

# Stochastic models to simulate paratuberculosis in dairy herds

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## Summary

Stochastic simulation models are widely accepted as a means of assessing the impact of changes in daily management and the control of different diseases, such as paratuberculosis, in dairy herds. This paper summarises and discusses the assumptions of four stochastic simulation models and their use in the design of certification, surveillance, and control strategies for paratuberculosis in cattle herds. A detailed comparison is made between the Dutch JohneSSim and the Danish PTB-Simherd, using the same context of a set of control strategies in a typical Dutch/Danish herd. The conclusion is that while the models are somewhat different in their underlying principles and do put slightly different values on the different strategies, their overall findings are similar. Therefore, simulation models may be useful in planning paratuberculosis strategies in dairy herds, although as with all models caution is warranted when interpreting and generalising the results.

## Keywords

Control – Dairy cattle – Decision-making – Effect – Paratuberculosis – Stochastic simulation model.

## Introduction

Infection of dairy cattle with *Mycobacterium avium* subsp. *paratuberculosis* (MAP) may cause economic losses and reduced animal welfare and potentially be a food safety issue. Economic losses are primarily through reduced milk production, reduced slaughter value, premature culling, loss of genetic potential and continued spread of MAP.

Infections are met by cell-mediated immune responses to control the infection, but not necessarily to eliminate MAP from the host. At some point in time, the immune system becomes unable to sustain this control. The occurrence of the humoral immune response often suggests loss of this control in the infected individual (2). The transition from control to loss of control may occur relatively fast without detectable antibodies in some animals, or over a long period of time, i.e. several years, in others (14). The

variable incubation period means that timely and accurate diagnosis is challenging, particularly for detection of infected (i.e. non-shedding and non-diseased) animals (16).

Based on known risk factors for transmission of MAP, as well as knowledge and uncertainty regarding the incubation period, recommendations have been made regarding control strategies (15). These control strategies must be evaluated with respect to the economic and technical effects, e.g. the effects on the culling rate, reproductive performance, availability of replacement heifers, etc., in order to provide the farmer with relevant information to decide which course of action to adopt. However, intervention studies to assess the impact of control strategies are not readily performed because dairy production systems are complex and the possible effects of a control strategy that involves actions for the individual animal are long-term and affect the structure and dynamics

of the entire herd. Consequently, simulation models have long been advocated as an alternative.

The aim of this paper is to provide an overview of the possibilities for studying the technical and economic effects of MAP in dairy herds using simulation models.

## Stochastic simulation models

A simulation model is not a uniquely defined entity. Some research groups classify all epidemiological models that mimic the transmission of an infectious agent in a population as simulation models, whereas other groups reserve this term for models with discrete time steps (thus excluding analytical models). Epidemiological transmission models are characterised as, for example, stochastic, mechanistic, dynamic models, as opposed to deterministic, empirical, static models. While the meaning of these different classifiers is in no way unambiguous, there is an overall consensus, as described below.

*Stochastic* refers to a model in which the model parameters (and their effects) are subject to variation or uncertainty, i.e. parameters are drawn from random distributions and the same set of starting values might lead to different outcomes. The opposite is a *deterministic* model, where uncertainty regarding the parameters and variations of the parameter between individuals and herds are ignored, and the same output always occurs for a given set of parameters.

A *mechanistic* model mimics the system, e.g. insemination is modelled for a specific cow as an event, which might result in a pregnancy. To calculate the pregnancy rate in the herd, all simulated inseminations and the resulting simulated pregnancies are tallied to calculate the pregnancy rate, which is thus the result of simulating all inseminations and resulting pregnancies in the herd. This can be repeated with different scenarios, to estimate and compare, for example, pregnancy rates between strategies and the effects of different assumptions on herd dynamics. The alternative is an *empirical model* in which, for example, the pregnancy rate is modelled directly, with immediate inclusion of the effect of the suggested action/change in management. Thus, in the empirical model changes in herd dynamics are the result of a change in the pregnancy rate, rather than the pregnancy rate being the result of changes in herd dynamics.

Models that simulate the system through time are referred to as *dynamic* as opposed to *static* models, which can be seen as a here-and-now representation of the system.

Traditionally, models that explore dairy management have been stochastic, mechanistic, dynamic models; however, there is no reason why other models cannot be used. It depends entirely on the purpose of the model and the questions that need to be answered using the model.

## Transmission models described for *Mycobacterium avium* subsp. *paratuberculosis* infections

Nine models for within- and between-herd MAP transmission in cattle herds have been published so far. Amongst them, five are deterministic (1, 4, 13, 21, 22) and four are discrete-time stochastic models (7, 9, 11, 18). Three of the stochastic models represent MAP transmission within a dairy herd or within both dairy and beef herds, and the results obtained using these models have been published in follow-up papers (Table I). One model aims at representing MAP transmission within a beef herd only (9). However, this model was retained in the review because its modelling choices were unique and it could also be applied to dairy herds.

## Main assumptions in current stochastic transmission models

A number of assumptions are usually made in the different stochastic models. The main assumptions will be discussed briefly below.

### Host susceptibility

Host susceptibility has generally been modelled to be consistent with published knowledge, i.e. it is primarily related to age (26). However, these assumptions remain rather vague and could influence the results.

Susceptibility to MAP has been assumed to be age-related, with a maximum age at infection of 1 year of age (7, 11, 18), meaning that adult-to-adult transmission could not occur in these models. Cattle were considered to be resistant to the infection if they had not been infected at this age limit. Only one model considered adults to be susceptible irrespective of their age, although less susceptible than youngstock (9). In youngstock, susceptibility to MAP either remained constant (18), or varied with age class (9, 11), or with age class and route of infection (7).

**Table I**  
**Modelling options and conclusions of four stochastic *Mycobacterium avium* subsp. *paratuberculosis* (MAP) transmission models in cattle herds**

Reference*	Type of herd	Time step	Representation of horizontal adult-to-calf transmission	Output	Simulations and results	
					Length (years)	Main conclusions
7 (6, 8, 24, 25)	Dairy and beef	6 months	Through contact	Distribution of within-herd prevalence of infection Proportion of herds at each status of certification and surveillance plans Distribution of the concentration of MAP in bulk milk Losses due to paratuberculosis Costs of paratuberculosis control	20	Low true mean prevalence within 20 years only when all calf management tools are applied Test-and-cull strategy alone does not reduce the prevalence of paratuberculosis and is expensive Herd examinations by ELISA are sufficient in a bulk milk quality assurance programme
18 (3)	Dairy and beef	1 year	Through contact	Yearly incidence rate Yearly prevalence of infected animals Cumulated yearly disease extinction probability	30	In French cattle herds, the use of certification is not very economically profitable
9	Beef	6 months	Through the environment	Number of animals in each health state	n/a	This model suggests management factors that could be tested by experimentation or observation – currently no economic implementation
11 (10, 12)	Dairy	1 week	Through contact	Number of animals in each health state Prevalence of infected animals Losses due to MAP infections – both direct and indirect Costs of paratuberculosis control	10	Breaking of infection routes turns out to be the only strategy predicted to reduce the true prevalence of paratuberculosis in a dairy herd A risk-based approach is predicted to be very efficient with considerably less labour

\* The first reference describes the model, the following ones (within brackets) use and improve the models  
n/a: not available; ELISA: enzyme-linked immunosorbent assay

## Infection stages

The pathogenesis of MAP infections is such that different infection stages must be considered and modelled in association with different levels of shedding of the bacterium. The simplest representation considered susceptible, latently infected, clinically infected, and resistant animals (Fig. 1, in blue). In contrast, the most complex models (7, 11) defined six infection stages: susceptible, latently infected, subclinically infected (low and high shedder), clinically affected and resistant (Fig. 1, in black and red).

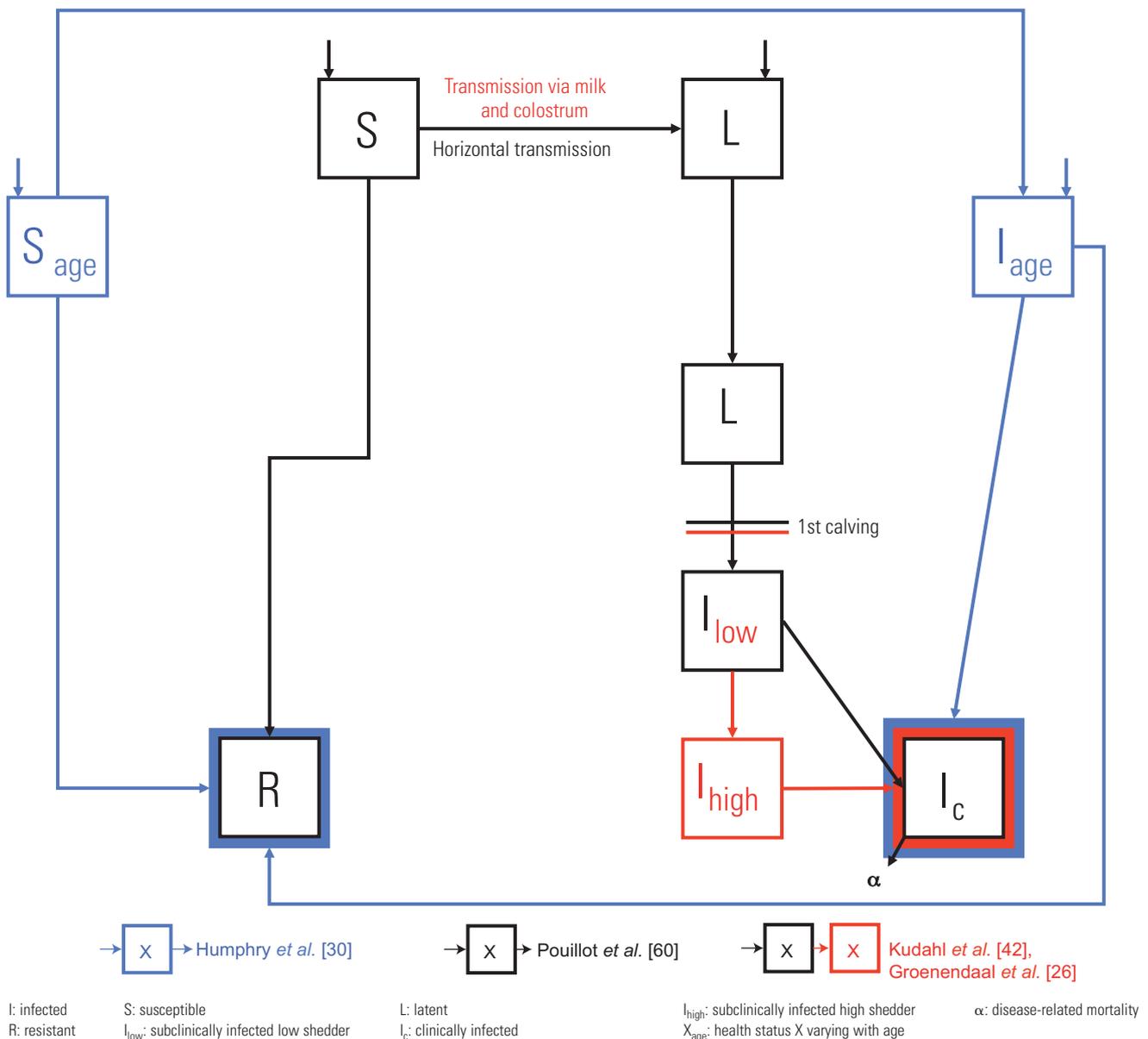
The characteristics of the infection dynamics have been integrated differently in the four models. In all the models, progression to the next infectious stage and increase of infectivity depend on the age of the animals (7, 9, 11, 18). However, only one model (7) considered the route of

infection and age at infection to influence the course of infection. Exposure to a large number of infectious animals influenced the probability of being infected but not the course of infection in infected cattle (9, 11, 18). Stressors such as calving or change of feed were taken into account in one model as factors influencing the course of infection (11).

Differentiation of infected animals into stages of infection is required. However, there is a lack of knowledge on the time spent in the different stages and on quantitative data regarding levels of shedding.

## Transmission pathways

Transmission pathways are generally considered to be well known, but the number of modelled transmission



**Fig. 1**  
Flow diagram of possible transition between different types of health status in four stochastic *Mycobacterium avium* subsp. *paratuberculosis* (MAP) transmission models in cattle herds

pathways varies between the published stochastic models. In one model, transmission was summarised using an overall transmission parameter, without modelling specifically how the infection was transmitted (18). The other models considered intra-uterine infection (7, 9, 11), infection at birth (7, 11), infection through colostrum and milk (7, 11), and faecal–oral infection (7, 9, 11). The infection status of the dam influenced the probability of *in utero* transmission and infection at birth, through colostrum and milk (7, 11), creating potential differences in infection risk between calves in a herd. The number of cattle in various infection stages in the herd influenced the probabilities of transmission through pooled colostrum and milk, and through faecal–oral transmission (7, 11).

In all but one model, faecal–oral transmission was modelled through a contact function between susceptible and infected cattle. The exception considered indirect transmission via the environment explicitly by taking into account the density of bacteria and their resistance in the environment (9).

### Shedding characteristics

In the models, cattle were usually categorised on the basis of the level of shedding in faeces. Older animals were more likely to shed MAP. None of the published models considered that calves could shed the bacteria (20).

Therefore, calf-to-calf transmission was not accounted for. However, the JohneSSim model (7) has been adapted recently to study the effects of infectious calves (23). Levels of shedding influence the infectiousness differently. Pouillot *et al.* (18) and Kudahl *et al.* (11) modelled different probabilities of infection depending on infection stage. Groenendaal *et al.* (7) differentiated high *versus* low shedders by the proportion of time they shed MAP. Humphry *et al.* (9) modelled the number of bacteria shed and their survival in the environment directly. Furthermore, higher levels of shedding were associated with a higher probability of being culled. Levels of shedding also influenced production parameters and test sensitivity and specificity. Differentiating several groups of animals with respect to MAP shedding allowed quantification of MAP in milk delivered to milk factories, to support the development of a milk quality assurance programme (25).

### Contact structure

'Contact' between a susceptible and an infectious animal is required for transmission of MAP. This is usually modelled to take into account 'efficient contacts', with the probability that one animal in the contact is susceptible and the probability that the other animal is infectious. However, contacts between animals in a herd are often not homogeneous because animals are usually grouped by age or production status. Housing these groups of animals separately can influence the bacterial density and the probability of infection.

Two models (7, 11) define groups for herd management purposes, while modelling the separation of various age groups by a reduction of the contact rates. In the other models, contacts are assumed to be the same between cattle of different ages. Nevertheless, in all models, the age of animals was considered because it influenced disease-related factors such as susceptibility. In the models, the contact pattern within an age group is assumed to be random and homogeneous, which is not always the case in practice. Patterns observed in practice can be difficult to mimic and such conditions should be considered while interpreting the modelling results. Further details of JohneSSim and PTB-Simherd are given below.

## JohneSSim

The JohneSSim model is a stochastic, dynamic and mechanistic simulation model that simulates:

- a) the herd dynamics
- b) the disease dynamics within the herd
- c) the control of MAP infection
- d) the economic consequences at the herd level (7).

In short, the model simulates a period of 20 years with, in the background, time steps of 6 months, and generates output data with time steps of 12 months. The herd dynamics of a typical Dutch dairy herd are simulated, including calves and replacement heifers. All animals in the herd have various attributes (such as parity, stage of infection, month in lactation, and milk production). The model contains probability distributions for uncertain events (such as replacement, infection, progression of the stage of infection, testing). Both voluntary culling and involuntary culling are considered. The percentage of cows culled involuntarily is specified per lactation. Voluntary culling is based on the retention pay-off, i.e. the expected profit from trying to keep the animal until its optimal life-span is complete compared with immediate replacement, taking into account the risk of involuntary premature removal.

In the model, five infection routes are considered:

- a) intra-uterine infections
- b) infections at birth
- c) infections due to drinking colostrum
- d) infections due to drinking whole milk
- e) infections due to environmental contamination with MAP.

Six stages are distinguished in the infection and disease processes in individual cattle:

- a) susceptible (i.e. uninfected, < 1 year of age)
- b) non-susceptible (i.e. uninfected,  $\geq$  1 year of age)
- c) latently infected
- d) infectious at a low level
- e) highly infectious
- f) clinical disease.

The progress of the infection and disease processes in infected cattle is influenced by the age at infection.

The probability distributions for uncertain events are used for random sampling. Repeated runs of the model provide insight into the variation in outcomes at the farm level. Results at a higher aggregation level (e.g. national level) are obtained by simulating different types of dairy herd and aggregating the results according to their relative abundance.

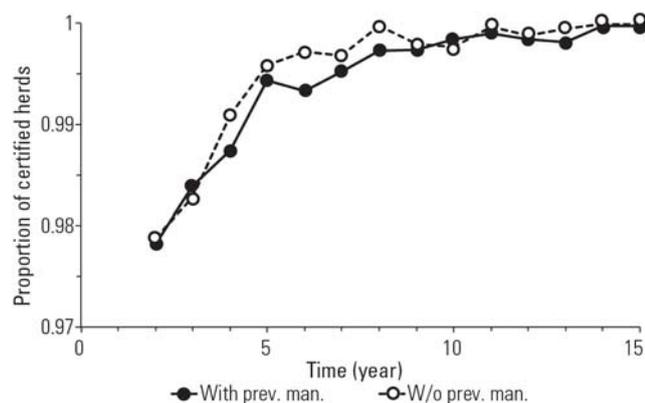
The JohneSSim model has been used to study the cost-effectiveness of various alternative paratuberculosis control programmes (5, 6), and to study certification and surveillance programmes that aim to reduce risks when trading cattle between herds (24) and ensure the quality of the milk delivered to the milk processing industry (25). For instance, the model was used to predict the proportion of herds certified in a bulk milk quality assurance

programme that have a concentration of MAP organisms in bulk milk less than  $10^3$  per litre (Fig. 2).

## Paratuberculosis (PTB)-Simherd

Paratuberculosis (PTB)-Simherd is based on the stochastic, dynamic, mechanistic dairy herd simulation model Simherd (19). The original Simherd model was created in 1992 and since then it has been developed for use in a series of research projects analysing the effects on production and economy of alternative management strategies concerning numerous diseases, reproduction, replacement, use of sexed semen, etc. Compared with JohneSSim this model simulates in shorter time steps of 1 week, and replacement is mechanistic. A culled or dead cow is replaced by a calving heifer if available. If one is not available, a calving heifer (with a specified risk of being latently infected with MAP) is purchased unless the herd is specified to be closed. Thereby many interactions are represented and the effects on herd dynamics, production and economy come very close to real life.

Every cow and the individual youngstock in a specified herd are described by 37 attributes, including the true MAP infection stage, the last test results of milk antibody enzyme-linked immunosorbent assay (ELISA), faecal culture, and the risk group indicating infectiousness on the basis of the antibody profile of the last four milk ELISA



**Fig. 2**  
**Predicted proportion of certified herds with  $< 10^3$  *Mycobacterium avium* subsp. *paratuberculosis* (MAP) per litre of milk in a bulk milk quality assurance programme consisting of annual herd examinations by serum enzyme-linked immunosorbent assay**

Results for herds with (With prev. man.) and herds without (W/o prev. man.) additional preventive management measures imposed on their background management were similar, indicating that information on the preventive management is not required to certify test-negative herds (25)

tests. Control strategies can be specified as either improved management, simulated as reduced risks of infection (specified for each infection route), or as different test-and-cull strategies. If test-and-cull strategies are specified to control MAP infections, the simulated effects depend on the replacement strategy that is specified by the user, e.g. should positive cows be culled immediately, or when the milk yield drops below a specified level? Culled cows are replaced by calving heifers (with a lower milk yield), and low-yielding cows that are on the culling list as a result of other diseases have to be kept in the herd for a longer period. In herds with poor reproduction strategy, the purchase of heifers (with a specified risk of being latently infected) is often necessary. If such a herd is specified to be kept as a closed herd, the herd size will decrease over the years.

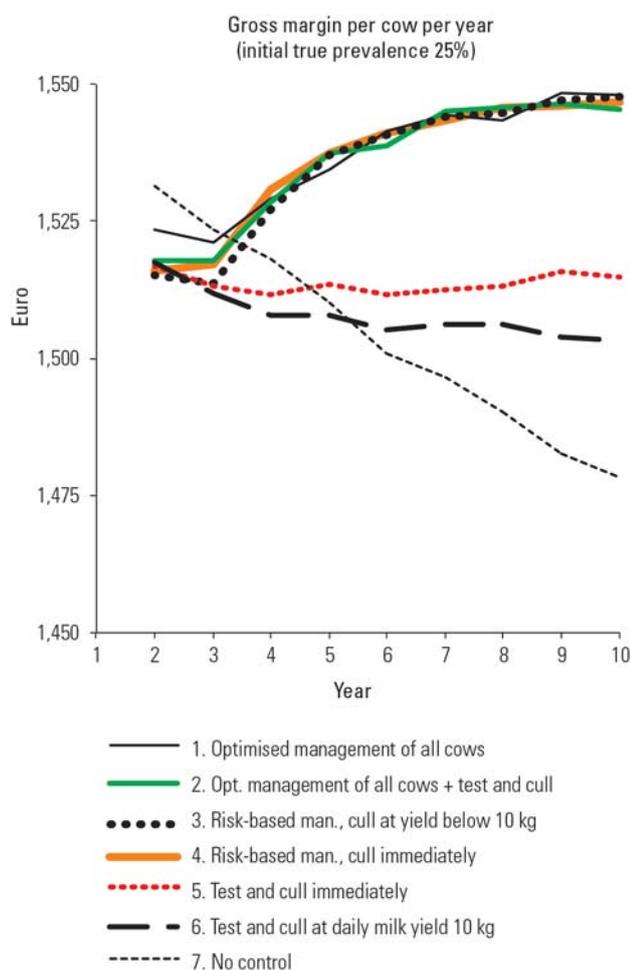
The first version of PTB-Simherd was described in detail by Kudahl *et al.* (11), and epidemiological and production-related effects of seven control strategies were evaluated. Since then the model has been developed further to evaluate potential long-term effects of control strategies recommended in the Danish national voluntary MAP control programme. Different test intervals have been evaluated (Kudahl, unpublished data) and animals are grouped according to their risk of being infectious, on the basis of antibody profiles. Risk-based control strategies focusing on closure of the infection routes from the most infectious animals were predicted to be more cost-effective than earlier strategies based on the closure of infection routes from all cows (10). In the future the model will be used to evaluate the optimal time of culling and to investigate the potential of using sexed semen in the control of MAP infections.

As an example, PTB-Simherd simulations of the economic effects of various control strategies (Fig. 3) predict that it will take at least 3 years before control can turn a decreasing gross margin into an increasing gross margin (10). This is only possible with control strategies that include the closure of infection routes, not with test-and-cull-strategies.

## Comparison of JohneSSim and PTB-Simherd

To compare the results of the JohneSSim and PTB-Simherd models, four scenarios were simulated with both models:

- poor preventive management without a test-and-cull scheme
- poor preventive management with a test-and-cull scheme



**Fig. 3**  
**Economic effects of seven control strategies simulated by PTB-Simherd**

Optimised management implies total closure of all infection routes. In risk-based management (man.), infection routes only from cows at risk of being infectious are closed (not all cows), and cows with high risk of being infectious are culled. Test and cull: only cows at high risk of being infectious are culled, and management is not changed

- good preventive management without a test-and-cull scheme
- good preventive management with a test-and-cull scheme.

Poor preventive management consisted of: calves not separated from their dam immediately after birth, waste milk and bulk milk fed to calves, and calves 0 to 6 months of age housed together with adults. Good preventive management was defined as: separating calves from their dam immediately after birth, using artificial milk replacer only, and keeping calves 0 to 6 months of age separate from adult cattle. In both the poor and good preventive management schemes, calves were fed colostrum from their own dam only. All herds were assumed to be closed (i.e. no new introductions of MAP

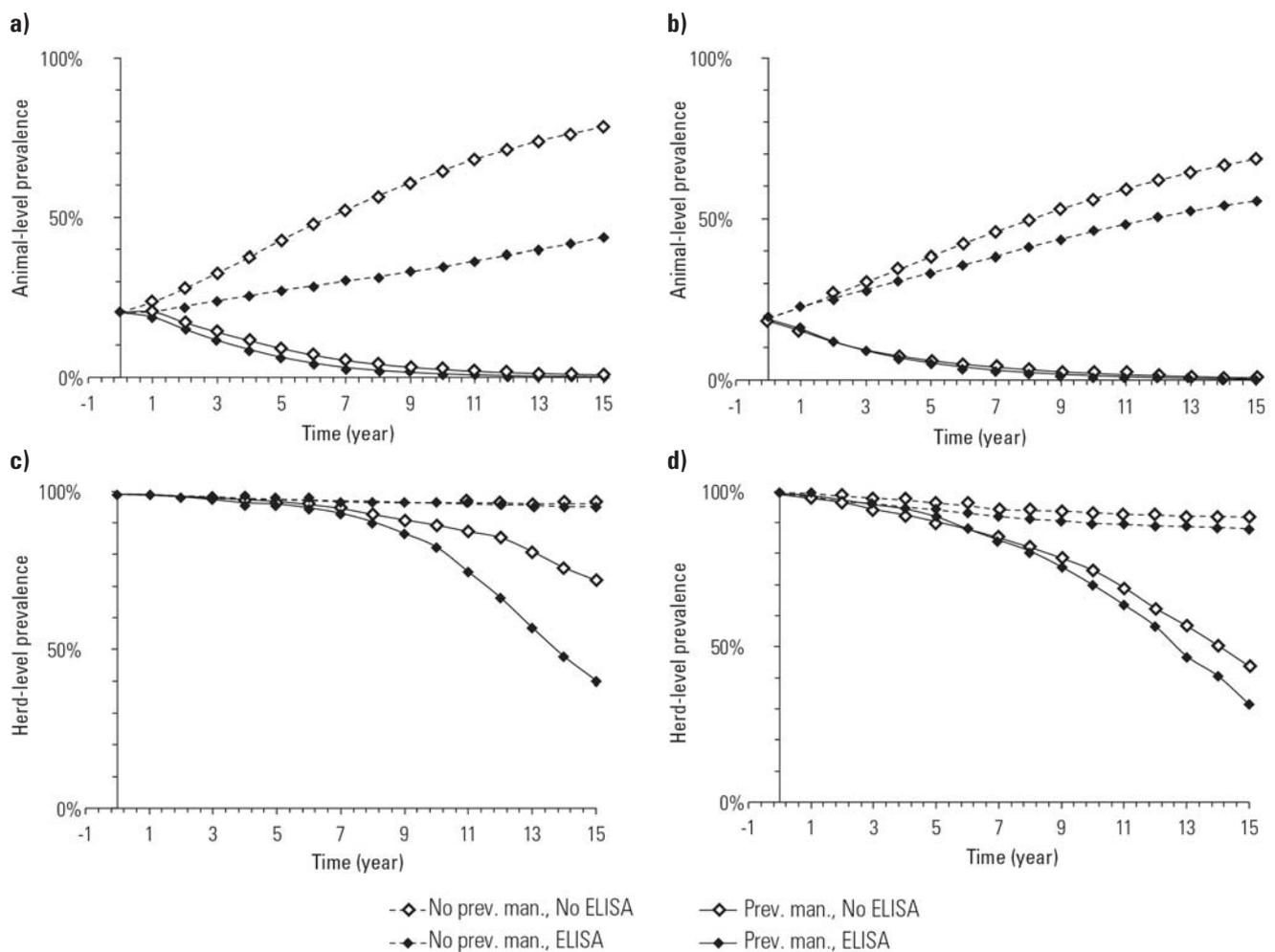
infection into any herd), and to have an initial herd size of 100 adult cattle. In the simulations with both models, a similar distribution of the initial within-herd animal-level prevalence of infected cattle was used, with an average initial animal-level prevalence of approximately 20%. For each of the simulated scenarios, the number of iterations was 1,000.

The simulated test-and-cull scheme consisted of herd examination by serum ELISA of all cattle  $\geq 2$  years of age twice per year, and selective culling of all ELISA-positive cattle (but not their offspring). The sensitivity of the ELISA to detect infected cattle was assumed to depend on the stage of the infection and disease process (sensitivity in latently infected cattle 0.01, cattle infectious at a low level 0.10, highly infectious cattle 0.60, clinically diseased cattle 0.80). The specificity of the ELISA was assumed to be 0.997.

The results of the simulations were similar across the two models (Fig. 4). In herds with poor preventive management without a test-and-cull scheme, the average within-herd animal-level prevalence increased over time from 20% to between 68% and 78% in year 15 (Figs 4a and 4b). In herds with poor preventive management with a test-and-cull scheme, the average within-herd animal-level prevalence increased over time to between 44% and 55% in year 15 (Figs 4a and 4b). In herds with good preventive management, the average within-herd prevalence decreased to  $< 1\%$  in year 15, irrespective of whether or not a test-and-cull scheme was executed (Figs 4a and 4b).

With all scenarios, only closed herds were simulated. This meant that no new MAP infections were introduced into any herd, whereas the infection became extinct in some herds as a result of random processes. Thus, the proportion of infected herds simulated decreased over time, depending on the scenario. In year 15, an estimated 92% to 96% of herds with poor preventive management and without a test-and-cull scheme remained infected (Figs 4c and 4d). In the same year, the estimated proportion of infected herds was 88% to 95%, 44% to 45%, and 14% to 32% in herds with poor preventive management with a test-and-cull scheme, herds with good preventive management without a test-and-cull scheme, and herds with good preventive management with a test-and-cull scheme, respectively (Figs 4c and 4d).

For all scenarios except the scenario with good preventive management and a test-and-cull scheme, the median within-herd animal-level prevalence in year 15 obtained with the JohnesSim model was significantly different from the corresponding result of the PTB-Simherd model (data not shown). However, it is important to realise that with



**Fig. 4**

**Results of simulations with the JohneSSim (Figs 4a and 4c) and PTB-Simherd (Figs 4b and 4d) models**

Models of four scenarios are shown: poor preventive management without a test-and-cull scheme, poor preventive management with a test-and-cull scheme, good preventive management without a test-and-cull scheme, and good preventive management with a test-and-cull scheme

Figures 4a and 4b: estimated average within-herd animal-level prevalence of infected cattle

Figures 4c and 4d: estimated true herd-level prevalence

ELISA: enzyme-linked immunosorbent assay

increasing numbers of iterations, small and irrelevant differences between the results of the two models can become significant. Therefore, a comparison of the results of the two models should focus on the relevance of any differences between their results, rather than on the statistical significance of those differences. At present, the distribution of the within-herd true prevalence of MAP infection is largely uncertain (17). With this background, the authors consider the differences between the results of the two models to be rather small. Moreover, the ranking of the effectiveness of the simulated control options is identical across the two models: preventive management measures are expected to be much more effective than a test-and-cull scheme based on biannual serological herd examinations. Furthermore, the results of both models indicate that the most effective control option is the combination of both preventive management measures and a test-and-cull scheme.

## Conclusions

Stochastic simulation models simulating the control and effects of MAP infections are widely used, and their use has supported the development of several nationwide strategies for the control of MAP infections. Simulation models are supposed to mimic very complex herd systems, but they rely on pre-existing knowledge and may therefore not always provide the correct answers. The fact that different models, such as the JohneSSim model and the PTB-Simherd model, are based on the same pre-existing knowledge and assumptions is also reflected in their apparently similar output. However, not all models have been compared in this paper, and with an increasing number of stochastic models available, diversity in model output can be expected. Models are useful for the synthesis of existing knowledge, with the limitations lying therein, and in studying the effects of change in complex systems. ■

## Modèles stochastiques permettant de simuler la maladie de Johne (paratuberculose) dans les élevages bovins laitiers

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### Résumé

Les modèles de simulation stochastiques sont réputés pour leur utilité pour évaluer l'impact des modifications introduites dans la gestion quotidienne des élevages ou celui des mesures de lutte appliquées contre diverses maladies, dont la maladie de Johne (paratuberculose) dans les élevages laitiers. Les auteurs résument et examinent les hypothèses de départ de quatre modèles de simulation stochastiques ainsi que l'utilisation qui en a été faite pour mettre au point des stratégies de certification, de surveillance et de prophylaxie applicables à la paratuberculose dans les élevages laitiers. Ils ont procédé à une comparaison minutieuse du modèle néerlandais JohneSSim et du modèle danois PTB-Simherd, en utilisant le même contexte, à savoir l'ensemble de mesures de prophylaxie classiques appliquées dans les élevages des deux pays. Ils en concluent que malgré quelques divergences mineures dans les principes sous-jacents, et de légères variations dans la valorisation des diverses stratégies selon les modèles, ceux-ci produisent des résultats globalement comparables. Par conséquent, si les modèles de simulation sont effectivement utiles pour planifier les stratégies de lutte contre la paratuberculose dans les troupeaux laitiers, il convient de faire preuve de prudence au moment d'interpréter et de généraliser leurs résultats, comme avec tout modèle.

### Mots-clés

Effet – Maladie de Johne (paratuberculose) – Modèle de simulation stochastique – Prise de décisions – Prophylaxie – Vaches laitières.



## Modelos estocásticos para simular la paratuberculosis en rebaños lecheros

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### Resumen

Los modelos estocásticos de simulación gozan de gran predicamento como medio de evaluar las consecuencias de todo cambio en el tratamiento y el control cotidianos de distintas enfermedades, como la paratuberculosis, en los rebaños lecheros. Los autores resumen y examinan las premisas de cuatro modelos estocásticos de simulación y su empleo en la concepción de estrategias de certificación, vigilancia y control de la paratuberculosis en rebaños bovinos. También proceden a una detallada comparación entre el modelo neerlandés JohneSSim y el danés PTB-Simherd, inscribiéndolos para ello en el contexto de un conjunto de estrategias de lucha en un típico rebaño neerlandés/danés. Llegan así a la conclusión de que ambos modelos, pese a que reposan en principios hasta cierto punto distintos y otorgan valores ligeramente disímiles a cada estrategia, arrojan globalmente resultados parecidos. Los modelos de simulación, por tanto, pueden ser útiles para planificar estrategias de lucha contra la paratuberculosis en los rebaños lecheros, si bien, como es el caso de cualquier modelo, conviene ser prudente a la hora de interpretar y generalizar los resultados.

**Palabras clave**

Adopción de decisiones – Control – Efectos – Ganado lechero – Modelo estocástico de simulación – Paratuberculosis.



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