In: Agricultural Production
Editors: Felix C. Wager, pp. 79-92

ISBN: 978-1-61668-695-6

Chapter 3

A STOCHASTIC EVALUATION OF THE VALIDITY OF AN ANIMAL-HEALTH SURVEY IN URUGUAY

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ABSTRACT

This paper introduces spreadsheet simulation models to evaluate the validity of national or regional disease surveys aimed at identifying infection in populations of farm animals. The process of evaluation includes specification or calculation of cluster-level diagnostic test sensitivity (the proportion of animals with the disease which test positive) and specificity (the proportion of animals without the disease which test negative), which are obtained from two probability distributions of the number of positive tests at individual-level expected from infected and non-infected clusters, respectively.

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Probability distributions for the number of positive clusters expected in a situation of the herd prevalence are specified and used to define survey properties (the survey being considered a diagnostic system), and receiver operating characteristic curves (consisting of a plot of sensitivity and specificity pairs for different cut-off values) are drawn. The result of a survey implemented to determine the prevalence of infectious bovine rhinotracheitis in dairy cattle in Uruguay, South America was used to illustrate this approach. The models can be adapted to a wide range of survey designs in animal health and production.

INTRODUCTION

The necessity to supply valid data on the disease status of an animal population in a given country or region is becoming more important, with the opening of the world market in the context of the World Trade Organisation. As a result, the epidemiological methods used and the interpretation of laboratory diagnostic test results will be open to examination. When making sure that an animal population in a country or a region is free from infection or disease, it is basically more crucial to identify the supposed clusters of infected animals than infected animals themselves. When a number of animals are being examined within clusters to specify the infection status of each cluster, the testing regimen should be assessed as a cluster-level test. The regimen is characterised by its sensitivity (the proportion of animals with the disease which test positive) and specificity (the proportion of animals without the disease which test negative), being dependent on some criteria incorporating the prevalence of infected animals within infected clusters, the cluster size, the number of animals tested, the characteristics of the animal-level test used and the cut-off number of positive animal-level tests chosen to proclaim a cluster as infected [1]. In addition, It was reported that sensitivity and specificity at cluster-level would be influenced by differences in test sensitivity and specificity at animal-level between clusters [2]. Subsequently, A simulation model was made to assess how cluster-level sensitivity differs with test characteristics at animal-level, within-cluster prevalence of infection, and sample size [3]. Over recent years, sample-size calculations in the context of surveys intending to prove freedom from infection or disease have depended on formulas and tables [4]. Significant presumptions for these calculations were that the sampled population was infinite, and that the testing procedure utilised was perfect (i.e. with a sensitivity and specificity of both 100%). However, the interpretation of animal-health survey results (both to prove freedom from infection and to define the true prevalence of infected or diseased herds in a population) is not simple and must take into account their inherent variability or uncertainty. This paper discusses stochastic simulation models that can be used to evaluate the validity of such surveys and to provide help for the interpretation of screening test results. The results of a survey implemented to estimate the prevalence of infectious bovine rhinotracheitis (IBR) in Uruguay are used to show the approach.

MATERIALS AND METHODS

The models has been made for the evaluation of the validity of surveys where a preset number of animals (the individual units within clusters of animals) is examined using a screening test (which may be a combination of animal-level tests) to determine if the clusters are infected or diseased. A number of clusters is examined in order to state that a country or region is free from infection or disease, or to identify that the infection or the disease arises. Therefore, the survey itself is regarded as a screening process or a diagnostic system. In this paper, a cluster can be any group of individual animals such as a herd, a flock, a mob or a group in a pen (the word "herd" is basically used to describe the models hereinafter). In addition, the authors will make reference only to "infections" and "countries", but the reader will comprehend that the concepts also apply to diseases and regions, respectively. Infections as defined in this paper are caused by the presence of a contagious agent within an animal; the infection might cause only subclinical transformations such the development of antibodies or might cause the development of clinical signs (i.e. disease).

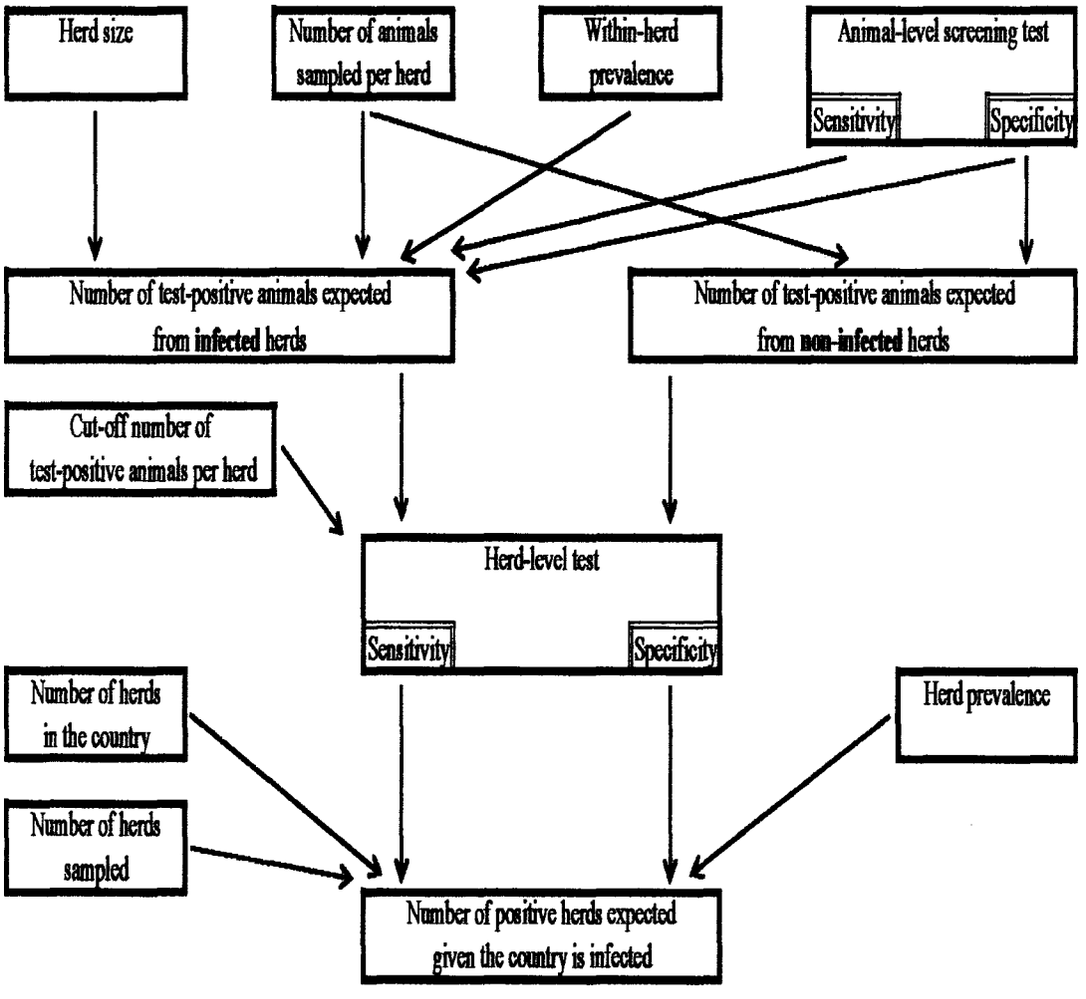

Figure 1. Structure of the simulation model.

Structure of the Simulation Model and Overall Process of Evaluation

The process of evaluation includes two steps; the specification of herd-level test sensitivity and specificity, and the specification of these properties at the country level. Therefore, this paper will bring the reader to three consecutive level of consciousness: the animal level, the herd level, and the country level (Figure 1). The formulas and probability distributions used in the models are shown in Table 1. The models were written in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and simulated using @Risk version 5.0.1 (Palisade Corporation, Newfield, NY, USA), a software allowing Monte Carlo simulation with Latin Hypercube sampling.

Number of Positive Animals Expected from Infected and Non-Infected Herds and Herd-Level Test Characteristics

The screening test results applied to a number of animals within a herd can be defined using the concepts of test sensitivity and specificity at herd-level [1]. Herd-level test sensitivity was interpreted as the probability of observing a number of test-positive results at animal-level (which may contain false-positive results) equal to or above a predetermined cut-off number, given that the herd is really infected. Herd-level test specificity was interpreted as the probability of observing a number of test-positive results at animal-level (which are all considered to be false-positive results) below this cut-off number, given that the herd is really non-infected. To evaluate a test at the animal level, its characteristics are determined from the distribution of test results [e.g. an optical density or percentage of reactivity for an enzyme-linked immunosorbent assay (ELISA)] from truly infected and truly non-infected animals. Likewise, herd-level test characteristics are determined from the distribution of results (i.e. the number of animals positive to the animal-level test) from truly infected and non-infected herds. As illustrated in Figure 1 and described in Table 1, these distributions depend on the following parameters:

- For truly infected herds: the number of infected and non-infected animals sampled per herd and the sensitivity and specificity of the animal-level screening test. The number of infected animals sampled from an infected herd depends on the size of the herd, the prevalence of infection within that herd, and the total number of animals sampled per herd.
- For truly non-infected herds: the number of animals sampled per herd and the specificity of the animal-level screening test.

Stochastic modelling allows the derivation of these two probability distributions from the parameters defined above and their inherent variability or uncertainty (Table 1).

- Most laboratories report sensitivity and specificity for diagnostic tests. When validation data to define these characteristics are available, Beta distributions can be used to model probability distributions for true sensitivity and specificity. The Beta

distribution models the probability of a unit (e.g. an animal) randomly recruited from a population having a particular characteristic such as being infected (i.e. a binomial event) if a number of units within a randomly recruited group of units has been found with the characteristic [5].

- National animal-population statistics are used to model herd size, and the most appropriate parametric or non-parametric probability distribution fitting these data is utilised. If these data are given as the number of herds per interval of herd sizes (i.e. as an histogram), they can be modelled using non-parametric distributions such as the histogram distribution function, or the discrete distribution of @Risk as in the IBR example presented in this paper. A combination of uniform and discrete distributions also can be used.
- The within-herd prevalence of infection is modelled using a RiskPert distribution with data chosen based on expert opinion and a review of published literature. The RiskPert distribution is believed one of the most-suitable distributions to model a continuous variable for which experts have been asked to provide three values (i.e. a minimum, a maximum, and a most-likely value) [5].
- The number of animals sampled per herd (N) is a fixed value. In this study the authors used the two different fixed values for N, such as five (model 1) and 10 (model 2). The authors compared these two models to select the better value for N. It is our thought that this model may be utilised in the planning stage of a survey to calculate that sample size, but it will be beyond the scope of this paper.
- The number of infected animals expected in the herd sampled is modelled using a hypergeometric distribution with parameters accounting for the number of animals sampled per herd, the number of infected animals in the herd, and the size of each herd. The number of infected animals in the herd is simply obtained from the value of the product of the herd size with the within-herd prevalence rounded to the unit with a minimum of one infected animal. The hyper geometric distribution is considered the most suitable as sampling is done without replacement. In situations where sampling fractions are low (e.g. below 10%), the hypergeometric distribution could be approximated by the binomial distribution with parameters explaining the number of animals sampled from each herd and the within-herd prevalence [6]. Thus, they are restricted by the minimum and the maximum value, which may be different from 0 and 1.

The two probability distributions are produced from a first-stage simulation with 1000 iterations. The 1000 values obtained for each distribution are saved into an Excel spreadsheet where the superimposed probability distributions (i.e. the relative frequency distributions of output values) can be drawn. These results provide point estimates of test sensitivity and specificity at cluster-level for each possible cut-off number of positive animal-level tests, and a receiver operating characteristic (ROC) curve is also drawn, and an area under the ROC curve (AUC) is calculated. The ROC curve shows the characteristics of a diagnostic test by graphing the false-positive proportion (1 - specificity) on the horizontal axis and the true-positive proportion (sensitivity) on the vertical axis for various cut-off numbers. The AUC is a popular measure of the accuracy of a diagnostic test. Other things being equal, the larger the AUC, the better the test is a predicted existence of the disease. The possible values of AUC

range from 0.5 (no diagnostic ability) to 1.0 (perfect diagnostic ability). These calculations are based on the presumption that the distributions of test-positive animals in both the infected and non-infected populations of herds are similar to the sample distributions (the distributions of 1000 values).

The cut-off number of test-positive animals is selected from the above probability distributions and ROC curve depending on the objective of the survey. For example, sensitivity at herd-level could be maximised to give high confidence in negative results at herd-level when attempting to substantiate freedom from infection.

Table 1. Description of model inputs for the example of IBR in Uruguay

Input variables	Notation	Formula used with @Risk (Microsoft Excel notation used)
Animal-level screening test characteristics		
Herd size	Size	RiskDiscrete (distribution of herd size for 19 departments, proportion of herds associated with each department)
Number of animals sampled per herd	N1	Fixed values ["5" for model 1 and "10" for model 2]
Within-herd prevalence	Prev	RiskPert (0.3, 0.7, 1.0)
Test sensitivity at animal-level	Ase	RiskPert (0.94, 0.98, 0.995)
Test specificity at animal-level	Asp	RiskPert (0.815, 0.97, 0.985)
Herd-level test characteristics		
Number of infected animals in a corresponding herd	Inf1	IF (ROUND (Prev * Size, 0) = 0, 1, ROUND (Prev * Size, 0))
Number of infected animals expected in the herd sampled	Inf2	RiskHypergeo (N1, Inf1, Size)
Number of test-positive animals expected from infected herds	Pos	SUM (IF (Inf2 > 0, RiskBinomial (Inf2, Ase), 0): IF (N1 - Inf2 > 0, RiskBinomial (N1 - Inf2, 1- Asp), 0))
Number of test-positive animals expected from non-infected herds	Neg	RiskBinomial (N1, 1- Asp)
Number of simulations used to derive the probability distributions of "Pos" and "Neg"	Iter	Fixed value [1000]
Number of simulations giving a value of "Pos" more than or equal to a cut-off number C	Cpos	
Number of simulations giving a value of "Neg" less than a cut-off number C	Cneg	
Test sensitivity at herd-level	Hse	RiskBeta (Cpos + 1, Iter - Cpos + 1)
Test specificity at herd-level	Hsp	RiskBeta (Cneg + 1, Iter - Cneg + 1)
Country-level test characteristics		
Number of herds in the country	Pop	Fixed value [51,072]
Number of herds sampled	N2	Fixed value [14]
Herd prevalence	Hprev	RiskPert (0.40, 0.57, 0.74)
Number of infected herds in a corresponding population	Inf3	IF (ROUND (Hprev * Pop, 0) = 0, 1, ROUND (Hprev * Pop, 0))
Number of infected herds expected in the population sampled	Inf4	RiskHypergeo (N2, Inf3, Pop)
Number of positive herds expected given the country is infected	Pos2	SUM (IF (Inf4 > 0, RiskBinomial (Inf4, Hse), 0): IF (N2 – Inf4 > 0, RiskBinomial (N2 – Inf4, 1- Hsp), 0))

Number of Positive Herds Expected and Survey Properties

The next section of the spreadsheet models is used to approximate the properties of the survey (i.e. its sensitivity and specificity) and AUCs. Survey (or country-level) sensitivity is determined as the probability of proclaiming the country as infected, given that the infection exists. Survey (or country-level) specificity is determined as the probability of proclaiming the country as free from infection, given that it really is. Survey properties are determined from results (i.e. the number of positive herds to the herd-level test) of two groups of a large number of surveys conducted in the same country using the same population of herds. For one group of surveys (Group 1), one thinks that the country is truly infected while for the other (Group 2), one thinks that the country is truly free from infection. As illustrated in Figure 1 and described in Table 1, these distributions are obtained from the following criteria:

- Group 1: The number of infected and non-infected herds sampled in the survey and the test sensitivity and specificity at herd-level.
- Group 2: The number of herds sampled and the test specificity at herd-level.

These two probability distributions of the number of positive herds expected are obtained from the parameters defined above and their inherent variability or uncertainty (Table 1).

- Test sensitivity and specificity at herd-level are modelled as Beta distributions using results from first-stage simulation data, similar to the way of animal-level screening test characteristics modelled from laboratory validation data.
- The herd prevalence depends on the epidemiology of the infection concerned within the considered country, that is:

For infections that do not transmit (or that are not likely to transmit) quickly between herds (such as bovine leucosis or bovine tuberculosis), the herd prevalence is fixed at a threshold minimum level under which one would accept to regard the country as "free from infection". For infections that are known to transmit quickly between herds after introduction into a country (such as in the IBR example demonstrated in this paper) the herd prevalence is modelled to give a more-realistic scenario. As for the within-herd prevalence defined formerly, the herd prevalence is modelled using a RiskPert distribution with maximum, minimum and most-likely values selected based on expert opinion or a review of published literature [5].

- The number of herds sampled for the survey (N2) is a fixed value. The calculation of this sample size will not be further developed in this paper.
- The number of infected herds expected in the population sampled, if the country is infected, is modelled using a hypergeometric distribution with parameters accounting for the number N2, the number of infected herds in a corresponding population, and the number of herds in the country. The number of herds in a corresponding population is simply obtained from the value of the product of the number of herds in the country with the herd prevalence rounded to the unit with a minimum of one infected herd. The number of herds in the country (i.e. population size), however,

could be omitted if the sampling fraction of clusters is low (e.g. below 10%). In this situation, the hypergeometric distribution could be approximated by the binomial distribution (i.e. sample with replacement) [6].

Probability distributions of the number of positive herds expected are obtained from a second-stage simulation with 1000 iterations. The model lets one to acquire such distributions for a range of input herd prevalence entered deterministically (fixed minimum threshold value) or stochastically (modelled realistic values). The spreadsheet models are used to draw superimposed probability distributions, obtain survey sensitivity and specificity for each input herd prevalence and possible cut-off number of positive herds, and respective ROC curves.

The Example Survey: IBR Survey in Uruguay

A serological animal-health survey conducted in Uruguay between November 2008 and May 2009 was used to evaluate the validity of the spreadsheet simulation models. For this survey, the presumptions and several model parameters were as follows:

- Blood samples from 90 different cattle were collected from each of the 14 study herds. However, for the sake of illustration, the numbers of animals sampled per herd in the spreadsheet simulation models were determined as five and 10 for the models 1 and 2 mentioned above, respectively.
- Sera were analysed using a commercial indirect ELISA (Chekit® Trachitest IBR Antibody Test Kit, IDEXX, Switzerland). The published test sensitivity and specificity were modelled using a RiskPert distribution with minimum, most-likely, and maximum values being 94%, 98% and 99.5% for sensitivity, and 81.5%, 97% and 98.5% for specificity, respectively [7, 8].
- Herd sizes were modelled using 2008 statistics for cattle herds in Uruguay obtained from the website of Directorate General of Livestock Services of the Government of Uruguay (http://www. mgap.gub.uy/dgsg/DICOSE/DatosDJ_2008.htm). For this simulation study, herd sizes were obtained within each herd-size interval from the integer value. A discrete probability distribution was fitted to give the integer values with weights accounting for the relative frequencies of herds within each herd size interval.
- The within-herd prevalence was modelled using a RiskPert distribution with the results of the serological survey mentioned above. Minimum, most-likely, and maximum values for within-herd prevalence were 30%, 70% and 100%, respectively. While the herd prevalence was modelled using a RiskPert distribution with a review of published literature regarding a meta-analysis for IBR in Uruguay [9]. Minimum, most-likely, and maximum values for herd prevalence were 40%, 57% and 74%, respectively.

RESULTS

Descriptive statistics for a selection of key output variables for the IBR survey are shown in Table 2.

Table 2. Descriptive statistics of animal- and herd-level test characteristics, and numbers of positive herds expected by the models from an IBR survey in Uruguay

Inputs/outputs	Minimum	5th percentile	Mean	95th percentile	Maximum	SD
Animal- and herd-level test characteristics						
Ase	0.944	0.958	0.976	0.990	0.995	0.010
Asp	0.839	0.894	0.947	0.980	0.985	0.027
[Model 1]						
Hse	0.907	0.921	0.934	0.946	0.956	0.008
Hsp	0.950	0.961	0.970	0.978	0.988	0.005
[Model 2]						
Hse	0.972	0.981	0.987	0.992	0.995	0.004
Hsp	0.965	0.975	0.982	0.988	0.993	0.004
Number of positive herds expected by the models						
Model 1	2	4	7.6	11	13	2.0
Model 2	2	5	8.0	11	14	2.0

Ase and Asp: Animal-level test sensitivity and specificity, respectively. Hse and Hsp: Herd-level test sensitivity and specificity, respectively. Model 1 and 2: the model with five and 10 animals sampled per herd, respectively (number of herds sampled = 14).

Number of Positive Animals Expected From Infected and Non-Infected Herds and Herd-Level Test Characteristics

At the animal level, the sensitivity of the ELISA used in the IBR survey ranged from 94.4% to 99.5% with a mean of 97.6%. Specificity of this test ranged from 83.9% to 98.5% with a mean of 94.7%. Output probability distributions of the expected numbers of positive animals from non-infected and infected herds for the models 1 and 2 are presented in Figures 2 and 3, respectively, while the ROC curves of the herd-level test used for the models 1 and 2 are presented in Figures 4 and 5, respectively. From these simulated data, the authors selected the cut-off numbers of positive animals under which a herd would be considered as non-infected to be 2 and 3 for the models 1 and 2, respectively. The AUCs for the models 1 and 2 were 98.4% (95% CI: 98.2-98.7%) and 99.7% (95% CI: 99.6-99.9%), respectively. In this simulation using 1000 iterations 66 iterations showed no positive animals from infected herds, and 30 iterations showed at least one positive animal from non-infected herds for the model 1. Therefore, point estimates of herd-level test sensitivity and specificity for the model 1 were 93.4% and 97.0%, respectively. While for the model 2, 13 iterations showed no positive animals from infected herds, and 18 iterations showed at least one positive animal from non-infected herds. Therefore, point estimates of herd-level test sensitivity and specificity for the model 2 were 98.7% and 98.2%, respectively. These data were used for the second-stage simulation to model the number of positive herds expected using Binomial distributions as described in Table 1.

Number of Positive Herds Expected and Survey Properties

Output probability distributions for the number of positive herds expected from an IBR survey conducted in Uruguay under the assumed prevalence of 57% (modelled between 40% and 74%) are superimposed in Figure 6. Descriptive statistics for the number of positive herds expected under the two different models mentioned above are presented in Table 2. In the context of the IBR survey, the number of positive herds expected ranged from 2 to 13 with a mean of 7.6 for the model 1. For the model 2, the number of positive herds expected between 2 and 14 with a mean of 8.0. The ROC curves of the survey (i.e. the diagnostic system) for the two different models were produced (figures not shown). As the country-level test characteristics, the model 1 had the AUC of 99.98% with the sensitivity of 99.8% and specificity of 99.1%. Meanwhile the model 2 had the AUC of 99.99% with the sensitivity of 99.5% and specificity of 99.9%. The survey appeared to be almost perfect in identifying IBR infection if country-level prevalence was 57% (modelled between 40% and 74%). Seven out of 14 study herds in this survey had prevalence of more than 57%, almost corresponding to the results of the simulation.

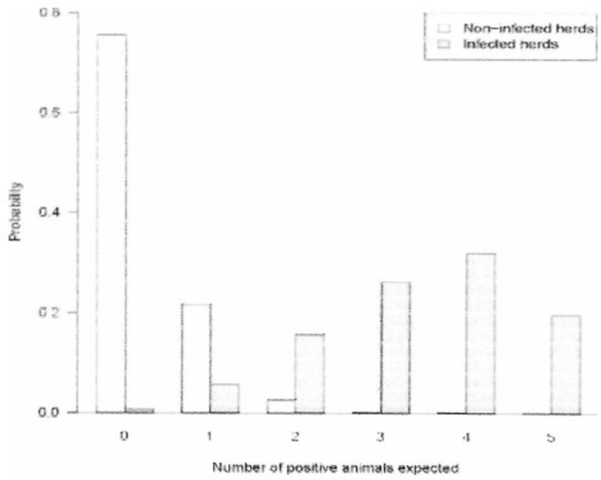

Figure 2. Output probability distributions of the number of positive animals expected against IBR amongst five animals randomly selected from non-infected herds and infected herds.

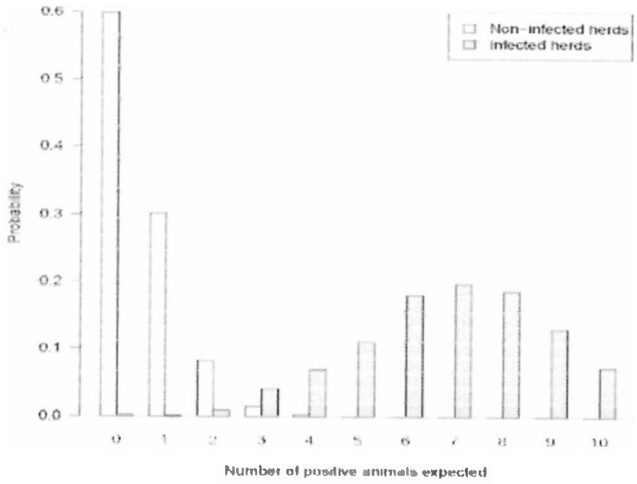

Figure 3. Output probability distributions of the number of positive animals expected against IBR amongst 10 animals randomly selected from non-infected herds and infected herds.

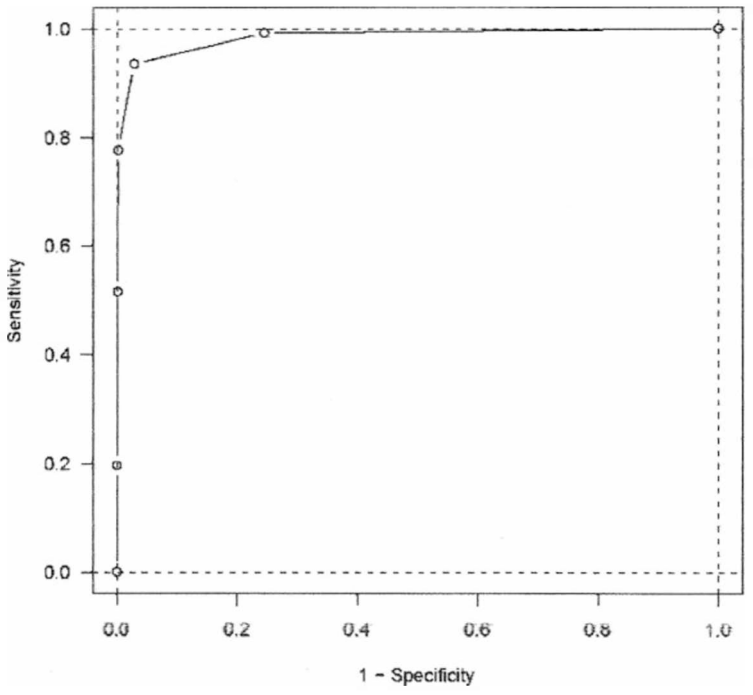

Figure 4. Output receiver operating characteristics (ROC) curve of herd-level test for seropositivity against IBR from five animals sampled per herd.

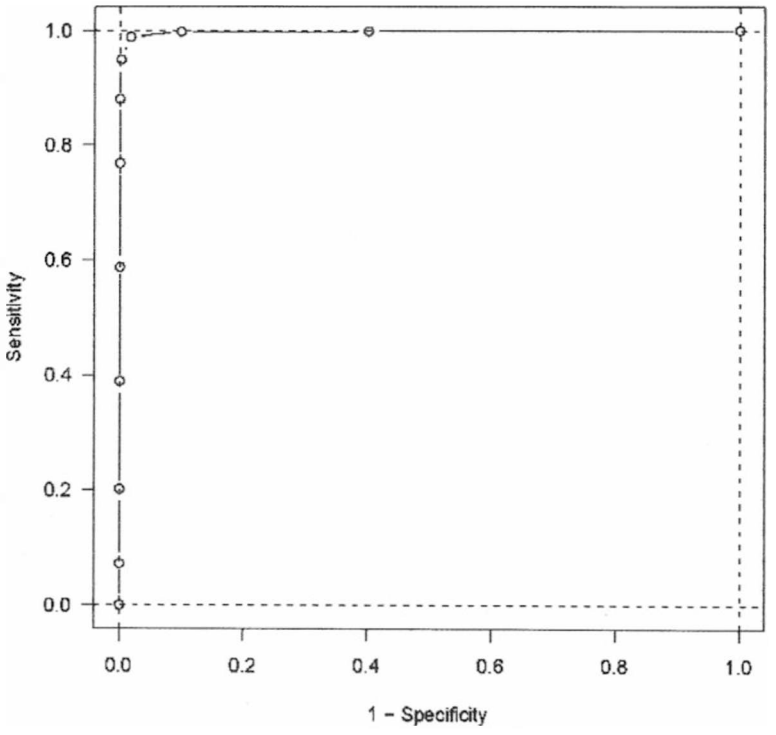

Figure 5. Output receiver operating characteristics (ROC) curve of herd-level test for seropositivity against IBR from 10 animals sampled per herd.

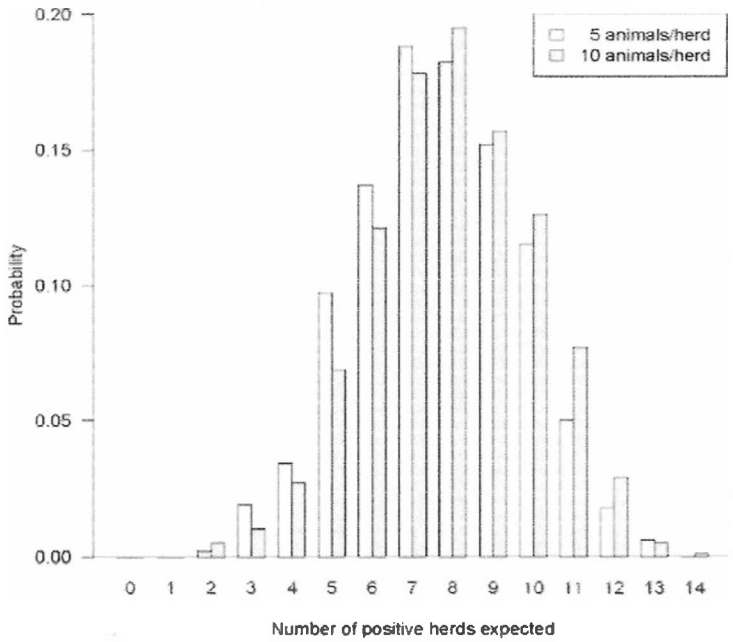

Figure 6. Output probability distributions of the number of positive herds expected against IBR amongst 14 herds sampled by the models with five and 10 animals sampled per herd, respectively.

DISCUSSION

Simulation techniques have already been used to model the cluster-level sensitivity of a diagnostic procedure [3], but it was in the context of a herd-health programme for pigs, and the process was not extended beyond the herd-level. A survey aimed at demonstrating Norway's prevalence of IBR has provided estimates of herd-level diagnostic regimen using a combination of two tests [10]. To our knowledge, this concept has not yet been discussed and reported at the country level. At the animal-level, it is important to obtain precise estimates of the characteristics of the screening test used. In our thought, Beta distributions are functional for modelling the real animal-level test characteristics using validation data from the laboratory instead of deterministic point estimates. This modelling approach has been adapted from the modelling of the true animal-level prevalence in a population [5]. If there are doubts on the validity of some characteristics, probability distributions other than the Beta can be utilised to model the uncertainty associated with these characteristics. In this example, the authors considered it appropriate to use a RiskPert distribution to model the most-appropriate values. The probability distribution used in this paper to model herd sizes has been selected to fit the national statistics but it may be changed for other surveys depending on the nature of the data. This approach considers that herds are randomly selected from the population described by these statistics - which is not truly correct when sampling is performed at farms. It is crucial to make sure that herd sizes smaller than the number of animal selected per herd be excluded from the distribution; otherwise, some iterations will be unrealistic (i.e. when more animals are selected per sample than are present in the herd). In the context of the IBR survey, herds with less than 10 cattle were not taken into account. The prevalence of infection within infected herds is modelled using the RiskPert distribution, which is considered one of

the most-realistic distributions to model expert opinion [5]. When data are available from an infected country, other distributions may be used [3]. Stochastic simulations were run with the presumption that there is no relationship between the herd size and the within-herd prevalence. However, a quantification of such dependency is possible depending on the availability of data that may support it. The number of animals sampled per herd and the cut-off number of positive animals are fixed values and can be selected to optimise herd-level test characteristics. Various criteria may be used to determine the cut-off number of a test including cost considerations [11]. In the context of the IBR survey, the number of animals sampled per herd was determined prior to the development of the model using the approach proposed by Cannon and Roe (1982). Our evaluation (which in addition takes the animal-level test characteristics into consideration) shows that our choice was acceptable (Figure 2 and 3). The cut-off number of positive animals was selected to be two (for the model 1) and three (for the model 2), and resulting point estimates of herd-level test sensitivity and specificity were 93.4% and 97.0% (for the model 1), and 98.7% and 98.2% (for the model 2), respectively. To increase these sensitivity and specificity would have required increase in sample size but the survey cost considerations would be more necessary. As was true also for animal-level tests characteristics, Beta distributions are practical to model true herd-level test characteristics (instead of using the deterministic point estimates above). However, note that Beta distributions will never consider a herd-level test to be perfect even if point estimates of either or both sensitivity and specificity are 100%. Because our process uses simulated data, the correctness of the estimates depends on the number of iterations predetermined to run the model. In this paper, 1000 iterations were selected arbitrarily. The last part of the model brings the study to the country level. The process of evaluation is similar to that at the herd level. Probability distributions presented in Figure 6 are worthwhile for the evaluation of surveys, through the determination of their sensitivity and specificity.

CONCLUSION

The models have been created on simple spreadsheet models and can be adapted and utilised in the context of a wide range of other surveys used to identify infection status. The use of a standard spreadsheet allowing Monte Carlo simulation modelling also makes the process easier to a majority of people not familiar with computer programming. The current models are therefore very useful to survey managers and decision-makers.

ACKNOWLEDGMENTS

This study was carried out as part of the project for the capacity development for improvement of livestock hygiene in the southern part of South America through regional cooperation [in Spanish: Proyecto de desarrollo profesional continuo para los veterinarios del Sur (PROVETSUR)], funded by the Japan International Cooperation Agency.

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