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Simulation model-based evaluation of a survey program with reference to risk analysis

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Abstract : A stochastic simulation model incorporated with Reed-Frost approach was derived for evaluating diagnostic performance of a test used for a screening program of an infectious disease. The Reed-Frost model was used to characterize the within-herd spread of the disease using a hypothetical example. Specifically, simulation model was aimed to estimate the number infected animals in an infected herd, in which imperfect serologic tests are performed on samples taken from herds and to illustrate better interpreting survey results at herd-level when uncertainty inevitably exists. From a risk analysis point of view, model output could be appropriate in developing economic impact assessment models requiring probabilistic estimates of herd-level performance in susceptible populations. The authors emphasize the importance of knowing the herd-level diagnostic performance, especially in performing emergency surveys in which immediate control measures should be taken following the survey. In this context this model could be used in evaluating efficacy of a survey program and monitoring infection status in the area concerned.

Key words : diagnostic test, Reed-Frost, Risk analysis, simulation, survey

Introduction

In the case of an introduction of foreign animal diseases into a country with disease-freedom or with prevalence below a defined threshold, national quarantine authorities usually turn their concerns the source of the contagious agent which triggered epidemic in the country. At the same time, they also try to determine whether control measures should be initiated aggressively to effectively curb further transmission. From disease control point of view, when investigating the occurrence of infection in an animal population in a country or a region, it is generally more important to identify the clusters of infected animals than infected animal themselves. This situation indicates that overall accuracy of diagnostic tests used for active surveillance needs to be evaluated at herd-level not individual-level.

Most countries will conduct a survey using internationally recognized diagnostic tests on a large sample of animals in areas which infection is suspected. Although the choice of survey strategy depends on its purposes and practical constraints, serologic tests typically are used because they are inexpensive, and are rapid and easy to perform. However, such tests will always be imperfectly sensitive and specific, yielding false positives or false negatives. A survey that results in a few positive test results might not imply infection. The potential incubation period such as bovine tuberculosis, together with imperfect diagnostic tools for detecting preclinical animals, makes it important to the disease control at the herd- or flock-level [12]. In countries in which an infectious disease remains epidemic, a lack of information on important aspects of the epidemiology of the disease has prevented effective control and eradication.

The evaluation of within-herd level tests has been the subject of publications. The value of herd-level testing scheme, as opposed to testing one single animal which is referred to as animal-level testing, depends on several

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factors: herd size, infection prevalence within infected herds, the number of animals sampled [3], the cut-off number of individual-level positive tests required to classify herds as infected [5], and individual-level sensitivity and specificity among herd [10]. Diseases with a long incubation period are difficult to study because of the time that elapses before results are obtained and the cost of conducting experimental studies. Rather, simulation models offer an opportunity to test range of disease-control strategies in a timely manner, enabling cost-effective control programs to be implemented [4, 9].

It is generally accepted that the inclusion of randomness in a deterministic model increases the biological realism of such a model [11]. Therefore, we modeled the spread of a hypothetical infectious disease within an infected herd using a Reed-Frost approach in a hypothetical closed population, taking into account the number days from the infection.

Materials and Methods

Model assumptions

The Reed-Frost model is a state-transition model [1, 11]. Each individual in the population is assumed to exist in mutually exclusive states, susceptible, case, or immune. Transition between states is described by probability of effective contact. The spread of the disease in the herd (number of infected animals in an infected herd) was modeled by the equation: $I_{(t)} = S_{(t-1)}(1 - Q^b)$, where $b = I_{(t-1)} + I_{(t-2)}$, the subscript t serves a time counter, and the length of the time period usually is set to the incubation period of the disease concerned, $I_{(t)}$ the number of infectious cases at the end of time period t (and thus $I_{(t+1)}$ is the number of newly infected and clinically diseased animals at the start of time period $t + 1$), $S_{(t-1)}$ the number of susceptible animals in time period $t - 1$ (and thus $S_{(t)}$ is the number of susceptible animals in time period t), P the probability of one animal making effective contact with another given individual which would result in an infection if one were infectious and the other susceptible, and thus Q the probability of an animal avoiding such a contact, calculated as $1 - P$. This model is typically based on several assumptions, which were described elsewhere [1]. Briefly, the following assumptions were made: (1) infection is spread from an infectious animal to a susceptible only by a specific mode of contact; (2) if infected, an animal will be infectious in the next period only, and thereafter, remain immune and noninfectious; (3) each animal has a fixed and equal probability of adequate contact with other animals within one time period; (4) the study population is closed; (5) animals have equal probability of risk of, and exposure to, infection; and (6) time intervals t are equal to the average period of infectiousness for the disease simulated.

Table 1. Hypothetical number of animals per herd in a target population

Number of animals in the herd (A)			
Minimum	Maximum	Number of herds (B)	Estimated number of animal *
1	4	1000	RiskUniform (min, max)
5	9	1500	
10	14	2000	
15	19	3000	
20	29	800	
30	49	500	
50	99	400	
100	199	300	
200	299	100	
300	500	50	

*RiskUniform distribution was used for each category, and then RiskDiscrete (A, B) function was used to simulate for the number of animals in a herd (N).

Model formulation

For simulation purposes, date of infection (DI) was set to minimum 1 April (denoted as day 0) and maximum 10 April (day 10) in a given year. The incubation period (IP) was considered using the PERT distribution with the range of 3-20 days and the most-likely value of 7 days. This means that infected animals turned truly sero-positive after one time period (7 days). Thus the date of first clinical incidence (DFI) depends on DI and IP. The date of survey (DS) was based on hypothetical distribution on number of sample collected by the number of days since 1 April, and we modeled using discrete distribution. The number of animals in a hypothetical target herd (N) was assumed to follow the structure shown in Table 1. Number of days since the first incidence (NFI) was computed as DS-DFI. Finally, the number of infected and sero-positive animals at the time of survey (NSI) was modeled as followings: the

Table 2. Hypothetical number of animals sampled per herd in a target population

Herd size (head)		
Minimum	Maximum	Number of animals sampled
1	9	2
10	19	3
20	29	4
30	49	5
50	99	6
100	500	10

number of sero-positive animals at time period of t, $IA_{(t)}$, was sequentially calculated by the Reed-Frost equation. Then the number of sero-positive animals in a herd between t − 1 and t was defined as integer value taken from a uniform distribution from IA_{t-1} to IA_t. In this study, P was calculated by dividing the number of effective contacts by the total number of animals in a herd (P = 1 when the number of effective contacts are greater than the herd size). For emergency survey, government authority usually have on-site visit for blood sampling based on herd size. The number of animals sampled per herd (AS) was assumed to have the figures shown in Table 2. Therefore the number of positive

Table 3. Description of parameters for the model and parameter values for Reed-Frost model

Description of variables	Nota-tion	Formula in Excel add-in @Risk
A: Number of infected animals in an infected herd		
Incubation period	IP	RiskPert (3, 7, 20)
Date of infection	DI	RiskUniform (0, 10)
Date of first incidence	DFI	ROUNDUP (RiskPert (DI + IP), 0)
Date of survey	DS	RiskDiscrete using the actual distribution
Number of days since the first incidence	NFI	ROUNDUP ((DS-DFI), 0)
Number of infected and sero-positive animals at the time of survey	NSI	RiskUniform ($IA_{(t-1)}$, $IA_{(t)}$), (from RF model)
B: Deterministic Reed-Frost (RF) model		
Number of new infectious animals at the end of time t	I(t)	$S(t-1)(1-Q^{I(t-1)})$; I(t = 0) = 1
Number of total infectious animals at the end of time t	F(t)	I(t − 1) + I(t); F(t = 0) = I(t = 0)
Number of susceptible animals at the end of time t	S(t)	S(t − 1) + I(t); S(t = 0) = N − I(t = 0)
Number of infected, sero-positive animals at the time period of t	IA(t)	N − S(t); IA(t = 0) = 0; IA(t = 1) = 1
Number of animals in a herd	N	From herd-level sensitivity and specificity
Probability of an effective contact	P	RiskPert (2, 4, 8); if RN, then 1, otherwise R/N
Number of effective contacts per time unit	R	RiskUniform (2, 10)
Probability of avoiding effective contacts	Q	1 − P
C: Herd-level sensitivity and specificity		
Sensitivity	SE	RiskPert (0.9, 0.95, 1)
Specificity	SP	RiskBeta (9700 + 1,10000 − 9700 + 1)
Number of animals in a herd	N	RiskDiscrete (A, B) (from Table 1)
Number of animals sampled	AS	Sampling frame from Table 2
Number of positive animals in sampled animals	PAS	RiskHypergeo (AS, NSI, N)
Number of positive animals in an infected herd	PIS	RiskBinom (PAS, SE) + RiskBinom (AS − PAS, 1 − SP)
Number of positive animals in a disease-free herd	PDF	RiskBinomial(AS, 1 − SP)

animals in sampled animals (PAS) was modeled using RiskHypergeo function. The sensitivity of a serologic test was assumed to follow PERT distribution with minimum 0.9, most likely 0.95 and maximum 1.0. Specificity was estimated from the hypothetical test results of 10,000 samples from infection-free areas, with no true positives, 9,700 true negatives and 120 false positives. Microsoft Excel (Microsoft, USA) and its add-on software, Risk (Palisade, USA) were used to build a stochastic model with Monte-Carlo simulation and to determine the mean, minimum, maximum, and percentile values. Input parameters and their formulae used in the model are summarized in Table 3.

Results

Early detection is essential for infectious disease control, and it is necessary to evaluate those strategies before implementation or movement control in the control area because delayed implementation of control measures could extend the size and length of epidemic. To achieve this goal in performing an emergency survey, it is essential to know the number of animals in an infected herd expected to be test-positive. The mean distribution of NFI was 8.8 days (ranging from −9 to 29 days) with standard deviation of 5.9 days (Fig. 1). Negative values in the figure represent that herds were visited before the first infected animal developed the disease. These ineffective visits comprised approximately 7% of the total visits, indicating that most of herds had at least one diseased animal at the time of survey, if infected. The 90% of the visits covered from −1 to 19 days. The mean date of survey was 23.3 days and 90% of survey covers 19-32 days.

Based on the simulation results in this study, the probabilities that at least 1, 2, or 3 positive animals are detected in an infected herd are 58.9, 19.3, and 7.3%, respectively (Fig. 2). To maximize sensitivity, the cut-off number of positive animals was set to 1. These values can be considered as the point estimates of herd-level sensitivity, and is of our primarily concern. We considered these values reasonably acceptable. One explanation is that small herd sizes in the control area might contribute to the relatively high probability of detecting sero-positive animals in the infected herds. Based on the hypothetical test results of 10,000 samples, number of positive animals in a non-infected herd was estimated mean 0.1, with minimum 0 and maximum 2 heads (Fig. 3).

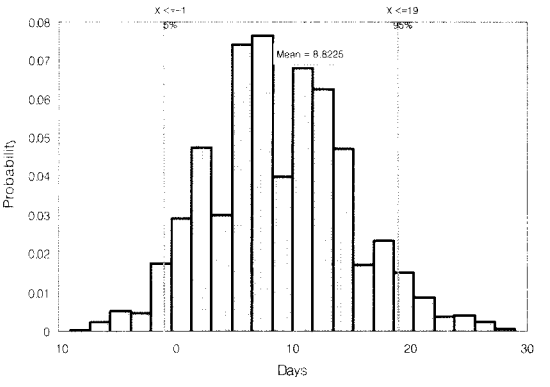

Fig. 1. Distribution of the predicted number of days after the first clinical incidence of a hypothetical disease at the time of survey.

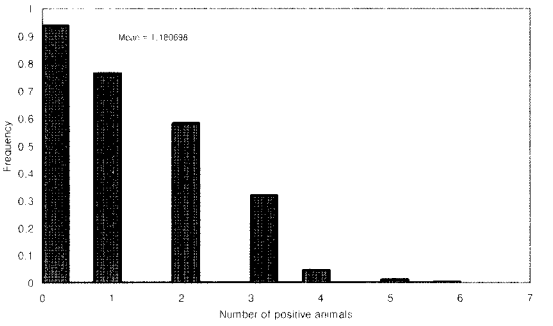

Fig. 2. Distribution of the predicted number of test positive animals in an infected herd.

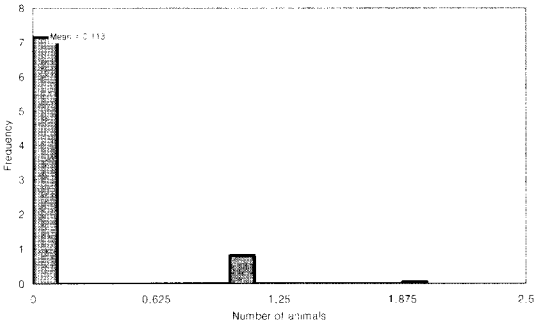

Fig. 3. Distribution of the number of test positive animals in infection-free herds.

Discussion

The Reed-Frost model has been widely used in infectious animal diseases such as bovine tuberculosis [17], bovine ephemeral fever [14], ovine brucellosis [2],

and paratuberculosis [4]. This model is particularly suitable for diseases with a short infectious period, direct transmission, complete immunity after infection, and when the group of individuals is homogeneous [13]. The current model can be used to characterize epidemic curve of an infectious disease and in planning control strategies to eradicate the epidemic through a combination of reducing adequate contact (slaughter, disinfection) and lowering the number of susceptible animals (vaccination) [11]. Specifically, if $PxS_{(t)}$ is greater than 1, the epidemic can occur; whereas if $PxS_{(t)}$ is less than 1, the epidemic will die out or not occur. The hypothetical example described here can also be used to evaluate whether a serological survey was started timely when epidemic has already occurred. In this hypothetical simulation, 7% of ineffective visits emphasize the importance of timely visits in planning a emergency survey. Even though all input parameters are hypothetical, this model could be extend for further simulation whenever herd-level performance of a diagnostic tests employed in emergency surveys is a matter of subject. There are many practical situations regarding this issue from the literatures such as foot-and-mouth disease [16], fish hatchery disease [7], and Newcastle disease [6].

This model is abridged version of the real world in that effective contact rates between animals were not considered. Generally, the higher the effective contacts, the lower the probability of failure to detect positive animals. Future research, therefore, will be done to determine the herd-level diagnostic performance taking into account a variety of within-herd transmission level. Accurate classification of herd status determined by survey program is essential in specific disease free in risk assessments of disease introduction, for diagnostic purposes, in disease-control programs, and for interventions. Thus, this model will be structured in such a way that understanding of the risk of introducing infectious disease through the importation of animal and animal products and adaptation to other infectious disease is possible. As illustrated by outbreaks of foreign animal disease in many countries, risks associated with importation can be of acute national concern. These can affect adversely the health of humans, animals and plants and, in turn, economic wellbeing. In this situation, a formal economic approach involving cost-benefit analysis could be incorporated in risk analysis to analyze the full extent of the consequences [15]. Many input components are involved in economic analysis, of which the key ones are the level of overall consequences in domestic susceptible populations associated with imported risks, and the level can be determined by survey programs [3]. That is, the simulated output of a survey program could be entered into input parameters of an economic model which is applied to evaluating alternative quarantine measures to reducing risk to the appropriate level of protection.

Provided these future improvements on concurrent model are made, we believe that this model could be a valuable tool for estimating the number of infected animals in infected herd, and for making decisions about the infection status of the animal populations, and for evaluating the effectiveness of control strategies in the premises surveyed.

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