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FREEDOM FROM INFECTION: A STOCHASTIC SIMULATION MODEL FOR EVALUATING THE EFFICACY OF NATIONAL OR REGIONAL SURVEYS APPLIED TO PRRS IN SWITZERLAND

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Avec la nécessité grandissante de fournir des données scientifiques fiables sur la situation sanitaire d'une population animale dans un pays ou une région donnée, surtout pour défendre un statut indemne d'infection, les méthodes épidémiologiques utilisées dans les enquêtes de prévalence seront sujet à évaluation.
Un modèle stochastique a été développé pour l'évaluation de l'efficacité des enquêtes. Le modèle spécifie ou calcule les distributions de probabilité pour la sensibilité et la spécificité des tests de diagnostic au niveau individuel et au niveau du troupeau. Les prévalences réelles à ces deux niveaux sont ensuite estimées. Le modèle permet aussi de calculer les distributions de probabilité des nombres théoriques d'animaux et de troupeaux positifs en considérant l'infection comme absente (statut indemne) ou présente à des taux de prévalence fixes ou estimés stochasticalement. Ces distributions permettent d'évaluer la pertinence des résultats de laboratoire avec un statut indemne d'infection, et de calculer la puissance de l'enquête pour déceler une infection à un niveau de prévalence critique.
Les données d'une enquête menée en Suisse pour confirmer son statut indemne vis-à-vis du Syndrome Reproducteur et Respiratoire Porcin (SRRP) ont été utilisées pour illustrer cette approche de modélisation. Cinq prélèvements ont été effectués par troupeau à l'abattage à partir de 108 élevages engraisseurs. Tous les serums ont été négatifs au test individuel, et les prévalences réelles ont toujours été estimées nulles. Avec un nombre limite de 12 troupeaux positifs permis avant de rejeter avec confiance le statut indemne, la puissance de l'enquête a été estimée à 70% pour déceler une prévalence d'infection minimum de 0.05. Ce modèle stochastique est donc un outil très utile pour la planification et l'interprétation des enquêtes de prévalence.

INTRODUCTION

With the opening of the world market in the context of the World Trade Organisation, the provision of valid data regarding the disease status of an animal population in a given region or country is becoming increasingly important. Ensuring freedom from disease in accordance with the definition given by the OIE may be difficult, and requires careful evaluation of the epidemiological methods used. In these circumstances, it is generally more important to diagnose infected herds than infected animals, and thus to consider the sensitivity and specificity of the test regimen at the herd level, which depend on the prevalence of infected animals within the tested herd, the number of animals tested, the characteristics of the individual test used and the threshold number of positive individual tests chosen to declare a herd infected (Martin et al., 1992).
This paper presents a stochastic spreadsheet model which may be used to evaluate the efficacy of surveys. Data from a survey carried out to investigate the presence of Porcine Reproductive and Respiratory Syndrome (PRRS) in Switzerland are used to illustrate this approach. This model will be fully described elsewhere and can be obtained from the principal author upon request.

MATERIALS AND METHODS

A serological survey was carried out in Switzerland in 1996 to assess the likelihood that the swine population was free from PRRS (Canon et al., in preparation). Five blood samples were taken at slaughter from each of 108 herds of fattening pigs. All 540 sera were tested negative for antibodies against PRRS using a newly developed indirect ELISA employing baculovirus-expressed antigen (Denac et al., 1997). This ELISA was reported to be 100% sensitive and 95.8% specific, but specificity was likely to be underestimated.
The spreadsheet model was built and run using the computer software @RISK (Palisade Corporation Inc., Newfield, NY USA), an add-in software for MS Excel (Microsoft Corporation, Redmont, WA USA). In a first part, it is designed to derive probability distributions for individual- and herd-level sensitivity and specificity, while in a second part individual- and herd-level prevalence are calculated. In addition, the model reports expected numbers of positive results should the infection occur at a suspected infection prevalence or not occur (freedom from infection).
The probability distributions for true individual test sensitivity and specificity were modelled from validation data using the Beta distribution and expert advice using the BetaPert distribution, respectively. Herd-level sensitivity was modelled from these later distributions and the number of infected and uninfected animals sampled (Martin et al., 1992). The number of infected animals sampled was modelled using an hypergeometric distribution with parameters accounting for the size of the sample, the number of infected animals within the herd (calculated from the herd size and expected within-herd prevalence) and the size of the herd. Sample size was designated to be

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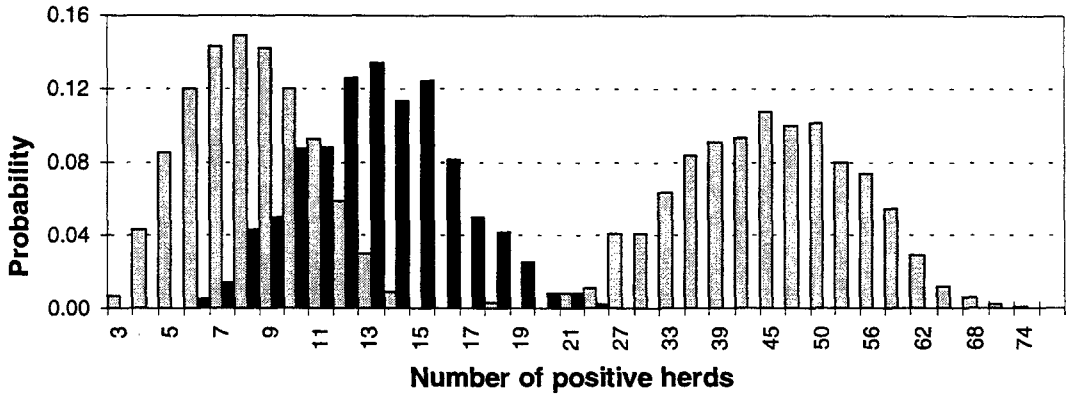
5. Herd sizes were not known as samples were taken at abattoirs, so they were modelled using a discrete probability distribution from national animal population statistics from 1995. The within-herd prevalence of PRRS was modelled using a BetaPERT distribution with 10, 80 and 100% being the maximum, minimum and most likely values (Meredith & Blaha, personal communications; Meredith, 1995). Herd-level specificity was determined algebraically using the specificity of the diagnostic test and the within-herd sample size. The number of positive sera allowed before a herd be classified as infected was set to zero to maximise herd-level sensitivity. Individual and herd true prevalence (*TP*) were estimated as reported by Gladen and Rogan (1977), and negative values of *TP* where replaced with zeros (Hilden, 1979).

The model computed also the numbers of positive individual and herd tests that would be expected should the country be free from infection and also should the country be infected at given prevalence levels. The later prevalence were entered deterministically at a low threshold level (0.01 and 0.05) and stochastically using a BetaPERT distribution with 10, 40 and 60% being the maximum, minimum and most likely values (Meredith & Blaha, personal communications; Meredith, 1995). Probability distributions of the numbers of expected positive herd tests presented in Figure 1 were used to estimate the survey sensitivity given the between-herd prevalence to detect and the threshold number of infected herds allowed before considering that infection occurs.

The model was run 1000 times using Latin hypercube sampling to evaluate actual laboratory results, i.e. that no positive sera were reported.

Figure 1

Probability distributions of the expected number of positive herds[1] under the assumption of freedom from PRRS infection (left light histogram), of endemic infection[2] (right light histogram) and of low prevalence of infection (0.05)(dark histogram), using 1000 iterations.



[1] 5 sera per herd were tested from 108 herds sampled at slaughter.
[2] The herd prevalence was modelled stochastically as described in the text.

RESULTS

The expected number of false positive individual tests ranged from 3 to 15 with a mean of 8.3 (standard deviation 2.5). The observed number of positive sera (i.e. zero) is below the minimum value of this distribution, so laboratory results are inconsistent with the suspected individual test specificity. It was believed that individual test specificity is likely to be actually very high and close to 100%. Estimated true individual and herd prevalence were equal to zero in all 1000 iterations. Hence, it was concluded that Switzerland was free from PRRS at the time of the survey.

Calculated survey sensitivities at different level of prevalence, and different threshold number of positive herds (thus survey specificity) are presented in Table 1. In our survey example, there was 18 and 71% sensitivity to detect a between-herd prevalence of 1 and 5%, respectively, when the threshold number of positive herds was set up to 12 (95% survey specificity).

From probability distributions shown in Figure 1, and calculated survey sensitivities in Table I, it appears clearly that a conclusion relative to the infection status can be easily drawn when infection prevalence is high, should it occur, but that this decision may be difficult if the between herd prevalence to detect is very low.

DISCUSSION

The spreadsheet model presented in this paper was developed to evaluate the results of a specific survey, but it can be applied to other survey situations. Providing an unbiased estimate of the true prevalence of infection within a given geographical area, or proving that the area is free from infection, requires careful interpretation of survey results with regard to the epidemiological methods used and many criteria related to the diagnostic test regimen both at the individual and herd level (Martin et al., 1992). The sampling strategy will be discussed elsewhere (Canon et al., in preparation).

Table I
Calculation of the survey sensitivity to detect PRRS infection, should it occur in Switzerland at a given between-herd prevalence[1]

Threshold number of positive herds	Percentiles Survey Specificity	Survey sensitivity to detect infection prevalence of[1]		
		0.01	0.05	0.10 - 0.60
5	0.05	0.98	1.00	1.00
5	0.10	0.98	1.00	1.00
8	0.50	0.72	0.98	1.00
11	0.90	0.29	0.80	1.00
12	0.95	0.18	0.71	1.00
13	0.99	0.05	0.45	1.00

[1] 0.01 and 0.05 are fixed values, while 0.10 - 0.60 means that it was modelled using the BetaPert distribution from expert knowledge as described in the text.

At the individual level, test characteristics depend on the validation work carried out at the laboratory. This study shows that it is often very difficult to obtain valid test characteristics for the population under study, and that the specificity of the ELISA test used is likely to be have been underestimated. Since no sera were positive, however, it does not invalidate the final conclusion. At the time of writing, the specificity was being checked using sera from New Zealand which has recently claimed to be free from PRRS infection (Motha et al., 1997).
It was important to evaluate the characteristics of the diagnostic test regimen at the herd level (Martin et al., 1992). Since herds were selected at slaughter, their size was not readily available, and thus modelled from official census data from 1995. This was the most practical approach. The threshold number of positive animals within herds has been set to zero since it was important to diagnose all infected herds and a high herd test sensitivity was favoured.
This paper presents expected results from three situations of PRRS infection, i.e. with two low suspected prevalences (0.01 and 0.05) set up deterministically, and a relatively high prevalence set up stochastically using expert advice and literature data. Probability distributions presented in Figure 1 are a valuable tool for the planification and evaluation of epidemiological surveys. The method of estimation of the survey sensitivity presented in Table I has not been described before. It can be used to estimate the minimum between-herd prevalence which would be detected with reasonable or high level of confidence. The survey design used in this study was able to detect a between-herd prevalence of 0.05 with 98% confidence should the threshold number of positive herds be set to 8 herds. By doing so, the specificity of the survey is shown to drop to 40%, where one is very likely to falsely declare a status of infection. The knowledge of the epidemiology of the infection, and the prior status of the country or region, therefore, is very important to consider. It is almost certain from expert advice and literature data (Meredith, 1995) that PRRS would affect a large proportion of herds, in particular if it affects a naive population. In such circumstances, the power of the survey presented here was always 100%, thus giving confidence that Switzerland was free from PRRS infection in Summer 1996.

Computer stochastic simulation provides a very efficient tool to interpret the result of surveys by taking into account the inescapable uncertainty associated with some of the input data. The use of a standard spreadsheet allowing Monte Carlo modelling makes also the process easier to a majority of people not familiar with computer programming. The model presented in this paper can be tailor-made and used in the context of a large variety of other surveys, and thus is very useful to survey managers and decision-makers.

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