Compartment Model for Controlling Infectious Livestock Disease: Cost Effective Control Strategies for Johne's Disease in Dairy Herds

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ABSTRACT

An animal compartment framework is used to develop a conceptual model which incorporates the complexity inherent in disease-specific epidemiology in livestock. This conceptual model is empirically implemented with a discrete optimal control model to evaluate the economic and epidemiological consequences of various control strategies for Mycobacterium avium subspecies paratuberculosis (MAP), the pathogen causing Johne's disease (JD), in dairy herds. The empirical results indicate that control of MAP will significantly improve profitability for dairy producers with a JD-affected herd. The empirical application will aid in developing a comprehensive and effective JD control program and the result will help dairy producers understand the economic benefits of controlling MAP by either hygiene management or testing and slaughtering test-positive animals.

Key Words: animal compartment model, dairy cattle disease, Johne's disease, livestock disease control, Mycobacterium avium subspecies paratuberculosis.

INTRODUCTION

Infectious diseases in livestock play a critical role in determining profitability of individual farms and maintaining the sustainability of livestock industries. Some of these

diseases are also linked to human diseases. This potential threat of infectious animal diseases to human health, coupled with their high cost to the livestock industry, has increased public interest in developing successful and cost-effective control programs that reduce the social and economic impact associated with livestock epidemics and to develop effective biosecurity programs.

Controlling infectious diseases in livestock is not straightforward, since the majority of these diseases have neither a fail-safe method of prevention nor a cure. In such cases, the success of infectious disease control in livestock becomes dependent on the producers' willingness to initiate a control program and the effectiveness of these controls in reducing transmission of the disease. Consequently, successful control programs need to be determined based on joint consideration of the economic gain for livestock producers and the effects of control strategies on the infection dynamics of the disease. This implies that control strategies in such programs should be cost-effective.

Prior literature on infectious livestock disease controls, however, has largely focused on either the reduction of farm-level economic losses while disregarding the infection dynamics of the disease (Mclnerney 1996; Chi et al 2002b; Gramig et al 2010) or else on the eradication of the disease while the economic costs and benefits of disease control are either ignored or computed only for the predetermined control strategies satisfying the eradication conditions (Diekmann et al 1990; Haydon et al 1997; Matthews et al 2006). Recently, the dynamic optimization approach with a simple susceptible-infected (SI) mathematical model has been increasingly applied to infectious wildlife disease control because it allows simultaneous evaluation of the economic and

epidemiological tradeoffs associated with disease control (Horan and Wolf 2005; Fenichel and Horan 2007; Horan et al 2008; Fenichel et al 2010). However, none of these studies applied this approach to infectious disease control in livestock given the consideration of disease control characteristics in livestock.

Wildlife disease control can be characterized as nonselective control since identifying infected wildlife prior to harvest is almost impossible and control options are basically limited to nonselective harvesting. In such a case, the epidemiological aspects of infectious diseases can be captured in a simple model, as the infection status is minimally important in nonselective disease control. In contrast, the health status of livestock can be largely controlled and monitored by producers. As a consequence, control strategies can be selectively applied to animals in different groups according to their production and health status. Therefore, a comprehensive disease-specific epidemiological model is often required in livestock disease control.

The objectives of this study are twofold: first, to develop a conceptual framework for evaluating the economics of an infectious disease control which can incorporate the complexity inherent in disease-specific epidemiology in livestock, and second, to evaluate the economic and epidemiological consequences of various control strategies for *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the pathogen causing Johne's disease (JD), which is a particularly serious infectious disease of dairy cattle due to its high prevalence and economic impact on the dairy industry.

Approximately 32% (Tiwari et al 2009) and 68% (USDA NAHMS 2008) of dairy herds had at least one MAP-infected cow in Canada and the U.S., respectively. Given this

high MAP prevalence, JD can have a devastating impact on the dairy industry; the annual cost per JD-infected cow has been estimated to be as high as CD$2472 (Chi et al 2002a) in Canada and US$1094 (Ott et al 1999) in the U.S.. This high economic cost of JD prompted the creation of a national voluntary control program in Canada (2005) and the U.S. (2002), but relatively few producers have participated given the lack of solid information and evidence that these programs will economically benefit producers.

A limited number of simulation and field studies have attempted to estimate the economic benefits of controlling MAP and JD (Ott et al 1999; Groenendaal et al 2002; Groenendaal and Galligan 2003; Dorshorst et al 2006; Pillars et al 2009). However, these studies did not take into account either the differences in the characteristics of various methods within a control strategy or their effects on the level of knowledge available to the producers in their decision making process. Moreover, given the nature of simulation and field studies, the results of most of these studies were limited to a predetermined set of control strategies.

Our empirical control model for the causal pathogen of JD, MAP, incorporates both the disease-specific epidemiology in dairy cattle and the effect of the various possible controls on the epidemiological process, incorporating the dairy producers' decision making process. The model allows the level of controls, such as optimal culling (harvesting) levels, to be endogenously determined, rather than predetermined as a scalar. The empirical results will help dairy producers understand the economic benefits of controlling MAP, resulting in reduction of the prevalence and economic costs of JD, by providing answers to producers' main questions, namely whether MAP control will

improve their profitability and which control measures generate the most economic benefits with consideration of the economic impact of JD.

ECONOMIC MODEL FOR INFECTIOUS ANIMAL DISEASE CONTROL

Animals within a herd or region can be grouped into different compartment $i \in I=\{1,\ldots,I\}$ according to their characteristics such as production- and infection-status. Let $x(t)=\{x_1(t),\ldots,x_I(t)\}$ be the set of $x_i(t)$, $i \in I=\{1,\ldots,I\}$, representing the number of animals in compartment i at time t. $y=\{y_1,\ldots,y_N\}$ is the set of control strategies y_n, $n \in N=\{1,\ldots,N\}$. $u=\{u_1,\ldots,u_M\}$ is the set of control options u_m, $m \in M=\{1,\ldots,M=\sum_{k=1}^{N}\binom{N}{k}\}$, that is a combination of control strategies such as improved hygiene management together with culling infected animals. Also, $w_{i,j}(x(t),u_m)$ is the transition rate[1] from compartment i to j and can be interpreted as the net growth rate when $i=j$. Finally, V_i is the set of adjacent compartments of compartment i, which implies that animals in compartments in set V_i are moved into or out of compartment i in the next time period $t+1$ due to aging, production stage change, or disease progress. Then, the state dynamics of animals in compartment i can be represented by

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[1] This is the general form of the transition rate between compartments since the rate is generally affected by control strategies in a control option and can be also affected by the number of animals in different compartments when this rate is frequency- or density-dependent.

$$\dot{x} \equiv x_i(t+1) - x_i(t)$$
$$= w_{i,i}(x(t),u_m)x_i(t) + \sum_{k \in V_i} w_{k,i}(x(t),u_m)x_k(t) - \sum_{j \in V_i} w_{i,j}(x(t),u_m)x_i(t) \tag{1}$$

The first term in the right hand side (RHS) of equation (1) represents the changes in the number of animals in compartment i due to net growth. The second term in the RHS of equation (1) represents the number of animals moved into compartment i from adjacent compartments $k \in V_i$. The third term in the RHS of equation (1) represents the number of animals moved to adjacent compartments $j \in V_i$ from compartment i. Compartments k and j can be identical to or different from each other depending upon the epidemiological process of a disease. When compartment i represents offspring from parent animals in compartment s, equation (1) can be augmented with the term $\sum_{s \in Z_i} b_{s,i}(x(t),u_m)x_s(t)$ where $b_{s,i}(x(t),u_m)$ is the birth rate of parent animals in compartment s that produce offspring in compartment i and Z_i is the set of compartments for parent animals.

Given a discount factor $\rho \in (0,1)^2$, net benefit function N, terminal function F, and control option u_m, a livestock producer or a social planner's economic objective is

$$\underset{\{x_i(t)\}_{i=1}^I}{Max} \sum_{t=1}^{T-1} \rho^t N(x(t),u_m) + \rho^T F(x(T)) \tag{2}$$

subject to a total of I equations of motion having the form of equation (1), initial number of animal stock $x(1) = \{x_1(1),...,x_I(1)\}$, and other possible feasibility conditions such as

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[2] ρ can be represented by $1/(1+r)$ where r is a discount rate.

capacity constraints that define and limit the domain of $x(t)$. Since this is a finite-dimensional optimization model, a solution exists provided that objective function and equations of motion are continuous and that $x(t)$ is a compact set.

In disease control, the majority of control strategies are generally treated as parameters (determined outside of the optimization process), as in equation (2), since such strategies (e.g. a certain level of hygiene management) are assumed to be determined at the initial period of control and consistently performed by producers. However, some control strategies can be variables (determined in the optimization process). For example, culling rates of cows associated with the control strategy involving diagnostic testing and slaughter of test-positive cows can vary depending on the number of cows in a herd and the capacity constraints of farm. In this case, the control strategy will also be a choice variable and affect the number of animals in associated compartments, such as compartments for cows and future newborn animals.

When set V_i in equation (1) is identical to set I, the above optimization model becomes the prototype bioeconomic model used in prior economic studies on wildlife disease control and analytic or qualitative solutions are generally obtained by using either dynamic programming- or maximal principle-techniques (Horan and Wolf 2005; Fenichel and Horan 2007; Horan et al 2008; Fenichel et al 2010). Otherwise, $V_i \neq I$ implies that animals in compartments belonging to V_i are linked to other compartments not belonging to V_i via different time lags due to the complex epidemiological progress of a disease, such as multi-stage infection. This complexity often precludes obtaining analytic or qualitative solutions and the optimization model may only be solved by numerical

computation, which is the case in the present study, which has 14 different animal compartments.

EPIDEMIOLOGY OF JOHNE'S DISEASE AND CONTROL STRATEGIES

JD is a chronic, infectious, untreatable disease of ruminants, caused by the pathogen MAP. Animal infection states of MAP in a dairy herd are classified as: susceptible, resistant, transient, latent, low-shedding, and high-shedding (Mitchell et al 2008; Lu et al 2010). Animals in the susceptible and resistant states are non-infected (free of MAP infection). Animals in the transient state are infected animals that shed MAP transiently at a low level and are not generally tested with currently available MAP diagnostic tests due to their young age. Animals in the latent state are infected animals that shed no MAP. Animals in the low-shedding state shed low levels of MAP, ≤ 30 cfu/g, while animals in the high-shedding state shed high levels of MAP, >30 cfu/g (Whitlock et al 2000).

Animals are typically susceptible to infection up to the age of 12 months and then become resistant (Collins and Morgan 1991). Susceptible animals can be infected following contact with MAP in fecal shedding from infected animals (Whitlock et al 2005), in colostrum and milk of infected adults (Sweeney et al 1992a), and in contaminated environments (USDA NAHMS 1997). Newly infected animals enter the transient state, which often develops within a few days of infection and continues up to 6 months (Rankin 1961). Some newborn animals from infected dams directly enter this state at the time of birth via in-utero infection (Sweeney et al 1992b). Given the duration of susceptible and transient states, animals in this state are typically younger than 18

9

months old. The latent state generally occurs following the transient state and continues for a long duration, but animals older than 24 months in this state begin to enter the low-shedding state and then the high-shedding state as the disease progresses.

Symptoms of JD are most commonly seen in adults and include reduced milk production, body weight losses, and increased mortality (USDA NAHMS 1997; Groenendaal et al 2002; NRC 2003; Nielsen and Toft 2008; Smith et al 2009). The transient and latent states are considered to be the incubation stage of JD since they are generally non-detectable with no symptoms. The low-shedding state can be considered to be the subclinical stage of JD as its symptoms begin to appear, that is, milk production and body weight begins to decrease. The high-shedding state can be considered to be the clinical stage of JD as considerable reduction in milk production and body weight is often present in animals in the high-shedding state. Animals in the high shedding state may develop diarrhea and have a higher mortality rate.

Typical MAP and JD control strategies include hygiene management and test-and-cull. Hygiene management reduces infection transmission rate in animals in the susceptible state by decreasing exposure to MAP. Test-and-cull is the diagnostic testing and slaughter of test-positive animals. A fecal culture (FC) test and an enzyme-linked immunosorbent assay (ELISA) test are the two main tests for detecting MAP infection (USDA NAHMS 2008), generally applied to adult cows. Test-and-cull reduces both MAP infection prevalence and JD-affected animals by removing infectious animals, but the efficacy of test-and-cull significantly varies depending on the test frequency and the

characteristics of MAP diagnostics such as the test sensitivity, test specificity, and identification ability.

Test specificity is the probability of classifying uninfected animals as test-negative. Since currently available MAP tests generally fail to detect infected animals shedding no MAP, animals in the test-negative classification are assumed to be a combination of animals free of MAP infection and infected animals shedding no MAP, which includes infected animals in the latent state of MAP infection. Therefore, a test with specificity less than 1 would generate false positive test results for not only animals free of MAP infection, but also infected animals shedding no MAP. On the other hand, test sensitivity is the probability of classifying infected, shedding animals as test-positive. In contrast to the test-negative classification, animals in the test-positive classification are assumed to be infected animals shedding MAP, which include animals in the low- and high-shedding states of MAP infection. Therefore, a test with sensitivity less than 1 would generate false negative test results for low- and high-shedding animals (Whitlock et al 2000; Lu et al 2008). Identification ability is the test's ability to detect specific MAP infection states of animals in the test-positive classification. A test, such as FC, that has identification ability allows producers to apply different culling rates for animals in low- and high-shedding states. With tests that do not have identification ability (such as an ELISA test), producers can only apply a single culling rate for test positive animals since they cannot separately identify whether these animals are low- or high-shedding.

EMPIRICAL MODEL

In this study, animals are grouped into 14 discrete and disjoint compartments (Table 1), $I=\{1,\ldots,14\}$, that are constructed based on the epidemiology of MAP infection described in the previous section. Each compartment $i \in I$ represents animals in different infection states and ages with 6-month time steps. Infection states are related to the level of infectiousness[3], productivity[4], and mortality[5]. Age is related to susceptibility to infection, duration of infection states, and production stage.

The equations of motion for animals in compartments 1 and 2 take the form of equation (1) with the additional term $\sum_{s \in Z_i} b_{s,i}(x(t),u_m)x_s(t)$ where $b_{s,i}(x(t),u_m)$ is the birth rate of newborn animals in compartment i from parent animals in compartment s and $Z_1=\{11, 12, 13, 14\}$ and $Z_2=\{12, 13, 14\}$ are the set of compartments for parent animals that produce offspring in compartments 1 and 2, respectively, while the equations of motion for animals in other compartments take the form of equation (1) without the additional term. All rates associated with the equations of motion for animals in each compartment are presented in Tables 2-3.

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[3] Infected animals shedding higher levels of MAP for longer periods infect more susceptible animals either directly or indirectly through contaminating their environments. Thus, horizontal infectiousness of infected animals follows this order: high-shedding, low-shedding, transient.

[4] Milk production and body weight begins to decrease in animals in the low-shedding state and they decrease considerably in animals in the high-shedding state.

[5] Only animals in the high-shedding state have a high mortality rate due to JD.

The relationship between compartments is illustrated in Figure 1, where x_i represents the number of animals in compartment $i \in I$ (Table 1), $b_{s,i}$ is the birth rate of parent animals in compartment s that produce offspring in compartment i (Table 2), $w_{i,j}$ is the transition rate from compartment i to adjacent compartment j (Table 3). This flow diagram of animal compartments is constructed based on our previous mathematical model for MAP infection in dairy herds (Mitchell et al 2008; Lu et al 2010). Detailed information on the animal movement between compartments is described in these previous papers.

In this study, vertical infections from parent animals to their offspring are captured in the birth rates for transient calves. These vertical infections are set at $\gamma_{12}=0.15$, $\gamma_{13}=0.15$, and $\gamma_{14}=0.17$ representing portion infected at birth given infected dams in compartments 12 (latent cows), 13 (low-shedding cows), and 14 (high-shedding cows) as in a prior modeling study (Lu et al 2010). Given these proportional parameters, the birth rates for transient female calves from infected dams ($b_{12,2}$, $b_{13,2}$, and $b_{14,2}$ in Table 2) are obtained from $b_{12,2}=b_{11,1}\gamma_{12}$, $b_{13,2}=b_{11,1}\gamma_{13}$, and $b_{14,2}=b_{11,1}\gamma_{14}$, while the birth rates for susceptible female calves from those dams ($b_{12,1}$, $b_{13,1}$, and $b_{14,1}$ in Table 2) are obtained from $b_{12,1}=b_{11,1}(1-\gamma_{12})$, $b_{14,1}=b_{11,1}(1-\gamma_{13})$, and $b_{14,1}=b_{11,1}(1-\gamma_{14})$, where $b_{11,1}=0.215$ represents the average birth rate for female calves on a 6-month basis (USDA NAHMS 2007).

Horizontal MAP infection is generally determined by the number of infected animals that shed MAP in transient (x_2, x_4, and x_7), low-shedding (x_{13}), or high-shedding states (x_{14}), since manure containing MAP is the main source of infection for susceptible

13

animals either directly or indirectly through contaminated environments. In a prior

modeling study (Lu et al 2008), this horizontal infection is captured in the force of

infection $\lambda(t)$:

$$\lambda(t) = [\beta_{Tr}\{x_2(t) + x_4(t) + x_7(t)\} + \beta_{13}x_{13}(t) + \beta_{14}x_{14}(t)]/N(t) \qquad (3)$$

where $N(t)$ is the total number of animals on a farm at time t and β_{Tr}=1, β_{13}=2, and

β_{14}=10 are transmission rates between susceptible animals and infected animals in

transient (compartments 2,4, and 7), low-shedding (compartment 13), and high-shedding

states (compartment 14), respectively.

The JD control strategies considered in this study include two different levels of

hygiene management and four different test-and-cull methods, summarized in Table 4.

These control strategies reduce the horizontal infection transmission rate in animals in the

susceptible state by decreasing the exposure of susceptible animals to infected manure.

Either improved or advanced hygiene management reduces the force of infection $\lambda(t)$ in

equation (3). Given the force of infection, together with the impact of hygiene

management, the transmission rates of animals from the susceptible state to the transient

state ($w_{1,4}(t)$ and $w_{3,7}(t)$ in Table 3) can be represented by $w_{1,3}(t)=w_{1,4}(t)=(1-\tau)\lambda(t)$, where

τ represents the effect of hygiene management on reduction of the force of infection with

the assumption of τ=0.85 for improved hygiene and τ=0.95 for advanced hygiene. These

estimates of τ are based on prior studies (Groenendaal et al 2002; Dorshorst et al 2006).

Susceptible animals remaining after infection with $\lambda(t)$ and natural death move to other

susceptible or resistant compartments due to aging. These movements are captured in

transition rates $w_{1,3}(t)$ and $w_{3,6}(t)$ in Table 3, which are obtained from

$w_{1,3}(t)=1-[(1-\tau)\lambda(t)+w_{1,1}]$ and $w_{3,6}(t)= 1-[(1-\tau)\lambda(t)+w_{3,3}]$, where both $w_{1,1}$ and $w_{3,3}$ are

-0.046, which is the natural death rates of calves (USDA NAHMS 2007).

Four different test-and-cull methods in Table 4 affect the removal rate of cows depending on test frequency and the characteristics of the test including specificity, identification ability, and sensitivity for low- and high-shedding cows[6]. In this study, cows are assumed to exit the herd in three different ways: a natural death, a general culling due to low production or diseases other than JD, or an additional culling due to test-and-cull for cows with a positive MAP test result. Given this assumption, the removal rate of cows ($w_{11,11}(t)$, $w_{12,12}(t)$, $w_{13,13}(t)$, $w_{14,14}(t)$ in Table 3) can be represented by:

$$w_{11,11}(t) = -[\mu_c + \{1-\phi(1-\varepsilon)\}\delta_c(t) + \phi(1-\varepsilon)\{\eta_L\delta_L(t) + \eta_H\delta_H(t)\}] \tag{4}$$

$$w_{12,12}(t) = -[\mu_c + \{1-\phi(1-\varepsilon)\}\delta_c(t) + \phi(1-\varepsilon)\{\eta_L\delta_L(t) + \eta_H\delta_H(t)\}] \tag{5}$$

$$w_{13,13}(t) = -[\mu_c + (1-\phi\theta_L)\delta_c(t) + \phi\theta_L\delta_L(t)] \tag{6}$$

$$w_{14,14}(t) = -[\mu_c + \alpha + (1-\phi\theta_H)\delta_c(t) + \phi\theta_H\delta_H(t)] \tag{7}$$

where μ_c=0.126 represents the natural death rate (USDA NAHMS 2007). δ_c represents the general culling due to low production or diseases other than JD. δ_L represents the additional culling due to test-and-cull for the low-shedding cows with a positive MAP test result. δ_H represents the additional culling due to test-and-cull for the high-shedding

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[6] Test specificity, identification ability, and test sensitivity are defined in the previous section.

cows with a positive MAP test result. The parameter ϕ represents test frequency, indicating either annually[7] (ϕ=0.5) or biannually[8] (ϕ=1). ε represents specificity of a MAP test with ε=0.95 for an ELISA test and ε=1 for a FC test. θ_L and θ_H represent test sensitivity for low- and high-shedding cows, respectively, with θ_L=0.3 and θ_H=0.75 for an ELISA test and θ_L=0.5 and θ_H=0.9 for a FC test (Whitlock et al 2000; Collins et al 2006; Nielsen and Toft 2008). η_L and η_H represent the proportion of cows with a positive test result that are erroneously identified as low- or high-shedding cows due to imperfect identification ability of a diagnostic test[9]. A FC test has identification ability, but an ELISA test does not. In this study, the proportions η_L and η_H are assumed to be determined by the ratio of the test sensitivity for low- and high-shedding cows as $\eta_L=\theta_L/(\theta_L+\theta_H)$ and $\eta_H=\theta_H/(\theta_L+\theta_H)$, where $\eta_L+\eta_H$=1.

In equations (4)−(7), the proportion of resistant and latent cows with a positive test result is represented by $\phi(1-\varepsilon)$ and these positive test results are false positive due to imperfect test specificity (ε<1)[10]. On the other hand, the proportion of low- and high-

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[7] An annual test is one in which all animals are tested once a year, half at midyear and the other half year-end.

[8] A biannual test is one in which all animals are tested twice a year, once at midyear and once year-end.

[9] η_L and η_H equal zero for a FC test since this test has identification ability, while they are non-zero for an ELISA test since this test does not have perfect identification ability.

[10] There will be no cows with a false-positive test result for a FC test since it is assumed to have perfect test specificity (ε=1), while some false-positive test results are observed for an ELISA test due to its imperfect test specificity (ε<1).

shedding cows with a positive test result is represented by $\phi\theta_L$ and $\phi\theta_H$, respectively, and these positive test results are true positive given the perfect test specificity associated with FC of low- and high-shedding cows. All cows in each compartment $i=\{11,12,13,14\}$ exit the herd at fixed rate μ_c due to natural death. All cows in the high-shedding state also exit the herd at an additional rate $\alpha=0.25$ due to the clinical symptoms of JD (Whitlock et al 2000). All cows with a positive test result can exit the herd by additional culling rates $\eta_L\delta_L+\eta_H\delta_H$ for resistant and latent cows, δ_L for low-shedding cows, and δ_H for high-shedding cows, where $\delta_L=\delta_H$ for a test does not have identification ability[11]. Thus, $\phi(1-\varepsilon)\{\eta_L\delta_L+\eta_H\delta_H\}$, $\phi\theta_L\delta_L$, and $\phi\theta_H\delta_H$ in equation (4)–(7) can be interpreted as the proportion of cows in each compartment that are removed from the herd because of test-positive status. Remaining cows, which are untested or have a negative test result, can exit the herd by a general culling rate δ_c due to low production or diseases other than JD.

In general, a dairy farm has an upper limit on the number of cows due to limited cow housing and management capacity and also a minimum number of cows necessary to generate cash flow for living and fixed expenses. These constraint factors can be imposed in the model by the following capacity constraint:

$$N_{\text{mincow}} \leq N_{\text{cow}}(t) \leq N_{\text{maxow}} \tag{8}$$

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[11] A test, such as FC, that has identification ability allows producers to apply different culling rates for cows in low- and high-shedding states. Otherwise, producers can only apply a single culling rate for test positive cows since they cannot separately identify whether these cows are low- or high-shedding. This is the case for an ELISA test.

where $N_{\text{cow}}(t)$ denotes the total number of cows at time t, N_{mincow} denotes the minimum number of cows, and N_{maxcow} denotes the maximum number of cows on a farm.

Given the epidemiological[12] and capacity constraints, the producer's objective is to maximize the expected net present value (NPV) from the sales of milk and cull cows for slaughter by deciding upon a combination of the control strategies in Table 5. Hygiene-associated control strategies are discrete and treated as parameters (determined outside of the optimization process) in the model since these are assumed to be determined at the initial period of control and we assume that producers do not alter their initial choices of hygiene management unless the disease is eliminated. On the other hand, culling-associated control strategies are continuous variables (determined in the optimization process) in the model and determine the number of cows in each compartment. In addition, this study assumed that the farm would no longer implement any control strategies when the disease was eliminated.

The expected NPV of a producer's net cash flow from the sales of milk and cull cows for slaughter is specified as:

$$
\begin{aligned}
\sum_{t=1}^{T-1} \frac{1}{(1+r)^t} & [P_{\text{milk}}Q_{\text{milk}}Z(t) + P_{\text{milk}}Q_{\text{milk}}(1-\varphi_L)L(t) + P_{\text{milk}}Q_{\text{milk}}(1-\varphi_H)H(t) \\
& + P_{\text{cull}}Q_{\text{cull}}Z(t)\delta_c(t) + P_{\text{cull}}Q_{\text{cull}}(1-\zeta_L)L(t)\delta_L(t) + P_{\text{cull}}Q_{\text{cull}}(1-\zeta_H)H(t)\delta_H(t) \\
& - C_{\text{calf}}N_{\text{calf}}(t) - C_{\text{heifer}}N_{\text{heifer}}(t) - (C_{\text{cow}} + C_{\text{mgt}} + \phi C_{\text{test}})N_{\text{cow}}(t)] \\
& + \frac{1}{(1+r)^T}[P_{\text{cull}}Q_{\text{cull}}N_{\text{cow}}(T) + P_{\text{sale}}\{N_{\text{calf}}(T) + N_{\text{heifer}}(T)\}]
\end{aligned}
\tag{9}
$$

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[12] Epidemiological constraints are the equations of motion for age-structured compartments describing the epidemiological process of Johne's disease.

This equation includes the expected revenue from milk sales, the expected revenues from cull cows sold for slaughter, and the operating cost of raising animals and the cost associated with a combination of control strategies in Table 5. The entire herd is liquidated at the beginning of the terminal year. For the sake of model brevity, all remaining cows in the terminal years are sold at the price of healthy cows. This is a reasonable approach given that, with controls, effectively no cows show symptoms of JD[13] in the final year of the 50-year simulation period. Young stock is all sold at the price of one year old animals, the average age of young stock. The variables and parameters in equation (9) are presented in Table 6.

The differences in the characteristics of various testing options affect the level of knowledge available to the producers in their decision making process. In equation (9), Z is suspected numbers of cows in the non-clinical stage (resistant and latent state), while L and H are suspected numbers of cows in the subclinical stage (low-shedding state) and the clinical stage (high-shedding state), respectively. Producers expect Z to have normal milk production and body weight, while they expect L and H to have lower milk production and body weight due to the disease. These production reductions due to JD are captured in the parameters φ_L, φ_H, ζ_L, and ζ_H in equations (9) and presented in Table 6.

Given imperfect specificity or sensitivity of currently available diagnostic tests, L and H represent producers' expectation on the number of low- and high-shedding cows in

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[13] Reduction in milk production and body weight.

their herd and they are determined based on the number of cows with a positive-test result as shown in equations (10) and (11).

$$L(t) = \begin{cases} \phi\theta_L x_{13}(t) \text{ for a FC test} \\ \phi\theta_L x_{13}(t) + \phi\theta_H x_{14}(t) + \phi(1-\varepsilon)\{x_{11}(t) + x_{12}(t)\}]\eta_L \text{ for an ELISA test} \end{cases} \quad (10)$$

$$H(t) = \begin{cases} \phi\theta_H x_{14}(t) \text{ for a FC test} \\ \phi\theta_L x_{13}(t) + \phi\theta_H x_{14}(t) + \phi(1-\varepsilon)\{x_{11}(t) + x_{12}(t)\}]\eta_H \text{ for an ELISA test} \end{cases} \quad (11)$$

Since a FC test has perfect identification ability and test specificity, cows with a positive-test result[14] are either low-shedding ($\phi\theta_L x_{13}$) or high-shedding ($\phi\theta_H x_{14}$) in equations (10) and (11). On the other hand, cows with a positive-test result[15] based on an ELISA test, which has imperfect test specificity, are either resistant ($\phi(1-\varepsilon)x_{11}$), latent ($\phi(1-\varepsilon)x_{12}$), low-shedding ($\phi\theta_L x_{13}$), or high-shedding ($\phi\theta_H x_{14}$) in equations (10) and (11). In addition, since an ELISA test doesn't have identification ability, a portion (η_L) of these cows is considered in low-shedding and the remaining portion (η_H) of these cows is considered in high-shedding[16]. The number of suspected cows (Z) in the non-clinical stage is the total

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[14] The proportion of low- and high-shedding cows with a positive test result is represented by $\phi\theta_L$ and $\phi\theta_H$ in equations (6) and (7), respectively.

[15] The proportion of low- and high-shedding cows with a positive test result is represented by $\phi\theta_L$ and $\phi\theta_H$ in equations (6) and (7), respectively. Similarly, a proportion of resistant and latent cows will have a positive test result given test specificity and this is expressed as $\phi(1-\varepsilon)$ in equations (4) and (5).

[16] η_L and η_H represent the proportion of cows with a positive test result that are erroneously identified as low- or high-shedding cows due to imperfect identification ability of a diagnostic test, $\eta_L+\eta_H=1$. These are previously discussed with equations (4) and (5).

number of cows (N_{cow}) minus the numbers of suspected low- and high-shedding cows (L and H, respectively).

$$Z(t) = N_{cow}(t) - L(t) - H(t) \qquad (12)$$

Since a mean true prevalence level of 10% MAP infection within a dairy herd is commonly assumed (Wells et al 2002; Van Schaik et al 2003; Dorshorst et al 2006), three initial MAP infection levels (0%, 10%, and 20%)[17] were considered for the baseline farm, in order to take into account the majority of dairy farm situations. The model described in this section was coded using the general algebraic modeling system (GAMS) software and empirically solved for a farm with these possible MAP infection levels.

RESULTS

For a farm free of MAP (0% MAP infection level), the NPV is $374,305 for the 50-year simulation period. The NPV is estimated to be considerably lower at $161,938 and $98,830 when the initial infection rate is 10% and 20%, respectively, in the absence of controls. This illustrates the potentially high cost of JD on dairy farms without control. The number of infected cows for a farm without MAP control in place increases continuously as reported in previous studies (Groenendaal et al 2002; Groenendaal and

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[17] An initial infection distribution for animal groups was simulated for a farm with an initial herd of 99 non-infected cows and 1 latently infected cow, and no control implemented. The initial conditions for the state variables for a farm with three different MAP infection levels were drawn from time-points in this simulation that matched the desired infection level. Each infection level represents a percentage of MAP infected cows per all cows in a herd.

Galligan 2003). These low NPV values would not be sustainable and implies that a farm would need to engage in some type of remedial action before JD becomes pervasive in the herd. Indeed, removing the lower cow number constraint eventually results in the sale of all cows, which would be expected with an epidemic infection rate.

With MAP present, the results show that culling all test-positive animals over time is optimal for maximizing the NPV of a farm's net cash flow. The optimal rate of base line culling[18] varies depending up on the number of healthy and MAP-infected cows, but the steady-state rate is 0.192 (19.2% replacement rate) when there are no MAP-infected cows. A herd size of 100 cows, the upper cow constraint, is the steady-state herd size when there are no MAP-infected cows or at the conclusion of a successful control program. The NPV and expected elimination[19] period of MAP and of test-positive animals for various control scenarios are summarized in Table 7.

The most cost-effective control option is improved hygiene management and test-and-cull using an annual FC test. This control option generates an NPV of $345,603 and $336,873, which are significantly higher compared to a farm without control given the initial infection rate of 10% and 20%, respectively. Implementing this option eliminates the MAP from the herd within 8 years for both MAP prevalence levels. Figure 2 shows the annual net cash flow associated with this control option together with no control for comparison. Although MAP control generates additional cost until the infection is

[18] The general culling rate δ_c in equations (4)-(7).

[19] MAP is considered to be eliminated when its prevalence rate is less than 1%, while test-positive cows are considered to be eliminated when the total number is less than 0.5.

22

eliminated, the overall benefit of control is much higher than no control with both 10%

and 20% prevalence. This figure also illustrates one reason farmers may not start a

control strategy; the control costs are much higher initially than the lost income from JD.

Reluctance to engage in MAP control is especially strong when farms would clearly

experience the definite control cost but with actual losses from JD being nebulous.

For producers whose goal is to control MAP by implementing only a single

control strategy, improved hygiene management generates the overall highest NPV

among all single control strategies available for a farm with JD present. Test-and-cull

using a FC test is an effective control strategy since it eliminates MAP, but this control

strategy requires a considerably longer elimination period compared to that for a farm

implementing improved hygiene management. On the other hand, test-and-cull using an

ELISA test is an ineffective control strategy. This control strategy decreases the MAP

infection prevalence, but fails to eliminate MAP over the extended planning duration of a

dairy farm.

Due to imperfect test sensitivity or specificity, it is difficult to identify whether

MAP has been eliminated or not when using a MAP test only, especially an ELISA test.

However, elimination of MAP can be ascertained in the model by observing the

computed net cash flow[20]. When the net cash flow associated with a control option

reaches a steady state net cash flow in our model, which equals $8,255 minus the cost of

implementing the control option, it implies that MAP has been eliminated. This is

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[20] Note that the NPV in this study is the sum of discounted net cash flows.

because a net cash flow of $8,255 is identical to the net cash flow for a farm free of MAP. Thus, a net cash flow of $8,255 minus the cost of implementing the control option implies that there are no losses caused by JD.

In reality, producers may halt a control program if there are no test-positive animals in their herd, but the disease would resurface due to undetected infected animals remaining or reintroduced into the herd. Table 7 shows the lag between the period of MAP elimination and the last period of detecting test-positive animals. Given the lag between those periods, it is important for producers to keep screening their herd using a MAP test after eliminating the last test-positive animals in order to eliminate the disease entirely. However, the ELISA test may not be efficient for this monitoring due to the imperfect test specificity, which generates false-positive test results in the herd free of MAP. Moreover, with the low test sensitivity of the ELISA test, infected animals may escape detection and infect many other animals before they are identified. Therefore, the FC test, which has near-perfect test specificity and high test sensitivity, is recommended even though the FC test is more expensive with slower results than the ELISA test. In short, a combination of improved hygiene management and test-and-cull using either an annual or biannual FC test is highly recommended since these are the most and second most cost-effective control options considered in this study.

The empirical results show the number of animals infected with MAP and animals in the subclinical and clinical stages of JD increases during the planning duration of 50 years in the absence of a control program as in previous studies (Groenendaal et al 2002; Groenendaal and Galligan 2003). However, in practice, it could be possible to observe

that even in the absence of an active control program, elimination of JD, though not necessarily of the causal pathogen MAP, has been successful in some infected herds. There could be several reasons for this discrepancy between field experience and our empirical results. The most probable explanation is that it is unlikely that a farm with a serious production problem would not engage in some form of implicit control. Therefore, low producing and sick cows are culled regardless of the causation and it could, in effect, eliminate JD, though animals infected with the causal pathogen MAP may still remain in the herd.

Another possible concern is that our empirical results imply that the causal pathogen MAP can be eliminated from the herd entirely, which although consistent with previous studies (Groenendaal et al 2002; Groenendaal and Galligan 2003), in practice is generally difficult to accomplish. One explanation for elimination in our empirical results is that our model does not allow the stochastic re-introduction of MAP into the herd once eliminated. However, in reality, re-introduction of MAP is possible through various routes including the purchase of infected animals from an outside farm or by humans who may introduce MAP into a farm via contaminated clothing, farm implements, etc.

CONCLUSION

This study presented a conceptual framework for developing an infectious disease control model in livestock which is applied as a discrete optimal control model to evaluate the long-term feasibility and profitability of various control methods for the causal pathogen MAP which causes Johne's disease in dairy herds. Results show that elimination of the

disease requires a long-term plan with implementation of at least one of the control strategies. Any MAP control method yields a higher NPV of the farm's net cash flow compared to no control. Implementing either additional calf-hygiene management or test-and-cull using a FC test can control the disease, but these are most effective when combined with each other in reducing the infection rate in MAP-infected herds.

Age \ Health	Susceptible or resident	Transient	Latent	Low-shedding	High-shedding
0-6 Months	x_1	x_2			
6-12 Months	x_3	x_4	x_5		
12-18 Months	x_6	x_7	x_8		
18-24 Months	x_9		x_{10}		
24+ Months	x_{11}		x_{12}	x_{13}	x_{14}

Flows: $w_{1,3}$, $w_{1,4}$, $w_{2,5}$, $w_{3,6}$, $w_{3,7}$, $w_{4,8}$, $w_{5,8}$, $w_{6,9}$, $w_{7,10}$, $w_{8,10}$, $w_{9,11}$, $w_{10,12}$, $w_{12,13}$, $w_{13,14}$

Outflows: $b_{11,1}$, $b_{11,2}$, $b_{12,1}$, $b_{12,2}$, $b_{13,1}$, $b_{13,2}$, $b_{14,1}$, $b_{14,2}$
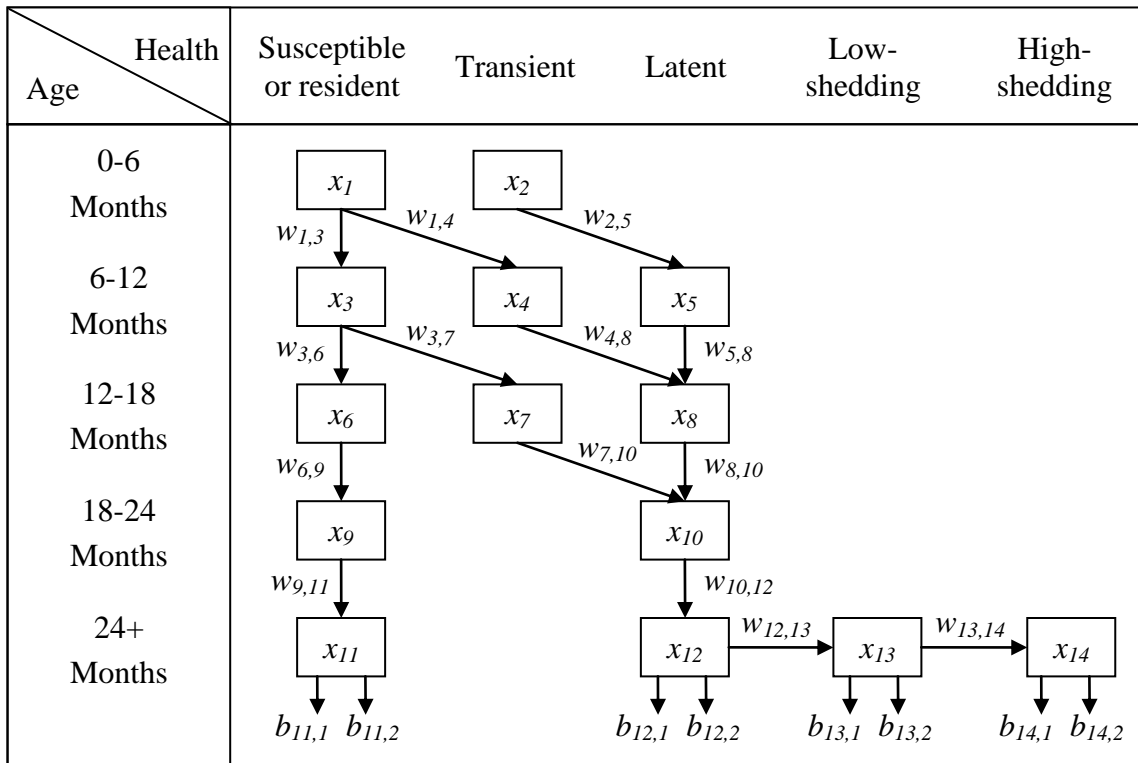
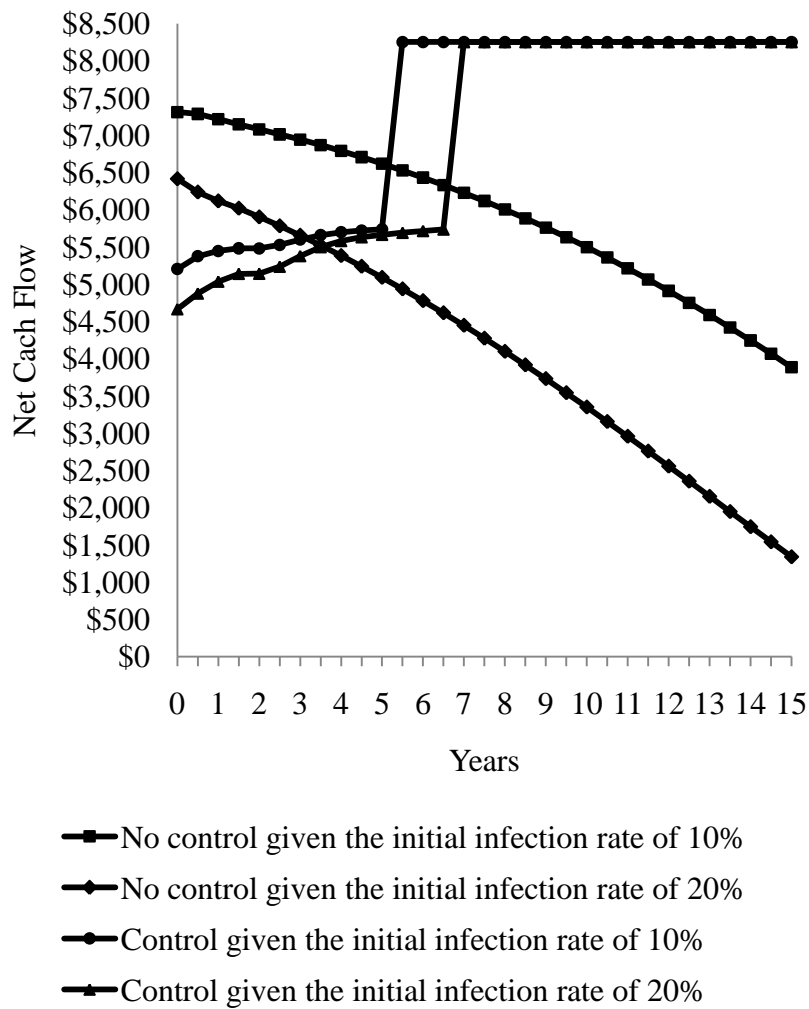Figure 1. The flow diagram of animal compartments and infection with MAP

Figure 2. Annual net cash flows over first 15 years with no controls and with controls of improve hygiene and culling using an annual fecal test

Note: The sudden increases in net cash flow are caused by discontinuation of controls.

Table 1. Definition of animal compartments

Compartment	Description
1	Compartment for calves 0-6 months in the susceptible state
2	Compartment for calves 0-6 months in the transient state
3	Compartment for calves 6-12 months in the susceptible state
4	Compartment for calves 6-12 months in the transient state
5	Compartment for calves 6-12 months in the latent state
6	Compartment for heifers 12-18 months in the resistant state
7	Compartment for heifers 12-18 months in the transient state
8	Compartment for heifers 12-18 months in the latent state
9	Compartment for heifers 18-24 months in the resistant state
10	Compartment for heifers 18-24 months in the latent state
11	Compartment for cows in the resistant state
12	Compartment for cows in the latent state
13	Compartment for cows in the low-shedding state
14	Compartment for cows in the high-shedding state

Note: The terms calves, heifers, and cows are defined as animals younger than 12 months, between 12 and 24 months, and older than 24 months that produce offspring and milk, respectively.

Table 2. Birth rate for female calves and net growth rate of animals (6 month basis)

Rate	Description	Value
$b_{11,1}$	Birth rate for susceptible female calves from resistant cows	0.215
$b_{12,1}$	Birth rate for susceptible female calves from latent cows	0.183
$b_{12,2}$	Birth rate for transient female calves from latent cows	0.032
$b_{13,1}$	Birth rate for susceptible female calves from low shedders	0.183
$b_{13,2}$	Birth rate for transient female calves from low shedders	0.032
$b_{14,1}$	Birth rate for susceptible female calves from high shedders	0.178
$b_{14,2}$	Birth rate for transient female calves from high shedders	0.037
$w_{i,i}$	Natural death rate of calves (animals in compartments i=1,2,3,4,5)	−0.046
	Natural death rate of heifers (animals in compartments i=6,7,8,9,10)	−0.009
$w_{11,11}$	Removal rate of resistant cows	Varies
$w_{12,12}$	Removal rate of transient cows	Varies
$w_{13,13}$	Removal rate of low-shedding cows	Varies
$w_{14,14}$	Removal rate of high-shedding cows	Varies

Sources: Birth rates are obtained from USDA NAHMS (2007) and Lu et al (2010). Natural death rates are obtained from USDA NAHMS (2007).

Note: In our age-structured compartment model, natural growth of herd size is allowed only through birth of newborn calves. Hence, the net growth rate of calves and heifers becomes the natural death rate of these animals and that of cows becomes the removal rate, which is the sum of natural death rate, general culling rate due to low production or diseases other than Johne's disease, and additional culling rate due to test-and-cull. General and additional culling rates associated with removal rate of cows are obtained by solving the control model empirically.

Table 3. Transition rate between adjacent compartments (6 month basis)

Rate	Description	Value
$w_{1,3}$	Susceptible calves 0-6 months → Susceptible calves 6-12 months	Varies
$w_{1,4}$	Susceptible calves 0-6 months → Transient calves 6-12 months	Varies
$w_{2,5}$	Transient calves 0-6 months → Latent calves 6-12 months	0.954
$w_{3,6}$	Susceptible calves 6-12 months → Resistant heifers 12-18 months	Varies
$w_{3,7}$	Susceptible calves 6-12 months → Transient heifers12-18 months	Varies
$w_{4,8}$	Transient 6-12 months → Latent 12-18 months	0.954
$w_{5,8}$	Latent 6-12 months → Latent 12-18 months	0.954
$w_{6,9}$	Resistant heifers 12-18 months → Resistant heifers 18-24 months	0.991
$w_{7,10}$	Transient heifers 12-18 months → Latent heifers 18-24 months	0.991
$w_{8,10}$	Latent heifers 12-18 months → Latent heifers 18-24 months	0.991
$w_{9,11}$	Resistant heifers 18-24 months → Resistant cows	0.991
$w_{10,12}$	Latent heifers 18-24 months → Latent cows	0.991
$w_{12,13}$	Latent cows → Low-shedding cows	0.500
$w_{13,14}$	Low-shedding cows → High-shedding cows	0.165

Sources: All rates are obtained from USDA NAHMS (2007) and previous studies on *Mycobacterium avium* subspecies *paratuberculosis* and Johne's disease in dairy herds. Detailed information on these rates is explained in the empirical model section.

Note: Movement of animals from one compartment to another is due to aging, infection, or infection progress. Transition rates due to aging are $w_{1,3}$, $w_{3,6}$, $w_{5,8}$, $w_{6,9}$, $w_{8,10}$, $w_{9,11}$, and $w_{10,12}$. Transition rates due to infection are $w_{1,4}$ and $w_{3,7}$. Transition rates due to infection progress are $w_{2,5}$, $w_{4,8}$, $w_{12,13}$, and $w_{13,14}$.

Table 4. Control strategies for Johne's disease

Control strategy	Description
Improved hygiene	Improved hygiene includes harvesting colostrum from cows with cleaned and sanitized udders and preventing contact of calves with adult cow manure
Advanced hygiene	Advanced hygiene includes feeding calves with only milk replacer or pasteurized milk, preventing contamination of calf feedstuffs, water, or bedding by effluent from the adult herd as well as hygiene practices included in improved hygiene
Test-and-cull using annual FC test	Testing cows once a year (half at midyear and the other half at the end of year) using fecal culture test and culling test-positive cows
Test-and-cull using annual ELISA test	Testing cows once a year using enzyme-linked immunosorbent assay test and culling test-positive cows
Test-and-cull using biannual FC test	Testing cows twice a year (once at midyear and once at the end of year) using fecal culture test and culling test-positive cows
Test-and-cull using biannual ELISA test	Testing cows twice a year using enzyme-linked immunosorbent assay test and culling test-positive cows

Note: Both improved hygiene and advanced hygiene include additional hygiene practices defined previously, as well as all hygiene practices assumed to be currently implemented by typical dairy farms. In particular, advanced hygiene is designed to provide a hygiene environment identical to off-farm calf rearing. The difference between improved hygiene and advanced hygiene is that while both are assumed to decrease infection transmission between susceptible and infectious animals, the latter is additionally assumed to decrease infection transmission between susceptible animals and surrounding environments contaminated mainly by manure containing *Mycobacterium avium* subspecies *paratuberculosis*.

Notation	Definition
u_1	Improved hygiene
u_2	Advanced hygiene
u_3	Test-and-cull using annual FC test
u_4	Test-and-cull using annual ELISA test
u_5	Test-and-cull using biannual FC test
u_6	Test-and-cull using biannual ELISA test
u_7	Improved hygiene with test-and-cull using annual FC test
u_8	Improved hygiene with test-and-cull using annual ELISA test
u_9	Improved hygiene with test-and-cull using biannual FC test
u_{10}	Improved hygiene with test-and-cull using biannual ELISA test
u_{11}	Advanced hygiene with test-and-cull using annual FC test
u_{12}	Advanced hygiene with test-and-cull using annual ELISA test
u_{13}	Advanced hygiene with test-and-cull using biannual FC test
u_{14}	Advanced hygiene with test-and-cull using biannual ELISA test

Table 5. Control strategy combinations

Table 6. Definition of variables and parameters used in the net present value equation

Rate	Description	Value[a]	Reference
C_{calf}	Base operating cost of raising a calf	395.00	Karszes et al 2008
C_{cow}	Base operating cost of raising a cow	1231.46	USDA NASS 2003-2007
C_{heifer}	Base operating cost of raising a heifer	395.00	Karszes et al 2008
C_{mgt}	Extra cost associated with advanced hygiene	26.25	Dorshorst et al 2006
	Extra cost associated with improved hygiene	15	Dorshorst et al 2006
C_{test}	Cost of ELISA test per sample	5.00	Collins et al 2006
	Cost of FC test per sample	19.00	Collins et al 2006
H	Suspected numbers of cows in clinical stage	Varies	Calculated
L	Suspected numbers of cows in subclinical stage	Varies	Calculated
N_{calf}	Number of calves	Varies	Calculated
N_{cow}	Number of cows	Varies	Calculated
N_{heifer}	Number of heifers	Varies	Calculated
P_{cull}	Cull-cow price per pound	0.4788	USDA NASS 2003-2007
P_{milk}	Milk price per pound	0.1539	USDA NASS 2003-2007
P_{sale}	Sale price of a one year old animal	867[c]	Karszes et al 2008
Q_{cull}	Pounds (weight) of cull cow	1500	USDA NASS 2003-2007
Q_{milk}	Pounds of milk production per cow	9719.5	USDA NASS 2003-2007
r	Discount rate	0.02	Assumed
T	Total follow up time of a dairy farm	100	Assumed
Z	Suspected numbers of cows in non-clinical stage	Varies	Calculated
δ_c	General culling rate for cows	Varies	Calculated
δ_H	Extra culling rate for low-shedders	Varies	Calculated
δ_L	Extra culling rate for high-shedders	Varies	Calculated
ϕ	Test frequency	0.5 or 1	Assumed[b]
φ_H	Production adjustment factor for high-shedders	0.1	Groenendaal et al 2002[d]
φ_L	Production adjustment factor for low-shedders	0.05	Groenendaal et al 2002[d]
ζ_H	Cull-weight adjustment factor for high-shedders	0.1	Assumed
ζ_L	Cull-weight adjustment factor for low-shedders	0.05	Assumed

a. Values are 6-month basis.

b. ϕ=0.5 represents annual testing and ϕ=1 represents biannual testing.

c. Sale price of a one year old animal is assumed to be identical to total cost of raising replacement heifer up to one year.

d. Production reduction due to Johne's disease has been reported 5% to 20%.

Table 7. Farm NPV and expected elimination period of the disease and of test-positive animals for a farm with a MAP-infected herd

Control option		Infection level	NPV	Elimination of MAP[a]	Elimination of test-positive cows[a]
Test-and-cull	Hygiene				
Annual FC test	None	10%	$331,502	31 years	16 years
		20%	$319,304	40 years	24.5 years
Annual FC test	Improved hygiene	10%	$345,603	6 years	4 years
		20%	$336,873	7.5 years	5.5 years
Annual FC test	Advanced hygiene	10%	$337,611	5.5 years	4 years
		20%	$329,091	6.5 years	5 years
Biannual FC test	None	10%	$332,975	12 years	9 years
		20%	$320,201	15.5 years	12.5 years
Biannual FC test	Improved hygiene	10%	$341,857	5 years	4 years
		20%	$333,404	6 years	5.5 years
Biannual FC test	Advanced hygiene	10%	$336,569	4.5 years	4 years
		20%	$326,262	5.5 years	5 years
Annual ELISA test	None	10%	$327,942	Never	Never
		20%	$313,313	Never	Never
Annual ELISA test	Improved hygiene	10%	$337,963	9 years	Never
		20%	$328,501	11 years	Never
Annual ELISA test	Advanced hygiene	10%	$329,376	7.5 years	Never
		20%	$321,258	8.5 years	Never
Biannual ELISA test	None	10%	$307,066	Never	Never
		20%	$298,546	Never	Never
Biannual ELISA test	Improved hygiene	10%	$334,697	7.5 years	Never
		20%	$322,893	9.5 years	Never
Biannual ELISA test	Advanced hygiene	10%	$327,352	6.5 years	Never
		20%	$314,935	8 years	Never
None	Improved	10%	$336,182	11 years	-
		20%	$319,040	14 years	-
None	Advanced	10%	$327,559	8.5 years	-
		20%	$310,351	10.5 years	-

a. MAP is considered to be eliminated when its prevalence rate is less than 1%. Test-positive cows are considered to be eliminated when total number of infected cows is less than 0.5.

Note: For a farm free of MAP (0% MAP infection level), the NPV is $374,305, while the NPV at 10% and 20% with no controls are 57% lower at $161,938 and 74% lower at $98,830 when the initial infection rate is 10% and 20%, respectively, in the absence of controls.

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