADIS ABM can comfortably extend beyond the Australian population of approximately 236,000 herds.

An advantage of a sequential processing approach is that it is possible to replay a scenario by specifying the pseudo-random number generator seed (and thus controlling the stream of random numbers used when sampling from probability distributions). This temporarily makes a stochastic model deterministic and allows specific aspects of a scenario to be isolated. For example, a particular control measure such as vaccination can be varied and the impact on the scenario outcome directly observed (in the absence of variability introduced through stochasticity). In a concurrent architecture, thread scheduling arbitrarily influences the order that components request random numbers. Such an approach introduces additional stochasticity (beyond the model's innate stochasticity), and a larger number of scenario iterations may be required for model outcomes to statistically converge.

Table 2
AADIS ABM vs. AusSpread microsimulation: runtime performance.

	Small pig herd (ID = 42189, size = 110)		Medium pig herd (ID = 7779, size = 1945)		Dairy herd (ID = 33812, size = 256)		Sheep herd (ID = 98, size = 3065)		Beef herd (ID = 315, size = 532)	
Model	AADIS	AusSpread	AADIS	AusSpread	AADIS	AusSpread	AADIS	AusSpread	AADIS	AusSpread
Number of iterations	1000	100	1000	100	1000	100	1000	100	1000	100
Outbreak length[a,b]	51(21–100)	54(39–97)	52(27–109)	47(31–88)	47(21–104)	51(31–101)	21(21–29)	22(22–28)	29(21–68)	36(22–64)
Median IPs[b]	15(1–127)	31(14–118)	19(4–124)	18(8–126)	12(1–98)	20(5–65)	1(1–2)	1(1–2)	3(1–21)	4(2–23)
Mean IPs[c]	33 ± 2	40 ± 4	36 ± 2	90 ± 58	25 ± 1	24 ± 2	1 ± 0	1 ± 0	6 ± 1	8 ± 1
Convergence[d]	12%	18%	9%	126%	9%	15%	14%	12%	12%	34%
Number of culled farms[b]	15(1–127)	31(14–118)	19(4–124)	18(8–126)	12(1–98)	20(5–65)	1(1–2)	1(1–2)	3(1–21)	4(2–23)
Total elapsed runtime	23 min	755 min	21 min	683 min	19 min	718 min	5 min	376 min	8 min	526 min
Mean time per iteration	1.4 s	7.55 min	1.3 s	6.83 min	1.2 s	7.18 min	0.3 s	3.76 min	0.5 s	5.26 min

[a] Day that the last IP was declared.
[b] Median with 90% probability interval.
[c] Sample mean ± standard error of the mean.
[d] Percentage standard error of the sample mean with 95% confidence per Driels and Shin, 2004.

4.2. Grid-based spatial indexing

There are several characteristics of the AADIS ABM data that are a good fit for a uniform grid-based spatial indexing system:

- There is no requirement to dynamically write data back into the PostgreSQL database. Epidemiological outputs are written to comma-separated value files for external statistical analysis. As the data are static and modestly sized, once the database has been initialised, all tables are cached, and the database is no longer referenced. As there is no need to access the database for non-spatial queries, it is a natural extension to not access the database for spatial queries as well.
- All spatially-referenced data (herds, farms, saleyards and weather stations) pertain to stationary entities. Although consignments of animals may move between herds, abattoirs and saleyards, herds are considered to have constant size over time, and a fixed location. Stationary spatial objects suit the simplicity of a uniform grid-based spatial indexing scheme, as there is no need to dynamically maintain the grid. Mobile spatial objects require a more complex dynamic indexing scheme to efficiently update object location mappings without impacting overall database performance (Kwon et al., 2002; Xia and Prabhakar, 2003; Lee et al., 2003).
- It is anticipated that the AADIS ABM will incorporate raster-based data sources such as weather, vegetation, wild animal and insect vector distributions. A lattice such as that used in a grid-based spatial indexing scheme is a natural fit for these data (Doran and Laffan, 2005).
- The data driving the AADIS ABM are specifically structured to eliminate the need for spatial objects. Herds and farms are represented as points rather than polygons. This simplifies spatial queries from polygon intersections to simple distances and bearing calculations. Weather stations, saleyards, local government areas (LGAs) and states/territories are also not represented as spatial objects. Each herd has attributes identifying the IDs of its jurisdictional area, LGA and closest weather station. A spatial query as to whether a herd is in a particular state/LGA, is thus simplified from the intersection of a point with an irregular area to a simple herd attribute read. When, for example, the model determines if an infected herd poses an airborne threat to a susceptible herd on a particular day, the prevailing weather conditions at the closest weather station are a simple indexed lookup based on the weather station ID. As part of this ID cross-referencing scheme, the model maintains various lookup tables (similar to the grid lookup table in Fig. 3), that map LGA IDs to lists of herd IDs, and jurisdiction IDs to lists of farm IDs.

One criticism of uniform grid-based spatial indexing is the non-efficient handling of skewed population densities (Lettich et al., 2014). The AADIS ABM herd population mapped onto a uniform grid indeed presents highly variable density. The default grid cell dimensions of 10 km $\times$ 10 km result in herd densities ranging from 0 to 264 with a median of four herds per cell. Further, of the 167,028 total cells approximately 86% of the cells are devoid of herds. The desire to efficiently handle variable population densities lead to the development of variable grid cell size schemes such as quad trees (Finkel and Bentley, 1974). High density cells are disaggregated into four sub-cells, and so on, until all populated cells are in the desired density range. The downside of variable cell sizes is an increase in the complexity of cell addressing and grid search schemes. A uniform grid with contiguous IDs is, however, accessed via simple arithmetic. It is trivial to calculate the home grid cell for any given point of latitude and longitude, and also to identify the extended Moore neighbourhood cells of any given cell.

An alternative approach to spatial indexing is to satisfy spatial queries through 'neighbour lists' (Dominguez et al., 2010). For example, all neighbouring herds within 3 km, 10 km, 50 km and 100 km can be precomputed for every herd. This approach may be appropriate when there is limited variability in spatial query distances, and when populations are moderately sized. However for highly stochastic models with large populations this approach is memory intensive and not particularly granular. A grid-based spatial indexing scheme is in effect a generalisation of neighbour lists with granularity determined by the cell size.

AusSpread is an example of a traditional approach to spatially-explicit modelling whereby the storage and querying of spatial objects is delegated to an underlying GIS platform, in this case MapInfo which employs R-Tree spatial indexing. The AADIS ABM on the other hand through a customised strategy of preprocessed data, caching, lookup-tables and a grid-based spatial indexing scheme, is able to avoid spatial objects entirely. The uniform grid-based spatial indexing scheme offers an eight-fold improvement in mean spatial query response time over the PostGIS R-Tree-over-GiST spatial indexing system. This in turn yields a two to three-fold overall improvement in the mean runtime of a scenario. The spatial query response time of PostgreSQL/PostGIS could likely have been improved through techniques such as server optimisation and server prepared SQL statements. However, the optimisation of relational databases, servers and SQL for geospatial efficiency is quite a specialised area. The AADIS ABM uniform grid-based spatial indexing scheme is simple to implement, test and maintain, and requires no specialised knowledge of mathematics, PostgreSQL and PostGIS. The tactic of eliminating spatial objects is possible as the entire database is easily cached in memory and spatial entities are stationary. Models with larger populations, more complex spatial requirements and/or the need to dynamically update data may be better suited a more database-centric approach to spatial processing.

5. Conclusions

ABMs have a natural affinity for capturing population heterogeneity, stochasticity, spatial relationships, social systems and policy elements. An example of a field where an agent-based approach works well is animal health policy development and disease planning. The ability to incorporate livestock population heterogeneity, regional variation, jurisdiction-dependent control policies, logistics and socio-political aspects into decision support tools, brings realism to the study of complex disease ecosystems. However, when populations are large, the associated computational load may require highly parallel hardware platforms and custom software implementations. This tends to limit large-scale modelling to universities, defence departments, and scientific research organisations.

We have described three strategies that allow the AADIS ABM to complete complex scenarios of disease spread and control in the national Australian population of FMD-susceptible livestock on a personal computer:

- A hybrid model architecture that reduces the ABM agent population from over 100 million animal agents to approximately 236,000 herd agents. Each herd agent has an embedded deterministic EBM that simulates the spread of disease within the herd. The spread of disease between herds and the control of disease are modelled stochastically and spatially with an agent-based approach.
- An asynchronous software architecture that features light-weight agents and a rich concurrent ABM environment.

- Grid-based spatial indexing that offers a significant improvement in the mean spatial query response time over the standard PostgreSQL/PostGIS R-Tree-over-GiST spatial indexing.

The AADIS ABM is able to complete one thousand iterations of a national-scale FMD outbreak in less than an hour on a quad-core laptop, with an iteration having on average 40 IPs. This scenario includes local, direct, saleyard, indirect and airborne spread, passive first IP detection, movement restrictions, surveillance, direct, indirect and saleyard tracing, suspect premises reporting, culling, disposal, disinfection, suppressive ring vaccination, dynamic resource management, detailed report writing, and 'real-time' graphical visualisation of the outbreak. When a stochastic ABM is computationally efficient it is possible to complete large numbers of iterations, which in turn improves statistical convergence.

The approach of embedding EBMs in lightweight agents, and an ABM environment that is active and concurrent, may have utility in other modelling domains that deal with large populations. Further, if a spatially-explicit ABM has simple stationary spatial objects, then uniform grid-based spatial indexing may offer computational advantages over R-Tree-over-GiST spatial indexing.

Acknowledgements

The AADIS ABM is a joint research venture between the Australian Department of Agriculture and Water Resources and the University of New England (UNE). The authors acknowledge both organisations for their support of the project. The authors would also like to thank Professor A.S.M. Sajeev who was a strong supporter of the project whilst at UNE. This work is funded under the Australian Government's Animal Biosecurity Response and Reform Program.

References

Australian Bureau of Statistics, 2014. Agricultural Commodities, Australia. http://www.abs.gov.au/ausstats/abs@.nsf/mf/7121.0.

Animal Health Australia, 2014a. Animal Health in Australia 2013. Animal Health Australia, Canberra ACT. http://www.animalhealthaustralia.com.au/programs/adsp/nahis/ahia.cfm.

Animal Health Australia, 2014b. Disease Strategy: Foot-and-mouth Disease (Version 3.4). Australian Veterinarian Emergency Plan (AUSVETPLAN), third ed. Standing Council on Primary Industries, Canberra ACT. http://www.animalhealthaustralia.com.au/programs/emergency-animal-disease-preparedness/ausvetplan/.

Balcan, D., Gonçalves, B., Hu, H., Ramasco, J.J., Colizza, V., Vespignani, A., 2010. Modeling the spatial spread of infectious diseases: the global epidemic and mobility computational model. J. Comput. Sci. 1 (3), 132–145. http://dx.doi.org/10.1016/j.jocs.2010.07.002.

Bansal, S., Grenfell, B.T., Ancel Meyers, L., 2007. When individual behaviour matters: homogeneous and network models in epidemiology. J. R. Soc. Interface 4 (16), 879–891. http://dx.doi.org/10.1098/rsif.2007.1100.

Bates, T.W., Thurmond, M.C., Carpenter, T.E., 2003. Description of an epidemic simulation model for use in evaluating strategies to control an outbreak of foot-and-mouth disease. Am. J. Veterinarian Res. 64 (2), 195–204. http://dx.doi.org/10.2460/ajvr.2003.64.195.

BBN, 2015. OpenMap. BBN Technologies. http://openmap.bbn.com/.

Bellifemine, F., Poggi, A., Rimassa, G., 2001. Developing multi-agent systems with a FIPA-compliant agent framework. Softw. Pract. Exp. 31, 103–128. http://dx.doi.org/10.1002/1097-024X(200102)31:2<103::AID-SPE358>3.0.CO;2-O.

Bradhurst, R.A., Roche, S.E., Garner, M.G., Sajeev, A.S.M., Kwan, P., 2013. Modelling the spread of livestock disease on a national scale: the case for a hybrid approach. In: Proceedings of the 20th International Congress on Modelling and Simulation (MODSIM2013), Modelling and Simulation Society of Australia and New Zealand, Adelaide, Australia, December 2013, pp. 345–351.

Bradhurst, R.A., Roche, S.E., East, I.J., Kwan, P., Garner, M.G., 2015. A hybrid modelling approach to simulating foot-and-mouth disease outbreaks in Australian livestock. Front. Environ. Sci. 3 (17) http://dx.doi.org/10.3389/fenvs.2015.00017.

Buetre, B., Wicks, S., Kruger, H., Millist, N., Yainshet, A., Garner, G., et al., 2013. Potential Socio-economic Impacts of an Outbreak of Foot-and-mouth Disease in Australia. Research Report 13.11, October 2013. Australian Bureau of Agricultural and Resource Economics and Sciences (ABARES). Commonwealth of Australia, Canberra, ACT, Australia. http://apo.org.au/research/potential-socio-economic-impacts-outbreak-foot-and-mouth-disease-australia.

Buschmann, F., Meunier, R., Rohnert, H., Sommerlad, P., Stal, M., 1996. Pattern-oriented Software Architecture — a System of Patterns. John Wiley & Sons, 1996.

Carley, K.M., Fridsma, D.B., Casman, E., Yahja, A., Altman, N., Chen, L., Kaminsky, B., Nave, D., 2006. BioWar: scalable agent-based model of bioattacks. IEEE Trans. Syst. Man Cybern. Part A Syst. Humans 36 (2), 252–265. http://dx.doi.org/10.1109/TSMCA.2005.851291.

Carpenter, T.E., Bates, T.W., Thurmond, M.C., 2003. The importance of including intra-herd transmission in a foot-and-mouth disease model. In: Proceedings of the 10th Symposium of the International Society for Veterinary Epidemiology and Economics, Vina del Mar, Chile, November 2003, New Concepts — Modelling Session, pp. 249–251.

Cash, J.R., Karp, A.R., 1990. A variable order Runge-Kutta method for initial value problems with rapidly varying right-hand sides. ACM Trans. Math. Softw. 16 (3), 201–222. http://dx.doi.org/10.1145/79505.79507.

Corkhill, D.D., 1991. Blackboard systems. AI Expert 6 (9), 40–47. http://dancorkill.home.comcast.net/~dancorkill/pubs/ai-expert.pdf.

Crooks, A.T., Heppenstall, A.J., 2012. Introduction to agent-based modelling. In: Heppenstall, A.J., Crooks, A.T., See, L.M., Batty, M. (Eds.), Agent-based Models of Geographical Systems. Springer, Netherlands, pp. 85–105. http://dx.doi.org/10.1007/978-90-481-8927-4_5.

Davidsson, P., 2001. Multi agent simulation: beyond social simulation. multi-agent-based simulation. Lect. Notes Comput. Sci. 1979, 97–107. http://dx.doi.org/10.1007/3-540-44561-7_7.

Dietz, K., Heesterbeek, J.A.P., 2002. Daniel Bernoulli's epidemiological model revisited. Math. Biosci. 180 (1), 1–21. http://dx.doi.org/10.1016/S0025-5564(02)00122-0.

Dominguez, J.M., Crespo, A.J.C., Gomez-Gesteira, M., Marongiu, J.C., 2010. Neighbour lists in smoothed particle hydrodynamics. Int. J. Numer. Methods Fluids 67 (12), 2026–2042. http://dx.doi.org/10.1002/fld.2481.

Doran, R.J., Laffan, S.W., 2005. Simulating the spatial dynamics of foot and mouth disease outbreaks in feral pigs and livestock in Queensland, Australia, using a susceptible-infected-recovered cellular automata model. Prev. Veterinary Med. 70 (1–2), 133–152. http://dx.doi.org/10.1016/j.prevetmed.2005.03.002.

Driels, M.R., Shin, Y.S., 2004. Determining the Number of Iterations for Monte Carlo Simulations of Weapon Effectiveness (No. NPS-MAE-04-005). Naval Postgraduate School, Monterey California, Department of Mechanical and Astronomical Engineering. http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA423541.

D'Souza, R.M., Marino, S., Kirschner, D., 2009. Data-parallel algorithms for agent-based model simulation of tuberculosis on graphics processing units. In: Proceedings of the 2009 Spring Simulation Multiconference (SpringSim '09), Society for Computer Simulation International, San Diego, USA, March 2009, Article 21, pp. 1–12 acm:1639831.

Finkel, R.A., Bentley, J.L., 1974. Quad trees: a data structure for retrieval on composite keys. Acta Inform. 4 (1), 1–9. http://dx.doi.org/10.1007/BF00288933.

Garner, M.G., Beckett, S.D., 2005. Modelling the spread of foot-and-mouth disease in Australia. Aust. Veterinary J. 83 (12), 758–766. http://dx.doi.org/10.1111/j.1751-0813.2005.tb11589.x.

Garner, M.G., Dubé, C., Stevenson, M.A., Sanson, R.L., Estrada, C., Griffen, J., 2007. Evaluating alternative approaches to managing animal disease outbreaks — the role of modelling in policy formulation. Veterinaria Ital. 43 (2), 285–298 pmid: 20411517.

Garner, M.G., Bombarderi, N., Cozens, M., Conway, M.L., Wright, T., Paskin, R., East, I.J., 2014. Estimating resource requirements to staff a response to a medium to large outbreak of foot and mouth disease in Australia. Transbound. Emerg. Dis. http://dx.doi.org/10.1111/tbed.12239, June 2014.

Germann, T.C., Kadau, K., Longini, I.M., Macken, C.A., 2006. Mitigation strategies for pandemic influenza in the United States. Proc. Natl. Acad. Sci. 103 (15) http://dx.doi.org/10.1073/pnas.0601266103.

Grassly, N.C., Fraser, C., 2008. Mathematical models of infectious disease transmission. Nat. Rev. Microbiol. 6 (6), 477–487. http://dx.doi.org/10.1038/nrmicro1845.

Guttman, A., 1984. R-Trees — a dynamic index structure for spatial searching. In: Proceedings of the 1984 ACM SIGMOD International Conference on Management of Data, vol. 14(2), pp. 47–57. http://dx.doi.org/10.1145/602259.602266.

Hamra, G., MacLehose, R., Richardson, D., 2013. Markov Chain Monte Carlo: an introduction for epidemiologists. Int. J. Epidemiol. 42 (2), 627–634. http://dx.doi.org/10.1093/ije/dyt043.

Hare, M., Deadman, P., 2004. Further towards a taxonomy of agent-based simulation models in environmental management. Math. Comput. Simul. 64 (1), 25–40. http://dx.doi.org/10.1016/S0378-4754(03)00118-6.

Hethcote, H.W., 2000. The mathematics of infectious diseases. Soc. Ind. Appl. Math. Rev. 42 (4), 599–653. http://dx.doi.org/10.1137/S0036144500371907.

Keeling, M.J., Woolhouse, M.E.J., Shaw, D.J., Matthews, L., Chase-Topping, M., Haydon, D.T., Cornell, S.J., Kappey, J., Wilesmith, J., Grenfell, B.T., 2001. Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. Science 294 (5543), 813–817. http://dx.doi.org/10.1126/science.1065973.

Keeling, M.J., Rohani, P., 2008. Modeling Infectious Diseases in Humans and Animals. Princeton University Press, Princeton and Oxford.

Kennedy, R.C., Lane, K.E., Arifin, S.M.N., Fuentes, A., Hollocher, H., Madey, G.R., 2009. A GIS aware agent-based model of pathogen transmission. Int. J. Intell. Control Syst. 14 (1), 51–61.

Kim, J.H., Han, S., Ko, H., Youn, H.Y., 2007. Prediction-based dynamic thread pool

management of agent platform for ubiquitous computing. In: Proceedings of the 4th International Conference on Ubiquitous Intelligence and Computing (UIC'07), Hong Kong, China, July 2007, pp. 1098–1107.
Kitching, R.P., Thrusfield, M.V., Taylor, N.M., 2006. Use and abuse of mathematical models: an illustration from the 2001 foot and mouth disease epidemic in the United Kingdom. Revue Sci. Tech. (Off. Int. des Epizoot.) 25 (1), 293–311 pmid: 16796055.
Kostova-Vassilevska, T., 2004. On the Use of Models to Assess Foot-and-mouth Disease Transmission and Control. Technical Report UCRL-TR-205241. Lawrence Livermore National Laboratory, Livermore, California, United States. https://e-reports-ext.llnl.gov/pdf/309485.pdf.
Kwon, D., Lee, S., Lee, S., 2002. Indexing the current positions of moving objects – using the lazy update R-Tree. In: Proceedings of the Third International Conference on Mobile Data Management (MDM 2002), Singapore, January 2002, pp. 113–120. http://dx.doi.org/10.1109/MDM.2002.994387.
Lee, M.L., Hsu, W., Jensen, C.S., Cui, B., Teo, K.L., 2003. Supporting frequent updates in R-Trees: a bottom-up approach. In: Proceedings of the 29th International Conference on Very Large Data Bases (VLDB 2003), Very Large Data Bases Endowment Inc., Berlin, Germany, September 2003, 29, pp. 608–619 acmid: 1315504.
Lettich, F., Orlando, S., Silvestri, C., Jensen, C., 2014. Manycore Processing of Repeated Range Queries over Massive Moving Object Observations arxiv: 1411.3212.
Longmore, M., Wilkinson, I., Baldwin, A., Wallin, E., 2014. Oxford Handbook of Clinical Medicine. Oxford University Press, United Kingdom.
Lysenko, M., D'Souza, R.M., 2008. A framework for megascale agent based model simulations on graphics processing units. J. Artif. Soc. Soc. Simul. 11 (4), 10. http://jasss.soc.surrey.ac.uk/11/4/10/10.pdf.
Meat and Livestock Australia, 2014. National Livestock Identification System. http://www.mla.com.au/Meat-safety-and-traceability/National-Livestock-Identification-System.
Meyer, R.F., Knudsen, R.C., 2001. Foot-and-mouth disease: a review of the virus and the symptoms. J. Environ. Health 64 (4), 21–23 pmid:11936028.
Odell, J.J., Parunak, H.V.D., Fleischer, M., Brueckner, S., 2003. Modeling agents and their environment. In: Agent-oriented Software Engineering III, pp. 16–31. Springer Berlin Heidelberg.
Oracle, 2015. Java. Oracle Corporation. http://www.java.com/en/.
OSGeo, 2015. PostGIS. The PostGIS Development Group. http://postgis.net/.
Parker, J., Epstein, J.M., 2011. A distributed platform for global-scale agent-based models of disease transmission. ACM Trans. Model. Comput. Simul. (TOMACS) 22 (1), December, Article 2.
Parry, H.R., Evans, A.J., 2008. A comparative analysis of parallel processing and super-individual methods for improving the computational performance of a large individual-based model. Ecol. Model. 214 (2–4), 141–152. http://dx.doi.org/10.1016/j.ecolmodel.2008.02.002.
Parunak, H.V.D., Savit, R., Riolo, R.L., 1998. Agent-based modeling vs. equation-based modeling: a case study and users' guide. In: Multi-agent Systems and Agent-based Simulation, Lecture Notes in Computer Science, vol. 1534, pp. 10–25. http://dx.doi.org/10.1007/10692956_2.
Pitney Bowes, 2015. MapInfo Professional, Pitney Bowes Inc. http://www.pitneybowes.com/us/location-intelligence-software/mapinfo-suite/mapinfo-professional.html.
PostgreSQL, 2015. PostgreSQL. The PostgreSQL Global Development Group. http://www.postgresql.org/.
Roche, S.E., Garner, M.G., Wicks, R.M., East, I.J., de Witte, K., 2014. How do resources influence control measures during a simulated outbreak of foot and mouth disease in Australia? Prev. Veterinary Med. 113 (4), 436–446. http://dx.doi.org/10.1016/j.prevetmed.2013.12.003.
Samet, H., 1995. Spatial data structures. In: Kim, W. (Ed.), Modern Database Systems: the Object Model, Interoperability, and Beyond. Addison Wesley/ACM Press, Reading, MA, USA, pp. 361–385.
Shi, Z.Z., Wu, C.H., Ben-Arieh, D., 2014. Agent-based model: a surging tool to simulate infectious diseases in the immune system. Open J. Model. Simul. 2 (1), 12–22. http://dx.doi.org/10.4236/ojmsi.2014.21004.
SQL Power Group, 2015. SQL Power Architect Data Modelling and Profiling Tool. SQL Power Group Inc. http://www.sqlpower.ca/page/architect.
Stata, 2015. STATA Intercooled Software v11.0. Stata Corporation. http://www.stata.com/products/which-stata-is-right-for-me/#IC.
Weisstein, E.W., 2015. Moore Neighborhood. MathWorld –A Wolfram Web Resource. http://mathworld.wolfram.com/MooreNeighborhood.html.
Welch, M.C., Kwan, P.W., Sajeev, A.S.M., 2014. Applying GIS and high performance agent-based simulation for managing an old world screwworm fly invasion of Australia. Acta Trop. 138S, S82–S93. http://dx.doi.org/10.1016/j.actatropica.2014.03.021.
Williams, E., 2011. Aviation Formulary V1.46. http://williams.best.vwh.net/avform.htm.
Xia, Y., Prabhakar, S., 2003. Q+Rtree: efficient indexing for moving object databases. In: Proceedings of the Eighth International Conference on Database Systems for Advanced Applications (DASFAA 2003), IEEE Computer Society, Kyoto, Japan, 26-28 March 2003, pp. 175–182. http://dx.doi.org/10.1109/DASFAA.2003.1192381.

References

Anderson, R., & May, R. (1979a). Population biology of infectious diseases: Part I. *Nature*, *280*, 361 - 367.

Anderson, R., & May, R. (1979b). Vaccination and herd immunity to infectious diseases. *Nature*, *318*, 323 - 329.

Anderson, R., & May, R. (1983). Vaccination against rubella and measles: Quantitative investigations of different policies. *Journal of Hygiene*, *90*, 259 - 325.

Anderson, R., & May, R. (1991). *Infectious Diseases of Humans: Dynamics and Control*. Oxford, UK: Oxford University Press.

Begon, M., Bennett, M., Bowers, R., French, N., Hazel, S., & Turner, J. (2002). A clarification of transmission terms in host-microparasite models: Numbers, densities and areas. *Epidemiology and Infection*, *129*, 147 - 153.

Clancy, D., & French, N. (2001). A stochastic model for disease transmission in a managed herd, motivated by *Neospora caninum* amongst dairy cattle. *Mathematical Biosciences*, *170*, 113 - 132.

Coleman, P., & Dye, C. (1996). Immunization coverage required to prevent dog rabies. *Vaccine*, *14*(3), 185 - 186.

Daley, D., & Gani, J. (1999). *Epidemic Modelling*. Cambridge, UK: Cambridge University Press.

Hethcote, H. (2000). The mathematics of infectious diseases. *Society for Industrial and Applied Mathematics Review*, *42*(4), 599 - 653.

Keeling, M., & Rohani, P. (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton, New Jersey, USA: Princeton University Press.

Laegreid, W., & Keen, J. (2004). Estimation of the basic reproduction ratio (R_0) for shiga toxin-producing *Escherichia coli* O157:H7 in beef calves. *Epidemiology and Infection*, *132*(2), 291 - 295.