

Economic decision analysis model of a paratuberculosis test and cull program

M. T. Collins, DVM, PhD, and I. R. Morgan, DVM, MS

Summary: A spreadsheet program was written to perform decision tree analysis for control of paratuberculosis (Johne's disease), when testing all adults in a herd and culling all animals with positive test results. The program incorporated diagnostic test sensitivity, specificity, and test cost with the cost or value of each of the 4 possible outcomes; true-positive, true-negative, false-positive, and false-negative test results. The program was designed to repeat the analysis for the independent variable pretest paratuberculosis prevalence (0 to 100%). Model output was graphed as profit or loss in dollars vs pretest prevalence. The threshold was defined as the pretest prevalence at which benefit-cost equaled zero. Reed-Frost disease modeling techniques were used to predict the number of Mycobacterium paratuberculosis-infected replacement heifers resulting from infected cows during a control program. Sensitivity analysis was performed on variables of the decision tree model; test sensitivity, specificity, test cost, and factors affecting the cost of paratuberculosis to a commercial dairy. A test and cull program was profitable when paratuberculosis caused $\geq 6\%$ decrease in milk production if the pretest prevalence was $> 6\%$, test sensitivity was 50%, test specificity was 98%, and the testing cost was \$4/cow. Test specificities $> 98\%$ did not markedly affect the threshold for tests with a 50% sensitivity and costing \$4/cow. Test sensitivity had minimal effect on the threshold. Using a diagnostic test with a 50% sensitivity and a 98% specificity as an example, test cost was shown to affect the threshold prevalence at which the test and cull program became profitable. Any test costing \leq \$8/cow was roughly equivalent in profit threshold. Given the characteristics of most diagnostic tests for paratuberculosis in use today, and assuming that paratuberculosis causes at least a 6% decrease in milk produc-

tion of cows, the decision analysis model suggested a test and cull program should be profitable when pretest paratuberculosis herd prevalence is $> 5\%$.

Veterinary diagnostic laboratories provide objective information to guide veterinarians and animal owners in the diagnosis and management of animal diseases. The net return on purchase of diagnostic test results to the herd owner depends on a number of factors including, but not limited to; the cost of the disease, the cost of the diagnostic test, the accuracy of the test, and the actions taken by an animal owner or veterinarian on the basis of the test results. Analysis of the benefit versus cost of a diagnostic test is one means of comparing tests to help the manager of a diagnostic laboratory decide which tests to offer.

A simple and effective method for comparing alternative courses of action is decision analysis, using a decision tree. It helps to clarify the decision making process and provides a means of measuring the net outcome of each decision. It has been a valuable tool in human medicine for many years,¹ and is increasingly used for analysis of the complex decisions facing veterinarians in production medicine.²⁻¹⁰

Diagnosis of clinical paratuberculosis (Johne's disease) is not a difficult problem. Diagnosis of the disease in its subclinical form, however, has been difficult for veterinarians and laboratory diagnosticians worldwide because of the lack of rapid, accurate, and cost-effective diagnostic tests. Recently several new techniques and commercial kits for diagnosis of the disease have become available.¹¹⁻²² Although precise estimates of the sensitivity, specificity, and cost of most of these tests have not yet been published, we developed a computer decision analysis model to examine factors that affect the net benefit-cost of using paratuberculosis diagnostic tests. Because the largest volume of testing for paratuberculosis is for disease control purposes at the herd level, we designed the model to evaluate a test for use in a test and cull program at a commercial dairy. The primary objective was to use the model to evaluate factors affecting the economics

From the Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, 2015 Linden Drive West, Madison, WI 53706 (Collins) and the Veterinary Research Institute, Attwood, Victoria, 3049 Australia (Morgan).

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of a paratuberculosis test and cull control program, not to predict the actual benefit-cost.

Materials and Methods

Overview of the model and definition of terms—The program was written by use of a software program^a and is similar in many respects to other decision analysis models with veterinary applications.^{3-6,9,10,23} We modified the threshold approach to decision making^{24,25} by graphing the benefit-cost against pretest prevalence of disease. The threshold for using a given test was the pretest prevalence of paratuberculosis at which the benefit-cost equaled zero. Standard equations for calculating apparent prevalence from true prevalence^{26,27} and the predictive value model equations^{28,29} were used to calculate the probabilities of getting true-positive, true-negative, false-positive, or false-negative test results (Fig 1). Testing and culling were done once a year, the basic unit of time in the model. Costs associated with each of these 4 possible diagnostic test outcomes were estimated from the literature. Sensitivity analysis was performed by holding all variables constant except the one under examination to determine how it influenced the benefit-cost outcome.¹

Input variables for the decision analysis model were:

- H = Herd size (ie, adults in the milking herd \geq 2 years old).
- R = Replacement rate (annual basis for milking adult cows).
- P₁ = Effective cow-calf contact rate on the farm. This parameter was used in Reed-Frost equations³⁰⁻³³ to calculate the probability an infected cow would infect a calf born on the farm that then became a herd replacement.
- Se = Diagnostic test sensitivity.
- Sp = Diagnostic test specificity.
- CT = Cost of the diagnostic test to the herd owner on a per cow basis.
- CR = Cost of replacement heifers.
- WN = Average weight of normal, non-*M paratuberculosis*-infected, cull dairy cattle.
- WI = Average weight of *M paratuberculosis*-infected cull dairy cattle.
- S\$ = Slaughter value of animals culled in dollars/45.5 kg.
- M\$ = Milk value in dollars/45.5 kg.
- Av = Herd milk production average (rolling herd average in kg).
- %M = Percent decrease in milk production expected per animal infected with *M paratuberculosis*.

Cost of paratuberculosis—In 4 studies it was shown that subclinical paratuberculosis causes a decrease in milk production ranging from 7.8 to 25%.³⁴⁻³⁷ Using the 1989 rolling herd average for Wisconsin herds³⁸ and a milk production decrease of 15%, this results in a loss of \$278/infected cow. The equation to calculate the net cost of paratuberculosis in lost milk revenues for a commercial dairy herd was: Prevalence \times H \times Av \times %M \times 0.01 M\$.

Infected cattle also were shown to have lower slaughter weights.³⁶ Loss attributable to the effects of paratuberculosis on slaughter weights was calculated as: (WN - WI) \times 0.01 S\$.

Another major cost of paratuberculosis was the potential for each infected cow to transmit the disease to susceptible calves, and the probability that an infected calf might become a replacement heifer for the herd resulting in a less productive herd member. The probable number of infected calves born on a farm was calculated by Reed-Frost methods.³³ The number of infected calves born in a given year that would become replacements in the herd was calculated as:

$$[1 - (1 - p_1)^{Ia}](H \times R)$$

where Ia = the number of infected adults. A simplifying assumption for the disease cost associated with each infected replacement produced on a farm was the equivalent of one year's lost milk revenue attributable to subclinical paratuberculosis. All replacements were considered to come from calves born on the premises (ie, a closed herd). The economic effects of mastitis and infertility induced by *M paratuberculosis* infections are controversial and not well documented. Thus they were not included in estimates of the cost of paratuberculosis in the model.

Cost of false-positive test results—In the model, all animals with positive test results would be culled. A loss would result if the result was incorrect (false-positive), because the owner slaughtered a non-diseased animal and bought a replacement. The cost of replacements was offset only by the slaughter value of the cow (WN \times S\$). In Wisconsin in 1989, that would translate to a net loss of about \$225/animal.³⁸

Value of true-positive test results—Correct positive test results caused culling of the cow and the same economic loss as for false-positive results. That loss however was partially offset by economic loss avoided attributable to the cost of the disease, assuming the culled *M paratuberculosis*-infected animal was replaced with a non-infected animal of equivalent production capacity. The salvage value might be lower depending on the slaughter weight (WI) of *M paratuberculosis*-infected animals selected at initiation of the model.

Cost of false-negative test results—Each missed

^aLotus 1-2-3, Lotus Development Corp, 55 Cambridge Parkway, Cambridge, Mass.

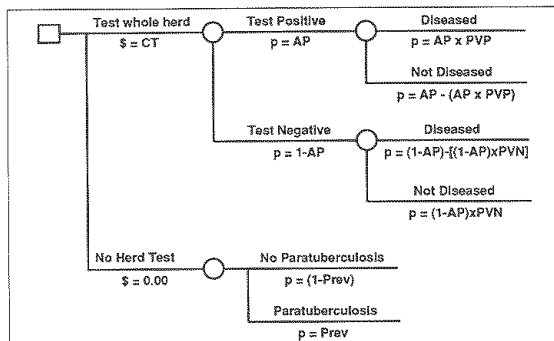


Figure 1—Decision tree model for a paratuberculosis test and cull control program. $AP = \text{Prev}(Se + Sp - 1) - SP + 1$; $PVP = (\text{Prev}(Se)/[(\text{Prev}(Se) + (1 - \text{Prev})(1 - Sp)]$; and $PVN = (1 - \text{Prev})(Sp)/[(\text{Prev})(1 - Se) + (1 - \text{Prev})(Sp)]$, where Prev = true prevalence, AP = apparent prevalence, Se = diagnostic test sensitivity, Sp = diagnostic test specificity, and p = probability of getting test result.

diagnosis by a test would cause an infected animal to be retained in the herd for another year (lactation). The net cost of this event was equal to the cost of the disease as calculated, including both the direct milk revenue losses and the loss attributable to infection of herd replacements.

Value of true-negative test results—The model made the assumption that the value of the knowledge gained from all the true-negative tests on the herd was equal to the positive value of the cost of the disease in a herd of the same size and prevalence but not testing for paratuberculosis. Thus if the net cost of paratuberculosis in a herd not testing was $-\$500$, then the value of all true-negative test results on animals in the herd that was testing would be $+\$500$.

Sensitivity analysis—Reasonable, mid-range values were selected for each of the variables in the model. These were then held constant except for the one being evaluated. The effect of each variable on the benefit-cost output of the model was calculated for 6 parameter values and plotted on a graph of pretest prevalence of disease versus benefit-cost. The prevalence at which the benefit-cost was equal to zero was defined as the decision threshold, that is above the threshold, the test and cull program was profitable, but below the threshold, it was not. Unless otherwise stated, the mid-range values selected were as follows: herd size = 100 cows; replacement rate = 25%; effective contact rate = 0.02; diagnostic test sensitivity = 50%; diagnostic test specificity = 98%; cost of testing = $\$4/\text{cow}$; cost of replacements = $\$1,000$; average weight of cull dairy cows³⁶ (non-*M paratuberculosis*-infected) = 556 kg; average weight of *M paratuberculosis*-infected cull dairy cows³⁶ = 498 kg; salvage value of slaughter cows = $\$40/45.5$ kg; rolling herd average for milk production = 6,364 kg; price received for milk = $\$12/45.5$ kg; and the decrease in annual milk production per *M paratuberculosis*-infected cow = 15%.^{35,37}

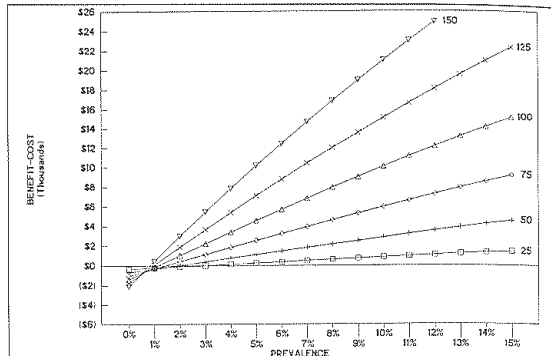


Figure 2—Effect of herd size (range 25 to 150) on the profitability of a paratuberculosis test and cull program.

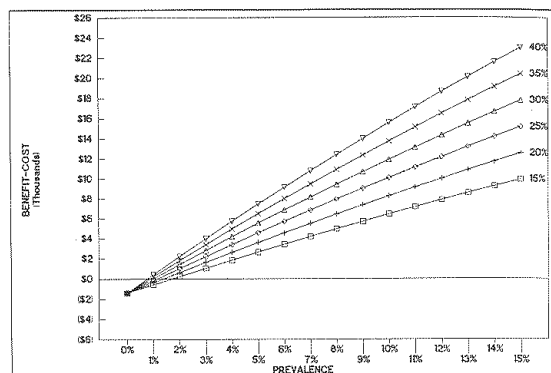


Figure 3—Effect of herd replacement rate (range 15 to 40%) on the profitability of a paratuberculosis test and cull program.

Effect of herd size—Herd size varied from 25 to 150 cows (Fig 2). The threshold was insensitive to herd size and the decision to test and cull was profitable when pretest prevalence was $\geq 1.0\%$. The larger the herd the greater the return on the investment in the test and cull program for paratuberculosis.

Effect of herd replacement rate—Herd replacement rates from 15 to 40% were tested (Fig 3). The threshold was influenced slightly by the replacement rate but was 1 to 2% for all rates tested. The higher the replacement rate the greater the profit on the investment in the test and cull program.

Effect of the contact rate between cows and calves—Over the range of values tested, 0.010 to 0.035, the curves generated (Fig 4) resembled those found when we studied herd replacement rate. The threshold was influenced only slightly, ranging from 1 to 2%, and the slope of the benefit-cost curves was directly related to the effective contact rate.

Effect of herd production average—Rolling herd production averages from 4,545 kg to 9,091 kg/cow were tested (Fig 5) and had no effect on the threshold for the benefit-cost analysis. The model indicated higher producing herds would obtain a greater return on the investment in the test and cull program than would low-producing herds.

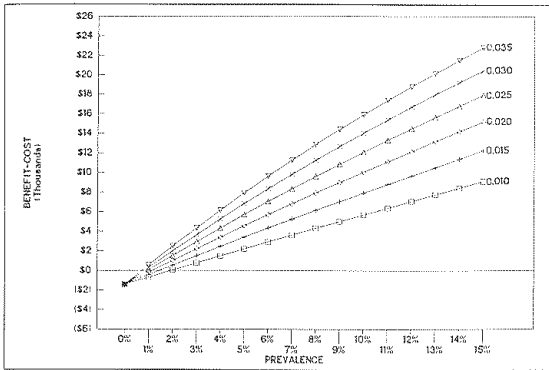


Figure 4—Effect of effective contact rate (range 0.010 to 0.035) on the profitability of a paratuberculosis test and cull program.

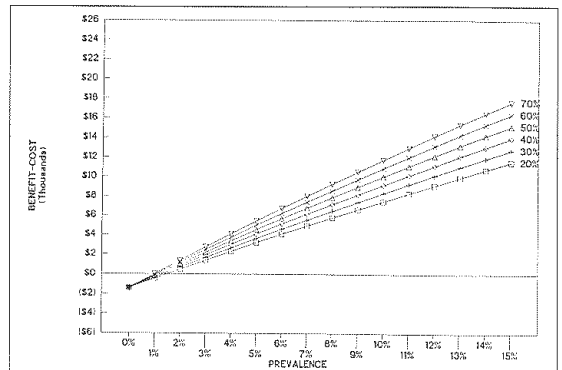


Figure 7—Effect of diagnostic test sensitivity (range 20 to 70%) on the profitability of a paratuberculosis test and cull program.

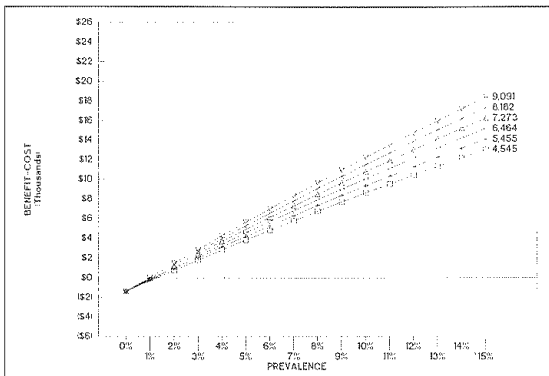


Figure 5—Effect of herd production average (range 4,545 to 9,091 kg) on the profitability of a paratuberculosis test and cull program.

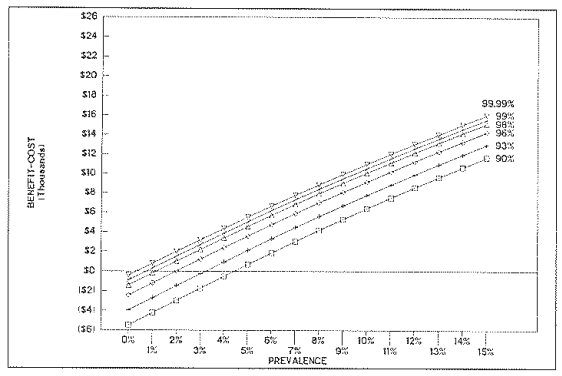


Figure 8—Effect of diagnostic test specificity (range 90 to 99.9%) on the profitability of a paratuberculosis test and cull program.

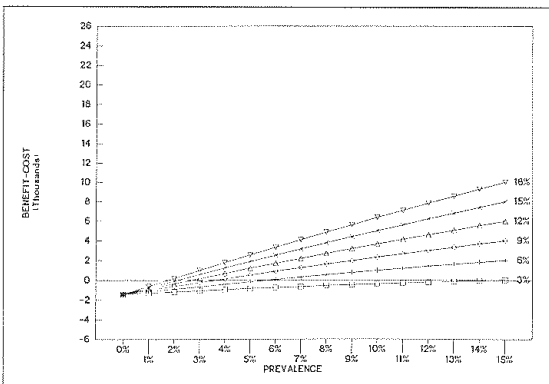


Figure 6—Effect of the degree of milk suppression (range 3 to 18%) caused by paratuberculosis on the profitability of a paratuberculosis test and cull program.

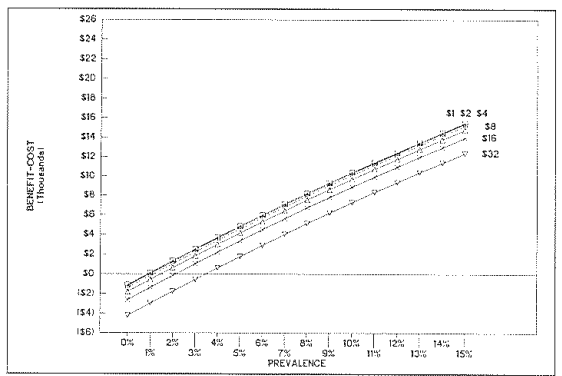


Figure 9—Effect of the cost of the diagnostic test (range \$1 to \$32) on the profitability of a paratuberculosis test and cull program.

Effect of the decrease in milk production caused by paratuberculosis—Milk production decreases from 3 to 18% were tested (Fig 6) and heavily influenced the profit on the investment in the test and cull program. If the disease only caused a 3% milk production decrease, the threshold for the benefit-cost analysis was a pretest prevalence rate of 15%. Alternatively, if the disease suppressed milk production at the rate of 18%, the threshold was reduced to 2%. Because, to our knowledge, no documented evidence exists on whether *M paratu-*

erculosis-infected cows eat more or less than noninfected cows, feed costs were ignored.

Effect of diagnostic test sensitivity—Test sensitivity increases from 20 to 70% were tested and there was little influence on the benefit-cost threshold (Fig 7). More sensitive tests, however, resulted in greater return on the investment in the test and cull program.

Effect of diagnostic test specificity—Test specificity increases from 90 to 99.9% were tested and were inversely related to the benefit-cost thresh-

old. Between test specificities of 98 and 99.99%, little difference in threshold was evident (Fig 8). The slopes of all 6 curves were the same, indicating no effect on the rate of return on the investment in the test and cull program between tests of different specificities.

Effect of diagnostic test cost—Diagnostic tests equivalent in sensitivity and specificity were evaluated at costs ranging from \$1 to \$32/cow (Fig 9). As expected, the benefit-cost threshold was lower for the less expensive tests. As in the test specificity analysis, all 6 curves had the same slope, indicating no effect on the rate of return on the investment in the test and cull program at various test costs.

Discussion

Paratuberculosis is a production disease and unlike brucellosis and tuberculosis in that it is not zoonotic and there are no mandatory state or federal control programs. However, because of the considerable impact of the disease on herd productivity, farmers should be advised to control the disease by minimizing the risk for infection of replacement calves and removal of infected cows from the herd.

Several new diagnostic tests are now available for paratuberculosis to aid in selection of animals for culling.^{2,13-21} They are primarily designed to detect *M paratuberculosis*-infected cattle without any signs of the disease. As such, the tests are applied to unselected populations and thus the principles contained in Bayes' Theorem and the predictive value model apply.²⁹ For unselected populations, the post-test probability of disease in the animals tested is governed by the test sensitivity, test specificity, and the pretest prevalence of disease in the population.^{28,29} Decision analysis methods combine the probability of each possible diagnosis with the economic consequences of the action taken on the diagnosis to allow calculation of the net profit or loss. The threshold approach to decision making further develops the method to produce a rational, quantitative approach to use of diagnostic tests.²⁴

Results of the paratuberculosis decision analysis model were consistent with those of another report.³⁹ If paratuberculosis causes at least a 6% decrease in milk production, it would generally pay to test and cull all test-positive animals once a year whenever the prevalence of the disease was > 6% with existing diagnostic methods. Walker et al^{40,41} came to similar conclusions when they used a more complex computer simulation model. In addition, larger, higher producing herds with higher replacement rates would realize a greater return on the investment in the test and cull program and could afford to do so at low (1 to 2%) pretest paratuberculosis prevalence (see Fig 2 and 3).

The effective contact rate was the least well

defined parameter in the model. This number represented the probability of infected cows on a farm transmitting the disease to calves. Contact rates around 0.02 have been used to model many infectious diseases^{30-32,42} and seems appropriate for modeling the spread of paratuberculosis in typical small to medium-size herds.³³ Decision analysis revealed that farms with poor hygiene, that is, those with higher effective contact rate, would economically benefit more from a test and cull program than herds with calf management practices that diminish the risk of disease transmission from cows to calves. Unfortunately there have not been any studies that quantitated the effective contact rates for farms with different calf management methods.

The model predicted that the "best" diagnostic test for use in a paratuberculosis test and cull program would be the one with the highest specificity and lowest cost, with test sensitivity of secondary importance (Fig. 7, 8, and 9). Specifically, low-cost, high specificity tests would be the ones most economical for an annual test and cull paratuberculosis control program. In light of the cost of various types of diagnostic technology, and if early reports of the accuracy of the absorbed ELISA for paratuberculosis are correct,¹⁷ absorbed ELISA may be the most efficient for paratuberculosis test and cull programs. Testing for paratuberculosis for other purposes such as animal export or herd certification, or in other types of herds such as registered herds where economic parameters are different, would require modification of the decision tree parameters.

Decision analysis shows the consequences of applying a diagnostic procedure to a herd. The results presented show the profit or loss after a single herd test with culling of all test positive cows. A similar procedure calculated iteratively could be used to examine the effect of a long-term test and cull program in a herd. It would likely indicate that testing was not economical when prevalence had been reduced, but at that stage, other factors would determine benefit-cost, that is, the value of total disease eradication. However, the effect of a test and cull program on the sensitivity and specificity of diagnostic tests must first be determined.

As with most models, the decision analysis model was not meant to describe the actual benefit-cost of a decision to test and cull for paratuberculosis but rather to evaluate the relative impact of the variables affecting the economics.

References

1. Pauker SG, Kassirer JP. Decision analysis. *New Engl J Med* 1987;316:250-258.
2. Collins MT, Sockett DC, Ridge S, et al. Evaluation of a commercial enzyme-linked immunosorbent assay for Johne's disease. *J Clin Microbiol* 1991;29:272-276.
3. Carpenter TE, Berry SL, Glenn JS. Economics of *Brucella ovis* control in sheep: Computerized decision-tree analysis. *J Am Vet Med Assoc* 1987;190:983-987.
4. Fetrow J, Madison JB, Galligan D. Economic decisions

in veterinary practice: a method for field use. *J Am Vet Med Assoc* 1985;186:792-797.

5. Parsons TD, Smith G, Galligan DT. Economics of porcine parvovirus vaccination assessed by decision analysis. *Prev Vet Med* 1986;4:199-204.

6. Mohammed HO, Loeffler S, Shearer J. Financial comparison of three testing strategies for detection of estrus in dairy cattle. *J Am Vet Med Assoc* 1990;196:865-869.

7. Galligan DT, Marsh WE, Madison J. Economic decision making in veterinary practice: expected value and risk as dual utility scales. *Prev Vet Med* 1987;5:79-86.

8. Ngategize PK, Kaneene JB, Harsh SB, et al. Decision analysis in animal health programs: merits and limitations. *Prev Vet Med* 1986;4:187-197.

9. Salman MD, Dargatz DA, Kimberling CV, et al. An economic evaluation of various treatments for contagious foot rot in sheep, using decision analysis. *J Am Vet Med Assoc* 1988;193:195-204.

10. Mousing J, Aalund O. Decision analysis: economically rational choice of control strategy at the herd level. *Dansk Vet Tidsskr* 1988;71:541-547.

11. Collins DM. Production of a DNA probe specific for *Mycobacterium paratuberculosis*. In: Milner AR, Wood PR, eds. *Johne's disease: Current trends in research, diagnosis and management*. Melbourne: CSIRO, 1989;136-141.

12. McFadden JJ, Green E, Hermon-Taylor J. DNA probes to identify and detect *Mycobacterium paratuberculosis* in clinical and veterinary samples. In: Merkal RS, Thorel MF, eds. In *Proceedings*. Second Int Colloq on Paratuberculosis. Maisons-Alfort: Laboratoire Central de Recherches Veterinaires, 1988;201-205.

13. Sherman DM, Gay JM, Bouley DS, et al. Comparison of the complement fixation and agar gel immunodiffusion tests for the diagnosis of subclinical bovine paratuberculosis. *Am J Vet Res* 1990;51:461-465.

14. Milner AR, Mack WN, Coates KJ, et al. The sensitivity and specificity of a modified ELISA for the diagnosis of *Johne's disease* from a field trial in cattle. *Vet Microbiol* 1990;25:193-198.

15. Vary PH, Andersen PR, Green E, et al. Use of highly specific DNA probes and the polymerase chain reaction to detect *Mycobacterium paratuberculosis* in *Johne's disease*. *J Clin Microbiol* 1990;28:933-937.

16. Hurley SS, Splitter GA, Welch RA. Development of a diagnostic test for *Johne's disease* using a DNA hybridization probe. *J Clin Microbiol* 1989;27:1582-1587.

17. Yokomizo Y. Evaluation on an enzyme-linked immunosorbent assay (ELISA) using *Mycobacterium phlei*-absorbed serum for the diagnosis of bovine paratuberculosis in a field study. *Jpn Ag Res Quarterly* 1986;20:60-67.

18. Tsai SJ, Hutchison LJ, Zarkower A. Comparison of a dot immunobinding assay, enzyme-linked immunosorbent assay and immunodiffusion for serodiagnosis of paratuberculosis. *Can J Vet Res* 1989;53:405-410.

19. Yokomizo Y, Nishimori K, Kishima M, et al. Evaluation of an enzyme-linked immunosorbent assay (ELISA) for the diagnosis of bovine paratuberculosis. A proposal of replacing the complement fixation test with the ELISA as the official diagnostic test for paratuberculosis in Japan. In: Merkal RS, Thorel MF, eds. In *Proceedings*. Second Int Colloq on Paratuberculosis. Maisons-Alfort: Laboratoire Central de Recherches Veterinaires, 1988;206-214.

20. Maes R, Buffereau JP. ELISA serodiagnosis of *Johne's disease* in cattle. *Int J Med Microbiol* 1989;271:180-185.

21. Collins MT, Kenefick KB, Sockett DC, et al. Enhanced

radiometric detection of *Mycobacterium paratuberculosis* using filter concentrated fecal specimens. *J Clin Microbiol* 1990;28:2514-2519.

22. Milner AR, Wood PR. *Johne's disease. Current trends in research, diagnosis and management*. Melbourne: CSIRO, 1989;1-167.

23. Carpenter TE. Epidemiologic programs for computers and calculators. Decision-tree analysis using a microcomputer. *Am J Epidemiol* 1986;124:843-850.

24. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *New Engl J Med* 1980;302:1109-1117.

25. Sackett DL, Haynes RB, Tugwell P. The selection of diagnostic tests. In: *Clinical epidemiology. A basic science for clinical medicine*. Boston: Little, Brown & Co, 1985;47-58.

26. Marchevsky N. Errors in prevalence estimates in population studies: a practical method for calculating real prevalence. *Zoonosis* 1974;16:85-109.

27. Schwabe CW, Riemann HP, Franti CE. The mathematical approach. In: *Epidemiology in veterinary practice*. Philadelphia: Lea & Febiger, 1977;66-97.

28. Vecchio TJ. Predictive value of a single diagnostic test in unselected populations. *New Engl J Med* 1966;274:1171-1173.

29. Dierksheide WC. Medical decisions: interpreting clinical tests. *ASM News* 1987;53:677-680.

30. Maia JDOC. Some mathematical developments of the epidemic theory formulated by Reed and Frost. *Human Biol* 1952;24:167-200.

31. Abbey H. An examination of the Reed-Frost theory of epidemics. *Human Biol* 1952;24:201-233.

32. Frost WH. Some conceptions of epidemics in general. *Am J Epidemiol* 1976;103:141-151.

33. Collins MT, Morgan IR. Epidemiologic model of paratuberculosis in dairy cattle. *Prev Vet Med* 1991;11:131-146.

34. Buergelt CD, Duncan JR. Age and milk production data of cattle culled from a dairy herd with paratuberculosis. *J Am Vet Med Assoc* 1978;173:478-480.

35. Abbas B, Reimann HP, Hird DW. Diagnosis of *Johne's disease* (paratuberculosis) in northern California cattle and a note on its economic significance. *California Vet* 1983;8:20-24.

36. Whitlock RH, Hutchison LT, Merkal RS, et al. Prevalence and economic consideration of *Johne's disease* in the northeastern U.S. in *Proceedings*. Annu Mtg U S Anim Hlth Assoc 1985;89:484-490.

37. Benedictus G, Dijkhuizen AA, Stelwagen J. Economic loss due to paratuberculosis in dairy cattle. *Vet Rec* 1987;121:142-146.

38. Wisconsin Agricultural Statistics Service. *Wisconsin 1990 agricultural statistics*. Madison, WI: Wisconsin Dept. Agriculture, Trade and Consumer Protection, 1990;1-94.

39. Moyle AI. Culture and cull procedure for control of paratuberculosis. *J Am Vet Med Assoc* 1975;166:689-690.

40. Walker K, French JJ, Kliebenstein J, et al. *An economic and epidemiologic simulation model of paratuberculosis (Johne's) disease in dairy herds. Part I. The analytical model*. Columbia, Missouri: Dept. Agricultural Economics, University of Missouri-Columbia, 1988;1-137.

41. Walker K, Kliebenstein J, McCamley F, et al. *An economic and epidemiologic simulation model of paratuberculosis (Johne's) disease in dairy herds. Part II. Model results*. Columbia, Missouri: Agriculture Experiment Station, University of Missouri-Columbia, 1988;1-23.

42. Hoiby N, Pedersen SS. Estimated risk of cross-infection with *Pseudomonas aeruginosa* in Danish cystic fibrosis patients. *Acta Paediatr Scand* 1989;78:395-404.