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Modeling of *Mycobacterium Avium* Subsp. Paratuberculosis Dynamics in a Dairy Herd: An Individual Based Approach

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Abstract

In the dairy industry, Johne's disease (JD), caused by *Mycobacterium avium subsp. paratuberculosis* (MAP) is one of the major investigated diseases. To date, researchers have suggested some control strategies for JD, such as test-and-cull based herd management, isolated calf rearing management, and vaccinations. Due to the slow progressing nature of MAP, tests with low diagnostic test sensitivity and specificity, and economic limitations, implementing these strategies has not resulted in elimination of MAP from farms. To date, no study has integrated detailed dairy herd dynamics with different MAP transmission routes. We have developed an individual-based dairy herd model by incorporating basic herd dynamics in a closed herd environment where no new animals have been bought from outside. The model considered three age groups of animals: calves, heifers and adults. It includes sequential life events of a dairy animal and such key dynamic processes of the dairy herd as lactation cycle, calving, voluntary waiting period, insemination, pregnancy, dry-off period and calf and heifer rearing. After initially validating that the model reproduced typical herd dynamics, it was extended by incorporating MAP infection dynamics, where each individual adult animal belonged to one of four infection compartments: susceptible, latent, low shedding and high shedding. The model includes two disease transmission routes: horizontal transmission (i.e., fecal-oral) and vertical transmission (i.e., in utero infection). The results confirm that this model can simulate a realistic dairy herd and that inclusion of the above-mentioned

dynamic processes provides useful information about individual infected animals to farmers. Access to the individual animal information offers more validity to assessment of appropriate control strategies for an endemically MAP infected herd. This model can serve as an accurate and novel tool not only to better understand MAP dynamics, but is also valuable as an individual based system of a typical dairy herd that can be applied to other research questions.

Keywords: Epidemiological modeling; Johne's disease; Individual based model; MAP infection; Stochastic modeling

1. Introduction

Johne's disease (JD) is chronic enteric disease of cattle and other ruminants caused by a pathogen named *Mycobacterium avium subsp. paratuberculosis* (MAP). According to a USDA report, MAP is pervasive on US dairy farms, with 68% of herds containing at least one MAP-infected animal (NAHMS, 2007). Clinical signs of JD include decreased milk production (Nielsen et al., 2009; Smith et al., 2009), weight loss, and diarrhea (NAHMS, 2007). It was estimated in 1999 that JD causes more than \$200 million financial loss to the dairy industry (Ott et al., 1999) while the cost of control can be high (Cho et al., 2013). This huge economic burden causes due to decreased milk production, premature culling (Smith et al., 2010), decreased pregnancy rates (Smith et al., 2010), and reduced slaughter value (Kudahl et al., 2008). There is no therapy available for MAP-infected animals; however, control measures of MAP can be adopted to decrease infection transmission and progression. In addition, MAP may pose a threat to public health, as MAP infections in humans have been linked with an increased risk of Crohn's disease in humans (Behr, 2010), though this is still debatable.

To date an enormous amount of literature has presented different models of MAP transmission dynamics from the mathematical point of view (Collins and Morgan, 1992; Beyerbach et al., 2001; Groenendaal et al., 2003; Kudahl et al., 2007; Lu et al., 2008, 2010; 2013 Mitchell et al., 2008; Marce et al., 2011). Among them, state transition deterministic models of MAP (Mitchell et al., 2008, Lu et al., 2008), a stochastic compartmental model with test-cull strategies (Lu et al., 2010), and models using different management practices (Lu et al., 2008) and hygiene practices (Benedictus et al., 2000; Benedictus and Kalis, 2003; Cho et al., 2012) provide several key processes of MAP. Also some optimum strategies suggest that control programs such as test-and-cull of adult animals and improved calf rearing management can reduce MAP infections in dairy herds (NRC, 2003; Dorshorst et al., 2006; Kudahl et al., 2008; Ridge et al., 2010). Theoretically, culling of test-positive shedding animal is the first step taken by the farm owner. Practically, due to infrequent testing and low diagnostic test sensitivity for animals shedding low amounts of MAP, the test-and-cull strategy alone may not be effective in controlling MAP

transmission (Lu et al., 2008; Behr and Collins, 2010). Others have suggested that improved calf rearing management can be implemented to protect susceptible calves from MAP infection (Kudahl et al., 2008; Ridge et al., 2010). For decreasing fecal-oral transmission, preventing contamination of feed and water via manure management can also be adopted (Collins et al., 2006). In some cases, vaccination of calves could be effective in preventing MAP invasion and reduce clinical disease (Lu et al., 2013).

Although previous state transition MAP models provide a reasonable reflection of the biological reality of MAP infection using homogenous population as it is currently understood, detailed daily characteristics of individual animals were mostly ignored. More specifically, previous models did not consider detailed life events of individual animal, i.e., demographic characteristics, lactation information, pregnancy information, and precise proportions of animals culled due to JD. Also, most of the previous models considered only calf infection, while adult-adult infection has now been documented (Mitchell et al., 2015; Smith et al., 2015; Schukken et al., 2015). All this information is important for the farmer to take optimal control decisions and management strategies. Therefore, the current models must be updated to include all the information not only related to individual animal's MAP infection status and but also their daily life events. In such a situation, an individual based model (IBM) can provide the individual heterogeneity and tracking abilities for such heterogeneous population problems. A recent IBM considered MAP dynamics to assess the quarterly enzyme-linked immunosorbent assay (ELISA) and ethanol vortex ELISA (EVELISA) testing method in terms of economic analysis (Robins et al., 2015). Another IBM developed by Davidson et al., (2012) showed the MAP infection model considering environmental contamination along with Latin Hypercube Sampling and reweighting parameterization. This model presented robust predictions of different control options from modelling approaches by emphasizing variation and uncertainty.

However, to date no models present MAP dynamics which can explain the transmission routes along with natural tracking of animals in a heterogeneous population distribution, the background of herd animal life events, or realistic herd management decisions. Also, translating the results of a mathematical model into real dairy herd problem requires information such as effects on the culling rate, reproductive performance, and availability of replacement heifers. In this study, we formulated an IBM capturing MAP infection dynamics as presented in previous compartmental models. Our plan was to build a model capable of providing the following details: which animal was MAP infected, when it was infected, and by whom it was infected. Before building the IBM for MAP, a dairy herd model which could consider all the relevant detailed processes of an individual animal's life related to MAP infection was required. Therefore, we first built and validated an IBM structure for a MAP-free dairy herd. The main objective was to determine whether an individual based model would be able to represent the details of a dairy herd while at the same

time considering MAP infection. The research questions considered for an uninfected dairy herd IBM were: a) whether an individual model could be built to show the life events of a dairy animal, b) how to maintain a constant milking herd size with accurate parameterization, c) whether the model would be considered realistic with life event tracking, and d) how culling strategies would work on this individual based model. For integrating the MAP infection into a dairy IBM, research questions were: a) how can a dairy IBM model be adapted to show MAP infection dynamics, b) how do the age compartment and infection compartment impact MAP infection, c) if the herd has a closed environment, how do the MAP dynamics vary with replacements within the herd environment, d) how could culling of high shedders be integrated with the detailed herd model where different life events of an animal are related to culling decisions and e) how appropriate are the outputs of the IBM model compared to observed MAP infection.

In this paper, section 2 describes the method for building an IBM for a normal lactating herd and then integrates MAP transmission dynamics into this IBM. Section 3 presents the model setup, results and relevant discussion for different simulated scenarios of both uninfected and MAP endemic herds. Section 4 summarizes the simulation results and states the overall contribution of this work while presenting the possible applications and extension of proposed model.

2. Materials and Methods

A discrete time IBM was created and implemented to provide the stochastic behavior of a lactating dairy herd. The lactating herd management considered here was a closed herd (new animals were not introduced or bought into the herd during the simulation period).

2.1 The Lactating Herd Model

The proposed IBM was composed of three major age groups: adult animals (milking herd, >24 months), calf rearing loop (≤ 2 months) and heifer rearing loop (2-24 months) (shown in Figure 1). The model considered two time scales: individual animal age and a model time variable for simulation (both in days). Each individual animal was initiated with a set of characteristics and passed through different life cycles: replacement, calving and culling. The model considered key life events of a lactating cow with MAP dynamics, excluding daily milk yield for simplicity.

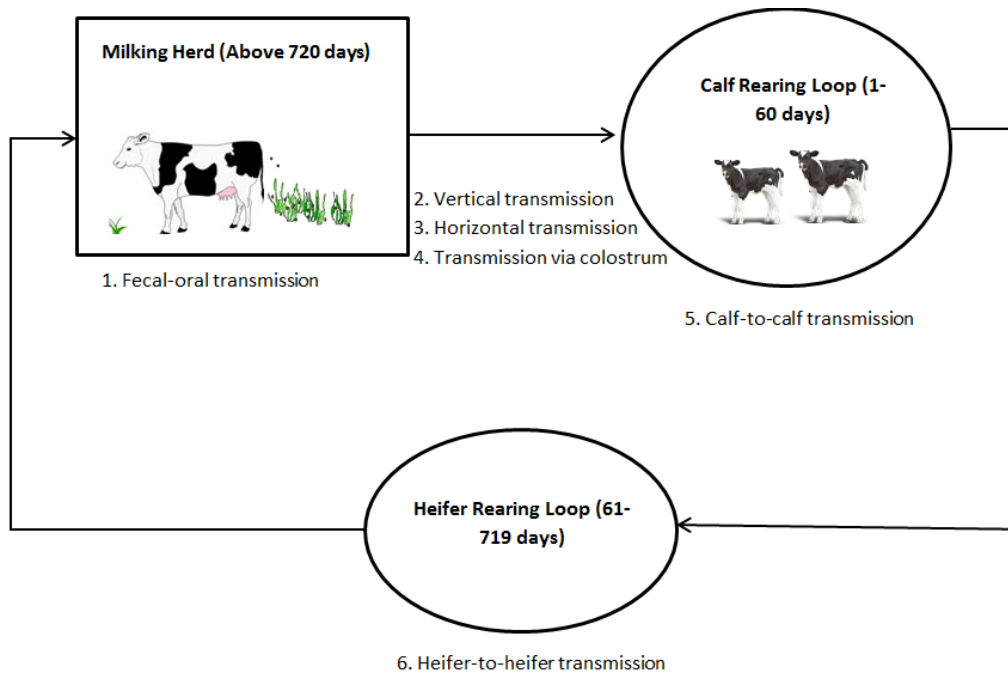


Figure 1. Three age compartment of animals in a dairy herd system. The main compartment is the milking herd consisting of adult animal aged above 720 days. The second compartment is calf rearing management, housing calves aged 2-60 days. The third compartment is heifer rearing management housing; where animals aged 61-719 days reside before serving as replacement animals for the milking herd after first calving.

Adults in a lactating herd must calve to produce milk; the lactation cycle refers to the period between one calving and the next. Generally, the lactation cycle is split into four phases: early, mid, and late lactation and the dry off period. The voluntary waiting period (VWP) is observed in early lactation as a period of time in which adults are not inseminated even if they display estrus, to allow for optimum uterine involution and recovery from negative energy balance. If adult animals do not become pregnant within the optimal interval post-calving, due to unsuccessful insemination, the length of the lactation increases, but milk yield will gradually decrease during that extra time. Thus, achieving maximum milk production in a lactating herd depends on an optimal calving interval and culling open animals if they have not conceived even after repetitive inseminations. Our model adopts the generalized four-phase lactation cycle: VWP (up to 60 days after every calving), insemination attempts (immediately after the VWP and every 21 days following until pregnancy), and pregnancy (280 days), dry-off period (60 days prior to calving). Figure 2 describes the life cycle of a dairy cattle. For simplicity, we included a pregnancy rate for each insemination based on the parity stratification from Hertl et al., (2014). Insemination was allowed to continue up to 225 days after calving. After 225 days, if the cow was not pregnant, it was

culled as an open cow. In our model, we introduced two types of culling: Voluntary culling referred to culling for economic purposes (primarily milk production) and involuntary culling refers to culling due to natural death and accidents (Fetrow et al., 2006; De Vries et al., 2010).

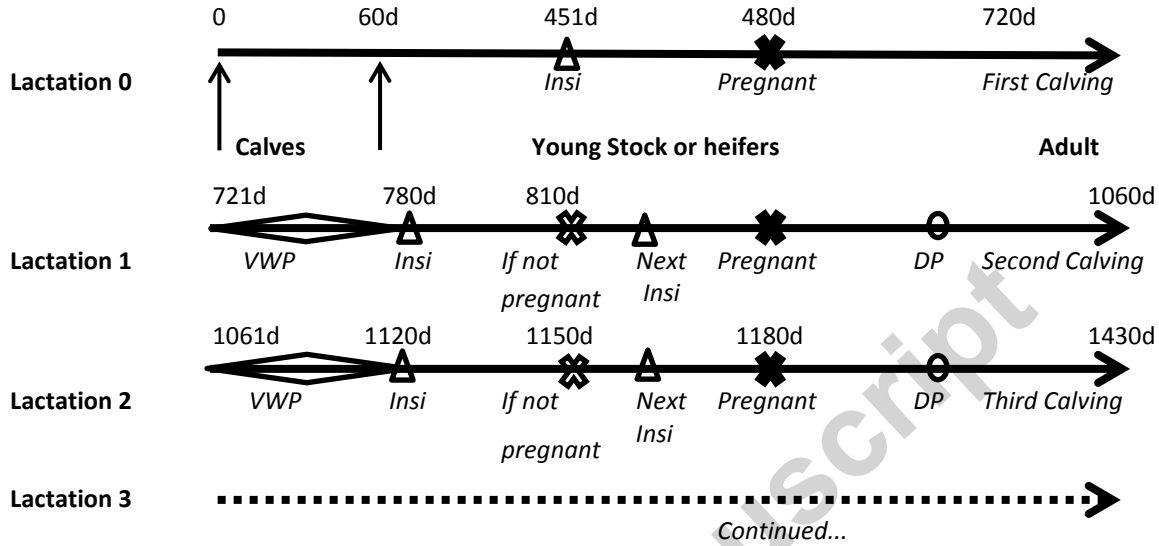


Figure 2: Diagram of a dairy cattle's life cycle including calving, voluntary waiting period (VWP), insemination, and pregnancy for a hypothetical animal. Duration is reported in days (d). Vertical arrows represent birth and transition between calves and heifers; horizontal arrows end with each calving. Empty diamonds represent the range of the VWP, empty triangles represent insemination (Insi), cross shapes indicate whether the animal is determined to be pregnant (filled) or not (empty) and open circles indicate the start of the dry-off period (DP). If the animal is pregnant then it continues through the lactation cycle. If the animal is not pregnant after several inseminations, it will be removed as open at 225 days. The broken horizontal line indicates that the process runs until the animal is culled/dead.

2.2 Lactating herd dynamics

The model was initiated with a pre-determined distribution of animals with different parities. Every day, the algorithm first determined the reproductive status (VWP, waiting to be inseminated, and pregnant) of all adult animals. Any animal on the 280th day after successful insemination was assumed to calve. Once an adult animal calved, it transitioned to VWP status and continued the milking herd loop until removed due to culling or death. Only female calves were kept in the herd, and male calves were removed immediately after birth. Female calves were transferred to the calf rearing loop from the maternity pen one day after birth. Mortality was allowed for in the calf rearing loop; otherwise, calves were transferred into the heifer loop at 60 days of age. In the heifer loop, heifers are inseminated at 15 months of age in order to become pregnant, so that they will calve at 24 months of age. When heifers were ready to calve

for the first time, they transitioned to the milking herd in the model. The flow of the processes is summarized in the flowchart in supplementary Figure S5.

2.3 Lactating herd with MAP infection

After constructing a MAP uninfected herd, we integrated MAP infection dynamics into the model. The infection compartments in the milking herd were divided into four categories: Susceptible (S), latent (H), low shedding (Y_1) and high shedding (Y_2) animals. The infection compartment detail is presented in Figure 3. We modified the state transition model structure proposed by Lu et al., (2008) for adult animals, where the transiently shedding calves and heifers belonged to calf and heifer loops of management. We ignored the resistant category from the previous model, as there is no perfect parameterization for how many individual animals remain resistant (Schukken et al., 2015) and it has been suggested that calves and heifers can also be infected by transiently shedding calves and heifers at any time in their respective loops. There are three categories of infected animals in the milking herd: latent, low shedders and high shedders. We considered transmission routes in three loops (milking/adult, calf and heifer) separately.

In the milking herd, a susceptible adult (S) can only be infected by low and high shedders via fecal oral infection path. Latent animals can progress to low shedding and low shedding animals can progress to high shedding, defined as a MAP load of $\geq 50\text{cfu/g}$ by fecal culture. It has been suggested that newborn calves are more susceptible than adult to MAP infection; they can be born vertically infected or infected via the fecal-oral route during their first day of life in the maternity pen. Once they transferred into calf rearing loop there will be two kinds of animals: susceptible calves (S_{calves}) and transiently infected calves (I_{calves}) (which are capable of infecting other calves). While in the calf rearing loop, calves can only be infected via the calf-to-calf transmission path. After transfer to the heifer rearing loop, infected calves become infected heifers. During this time they may infect susceptible heifers via the heifer-to-heifer transmission route.

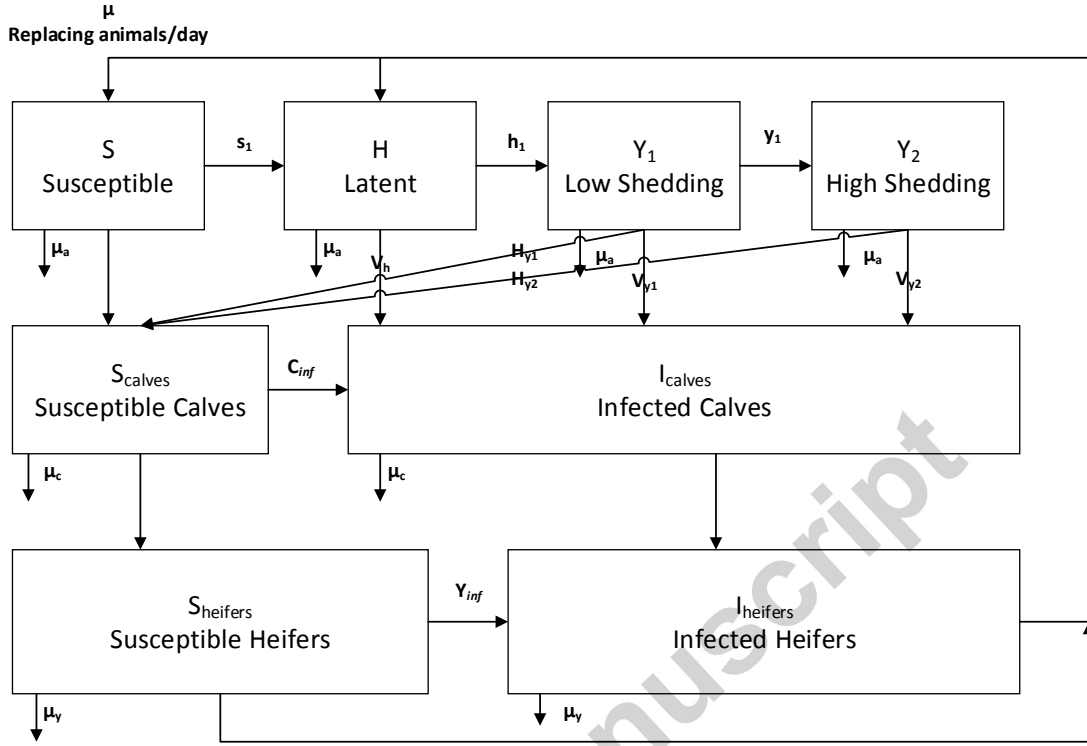


Figure 3. Flow diagram represents the infection categories of adult, calves and heifers in the herd. Each category (S, H, Y₁ and Y₂) classifies adults according to their initial setup. s_1 , h_1 , and y_1 are the probabilities of exit at each time point from susceptible to latent, latent to low shedding and low shedding to high shedding, respectively. V_h , V_{y1} and V_{y2} represent the vertical transmission probabilities from latent, low shedders and high shedders animals respectively. H_{y1} and H_{y2} present the horizontal transmission probabilities to calves from low shedders and high shedders animals, respectively. C_{inf} and Y_{inf} represent calf-to-calf and heifer-to-heifer transmission probabilities, respectively. μ_a , μ_c and μ_y are the natural dead/sold probabilities for adults, calves and young stock animals, respectively

In this model, we considered the six routes of transmission throughout the three loops: adult-to-adult (fecal-oral), adult-to-calf during one day (fecal-oral), adult-to-calf transmission via milk/colostrum, calf-to-calf (fecal-oral), heifer-to-heifer (fecal-oral), and dam-to-calf (vertical) (shown in Figure 1). The following equations provide the transmission probability of fecal-oral transmission for adult animals:

$$Inf_{adult-adult} = \beta_A(\beta_{Y_1}Y_1 + \beta_{Y_2}Y_2)/N \quad (1)$$

Susceptible adult animals in the milking herd compartment are susceptible to MAP infection by the contact of low shedding (Y₁) and high shedding (Y₂) animals with frequency dependent transmission rates

of β_{Y_1} and β_{Y_2} , respectively. β_A is the adult-to-adult transmission coefficient and N is total number of animals in the milking herd, $N=S + H + Y_1 + Y_2$.

A recent study shows that adult cows contribute to the force of infection of calves by contaminating the calving area from adult cow manure (Doré et al., 2012). In commercial dairy herds, however, the length of time that newborn calves are kept in the maternity area varies with herd policy. Some commercial herds separate calves immediately from dams, while other separate calves after 8 or 12 hours of birth and some herds keep calves with their dams for at least one or two days. During this short period calves can be infected, as they are believed to be 10 to 100 times as susceptible to MAP infection as adults (SDB bio, 2014). The daily horizontal infection probability can be determined by

$$Inf_{adult-calf} = \beta_a(\beta_{Y_1}Y_1 + \beta_{Y_2}Y_2)/N_c \quad (2)$$

β_a is the horizontal transmission coefficient for adult to new born calves and N_c is the total number of calves at every day, $N_c = C_s + C_I$. In the calf rearing loop, calves can only be infected horizontally by transiently shedding infected calves by

$$Inf_{calf-calf} = \beta_c C_I / N_c \quad (3)$$

β_c is the horizontal calf-to-calf transmission coefficient, though according to the literature the rate of calf-to-calf transmission is minimal (SDBbio, 2014).

Susceptible calves became susceptible heifers and transiently infected calves became transiently infected heifers. Transiently infected heifers can infect susceptible heifers by the heifer-to-heifer transmission path:

$$Inf_{heifer-heifer} = \beta_h Y_I / N_y \quad (4)$$

β_h is the horizontal heifer-to-heifer transmission coefficient and N_y is the total number of heifers and $N_y = Y_s + Y_I$. After one year, transiently infected heifers became latent heifers and eventually enter the milking herd as latent adults.

2.4 MAP infection in lactating herd

Adult animals maintain a life cycle operation according to their infection status, updating infection status followed by calving status. Updating infection status depended on current infection status:

- Susceptible adult animals only get infected by shedding animals in the milking herd via the fecal-oral transmission route. Each day, the algorithm checked the probability of each susceptible adult

getting infected. If an adult became infected, its infection status became latent; if not, it remained susceptible

- Latent adults could progress to low shedding based on their progression probability. If they became low shedding via progression, their status was updated to low shedding.
- Low shedding adults could progress to high shedding based on their progression probability. If they became high shedding via progression, their status was updated to high shedding.
- High shedding adults could not progress, and their infection status was not updated at any point.

Updating calving status was primarily described in previous section. The offspring from a susceptible dam were never vertically infected and would enter the susceptible calf category, but the calves of latent, low shedding, and high shedding adults could be vertically infected, in which case they entered the transiently infected calf category. During the first day after birth, susceptible calves could become horizontally infected and enter the transiently infected calf category. All calves were sent to the calf rearing loop after one day. The mechanism of MAP infected herd is shown in flowchart Figure 4.

2.5 Map infection in calf and heifer rearing loops

In the calf rearing loop, the model included two kinds of animals: infected and susceptible. But, susceptible calves can become infected during the calf rearing process (60 days) via calf-to-calf MAP transmission route. It is suggested that calves are most susceptible to MAP infection in the first year of their life (Mortier et al., 2015). Supplementary Figure S6 shows the flow chart of calf rearing loop events. In the heifer rearing loop, the young animals remain until their first calving. During this period infected heifers may transmit MAP to susceptible heifer via heifer-to-heifer transmission route. The heifer rearing loop event is shown in supplementary Figure S7.

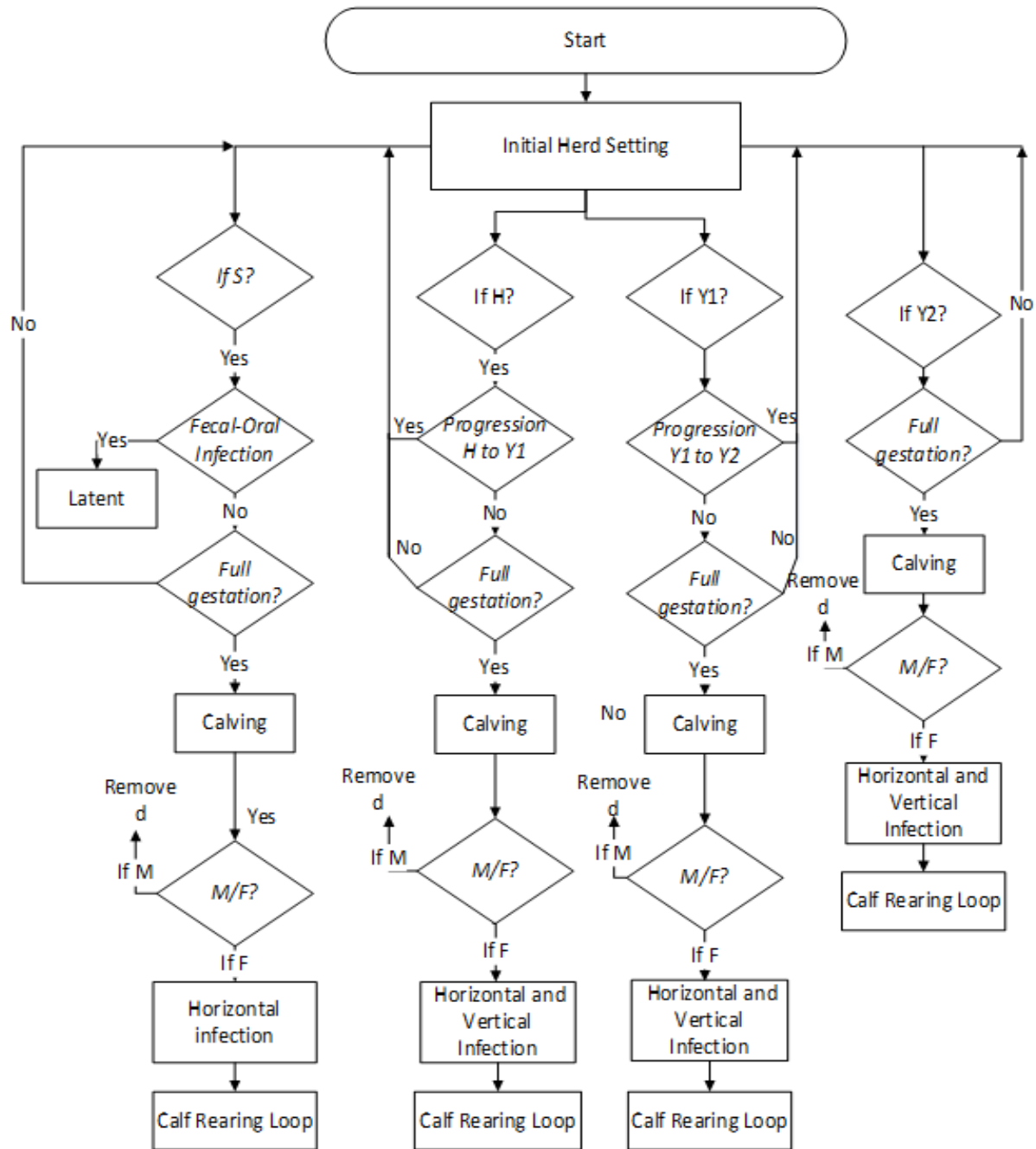


Figure 4: The flow diagram daily event decisions for an adult animal in the milking herd. Abbreviations: S-susceptible, H-latent, Y₁-low shedders, Y₂-high shedders, M-male calf, F-female calf and Full gestation- the lactation stages (VWP/insemination/pregnancy)

2.6 Model parameters

The parameters used in an uninfected herd are presented in Table 1. The parameters have been chosen from several published studies and dataset used in our study. MAP transmission parameters are given in Table 2. Most infections in dairy herds are believed to be caused by high shedding animals and the infectiousness of transiently or low shedding animals is relatively small, $\beta_{Y_1} = 2.0/\text{year}$. These values were chosen to maintain a very low MAP prevalence in US dairy herds. The transmission rate β_{Y_2} was assumed to have a range of 20.0/year, corresponding to the variable MAP prevalence in US dairy herds (Lu et al., 2008). Transmission via milk/colostrum (β_m) was designed using daily probability of a calf got infected by milk/colostrum during first 60 days of its life. All the given rates were converted into daily probabilities. Some model specific data have been extracted from Regional Dairy Quality Management Alliance (RDQMA) (Pradhan et al., 2009) to validate with the model's results. Briefly, three commercial dairy farms (farm A in New York State, farm B in Pennsylvania, and farm C in Vermont) in the northeast United States were followed intensively for 10 years (2004–2014), with all health and culling events recorded. An example of parameters calculation via equation 1-4 is given in supplementary section S1.

Table 1: List of other parameters used to build the model

Description	Value	References
Calves	0-60 days	USDA, (2007)
Heifers	61-720 days	USDA, (2007)
Adults	>720 days	USDA, (2007)
Voluntary waiting period	60 days	VanRaden et al., (2004)
Birth rate of female calf	0.5	Calculated
Length of pregnancy	280 days	USDA, (2007)
Maximum length of insemination period before culling	225 days	Calculated from RDQMA, (Pradhan et al., 2009)
Daily probability of adults death/sold (μ_a)	0.00055	Assumed
Daily probability of calves death (μ_c)	0.000167	Assumed
Daily probability of heifer death (μ_h)	0.0000278	Assumed
Pregnancy percentage (annual) (%)	70	Calculated from RDQMA, (Pradhan et al., 2009)
Annual culling (%)	30-40	Calculated from RDQMA, (Pradhan et al., 2009)

Table 2: Transmission parameters used to build the model

Symbols	Description	Value in the model	References
S:H:Y ₁ :Y ₂	Initial ratio of susceptible to latent to low shedders to high shedders in the adult herd	0.9:0.04:0.04:0.02	(NAHMS, 2007)

h_1	Disease progression rate from latent (H) to low shedding (Y1) (daily probability)	0.0013	van Schaik et al., (2003)
y_1	Disease progression rate from low shedding (Y1) to high shedding (Y2) (daily probability)	0.00077	van Schaik et al., (2003)
V_h	proportion of calves from latent animals infected at birth	0.15	Sweeney et al., (1992)
V_{y1}	proportion of calves from low-shedding animals infected at birth	0.15	Whitlock et al., (2005a)
V_{y2}	proportion of calves from high-shedding animals infected at birth	0.17	Whitlock et al., (2005b)
β_A	Adult-to-adult transmission coefficient	0.05	Assumed
β_a	Adult-to-calf transmission coefficient	0.383	Assumed
β_c	Calf-to-calf transmission coefficient	0.0025	Smith et al., (2015)
β_m	Adult-to-calf transmission via colostrum (daily probability)	0.072	Assumed
β_h	Heifer-to-heifer transmission coefficient	0.001	Assumed
β_{y_1}	Transmission rate between low shedders (Y1) and susceptible (S)	2/year	Assumed
β_{y_2}	Transmission rate between high shedders (Y2) and susceptible (S)	20/year	Assumed
$Inf_{adult-adults}$	Fecal-oral transmission (adult-adult)	Calculated by equation 1	(Calculated)
$Inf_{adult-calf}$	Fecal-oral transmission (adult-calf)	Calculated by equation 2	(Calculated)
$Inf_{calf-calf}$	Calf-to-calf transmission (daily probability)	Calculated by equation 3	(Calculated)
$Inf_{heifer-heifer}$	Heifer-to-heifer transmission (daily probability)	Calculated by equation 4	(Calculated)

2.7. Stochasticity

Stochasticity was introduced in the model in the form of random processes such as daily death of adults, calves and heifers, producing female calf, and success of each insemination. Stochasticity was also brought to the infection dynamics parameters such as fecal-to-oral transmission (adult-to-adult, adult-calf, calf-to-calf and heifer-to-heifer), vertical transmission (from H, Y1 and Y2 dams), and progression (H to Y1 and Y1 to Y2). These stochastic parameters play a crucial role to building reality into both the uninfected and MAP infected herd.

2.8. Global sensitivity analysis

We have selected 15 parameters ($\mu_a, \mu_c, \mu_h, \beta_a, \beta_c, \beta_m, \beta_h, \beta_{y1}, \beta_{y2}, V_h, V_{y1}, V_{y2}, y_1$ and h_1) from both Table 1 and Table 2 to run the sensitivity analysis, as parameters inevitably contain uncertainty to some extent, global parameter sensitivity analyses for prevalence over time can indicate which parameters are most influential (Saltelli et al., 2000; Lu et al., 2008). We explored the parameter space by performing an uncertainty analysis using Latin hypercube sampling (LHS) method (Saltelli et al., 2000) and sensitivity analysis was performed by evaluating partial rank correlation coefficients (PRCCs) (Lu et al., 2008). We performed global sensitivity analysis for 15 parameters using LHS with 1500 samples (i.e., 100 samples for each parameter). Selected parameters are varied within 20% of their values.

3. Results and Discussion

3.1. Initialization and simulation background

The model was initialized with 1000 adult animals with initial proportions of 45%, 25% and 30% in parity 1, parity 2, and parity 3 and above, respectively. For each parity, animals were in different stages of lactation as described in Figure 2. The model determined each individual animal's lactation stage from its initially assigned age. For example, an animal given an initial age of 760 days was in parity 1 and in VWP stage. The initial proportions were chosen to mimic a real herd scenario (Hertl et al., 2014). All simulations were run for 20 years.

3.2. Uninfected herd dynamics

First, we simulated the base uninfected herd model, including only the basic herd processes. As our initial objective was to investigate whether we could obtain an appropriate parameterization for an uninfected herd that could reach equilibrium after a certain time, we simulated the first scenario with the parameters in Table 1 and following the flow chart given in supplementary Figure S5. As our model was initialized without calves or heifers, two years of burn-in were required to have sufficient calves and young stock in the system to feed the model with replacement animals. Therefore, during the first two years, all replacements came from outside and it was assumed that all the replacements were heifers entering the herd with their first calving. The results presented here were calculated based on the remaining time after the first two years of simulation, so as to include only periods in which the herd supplied its own replacements.

3.3 Distribution of animals, calving interval, pregnancy and culling

The model calculated the number of available adults, calves and heifers annually. Maintaining a constant herd size requires balance between culling and replacements and pregnancy percentage, the rate at which

heifers move into the milking herd, and a good calf and heifer management policy where the mortality rate is low and can provide sufficient replacements to the herd. Figure 5a shows the distribution of the number of adult animals in the herd during the 20 years of simulation. The average number of adult animals was 1019 (95% CI: 1016 to 1021). Figure 5b shows the average distribution of animals in different parities over 20 years simulation period. The number of animals in each parity was stable after 20 years, with approximately 40% parity 1, 25% parity 2 and 35% parity 3 and beyond. It is noticeable that the animal distributions in different parities after 20 years are similar to the initial distribution. The amount of available calves and heifers were sufficient enough to provide replacements to maintain a constant herd size (Dairy Management-UW Extension, 2015). The distribution of calves and heifers are described in the supplementary Figure S1 in section S2.

To maintain the parity distribution it is important that calving interval is constant throughout the parities. In this model, we adjusted the probability of conceiving at each insemination by parity (Hertl et al., 2010). Figure 5c presents the variation in calving interval in different parity animals. The lower parity animals have a shorter calving interval than higher parity animals. It is clear from Figure 5c that parity 7 and 8 animals had the highest calving interval in the simulation. Figure 5d shows the time needed to impregnate the animal by parity in the model (solid line) compared with the RDQMA data (dashed line Figure 5d). Our model took an average of 125 ± 0.5 days to impregnate animals in parity 1 to 4 and slightly longer beyond parity 4 (on average 128 ± 2 days). These were longer than observed in the RDQMA data sets, in which some animals in parities 1 to 4 were inseminated after only 40 days of VWP. This shows the non-linearity in the insemination success in commercial dairy herds and indicates that real data are much more scattered than simulated results. The model also measured the yearly calving interval (shown in supplementary Figure S2.a), days taken to become pregnant over the simulation period (shown in supplementary Figure S2.a and described in supplementary section S3), the yearly pregnancy percentage and pregnancy percentage by parity (shown in supplementary Figure S3.a and S3.b, respectively). Moreover, maintaining a constant herd size depends on culling and replacement balance throughout the simulation period (displayed in in Figure S4 in supplementary section S4).

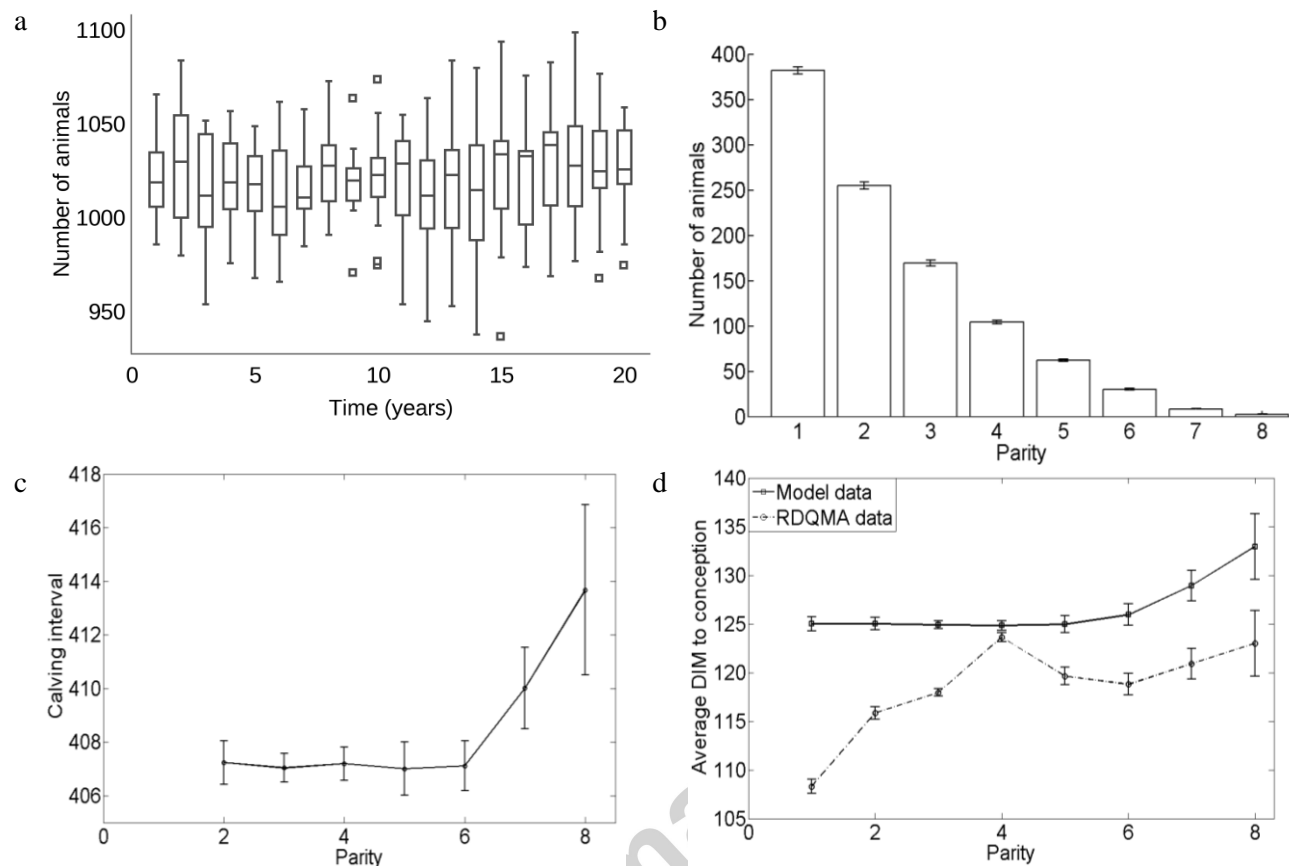


Figure 5. Distribution of animals in different categories, (a) total number of animals every year, (b) number of animals in each parity during the simulations, (c) parity-wise calving interval with standard deviation and (d) comparison between average days in milk when the animal became pregnant in our model data and Regional Dairy Quality Management Alliance (RDQMA) data. In the box plot, the bottom and top end of the bars are minimum and maximum values respectively, the top of the box is the 75th percentile, the bottom of the box is the 25th percentile, and the horizontal line within the box is median; outliers are presented as open squares.

3.4 Herd dynamics with MAP

As our model was shown to be capable of simulating an uninfected dairy herd with a constant herd size, we introduced MAP infection in the model as described in section 2. We assumed that at least 1% animals would be initially infected when we started our simulation from equilibrium state of the model (Lu et al., 2013); although most infected farms observe MAP prevalence between 3-10% (Collins et al., 2010; Lombard, 2011; Garry, 2011). This initial prevalence would allow us to determine whether the infection would persist or decrease, potentially fading out over the simulation period.

Our initial herd contained latent (0.4%), low shedding (0.4%) and high shedding (0.2%) adult animals and was run for 22 years to see the overall and age-specific prevalence. Figure 6a illustrates the total true prevalence of infected adult animals during the simulation period. The model considered 2 years of burn in times during the simulation. The results show that the total prevalence mounted to 49% when no culling strategies for low and high shedders were adopted. Individual proportions of latent, low and high shedders clearly indicate that introducing 1% infected animals resulted in 23% latent (H) animals that are not infectious to other adults and 26% infectious (Y_1+Y_2) adults. Based on ELISA testing with imperfect sensitivity (>90%) and specificity (99%), this would result in an average of 21% apparent prevalence (Nielsen & Toft, 2011). Figure 6b shows the number of infected calves and heifers over the simulation period.

Our model calculated 49% prevalence without adopting any control strategy, resembling several previous studies (Groenendaal et al., 2002; Pouillot et al., 2004; Kudahl et al., 2007 and Mitchell et al., 2008). All the previous models considered 100 animal herds and end prevalence was measured after 25 years with 1% initial prevalence. Not all studies include vertical infection and adult-to-calf horizontal infection as two separate transmission paths. In field data, however, these levels of prevalence are not expected, as intervention strategies are likely before such a high prevalence is reached.

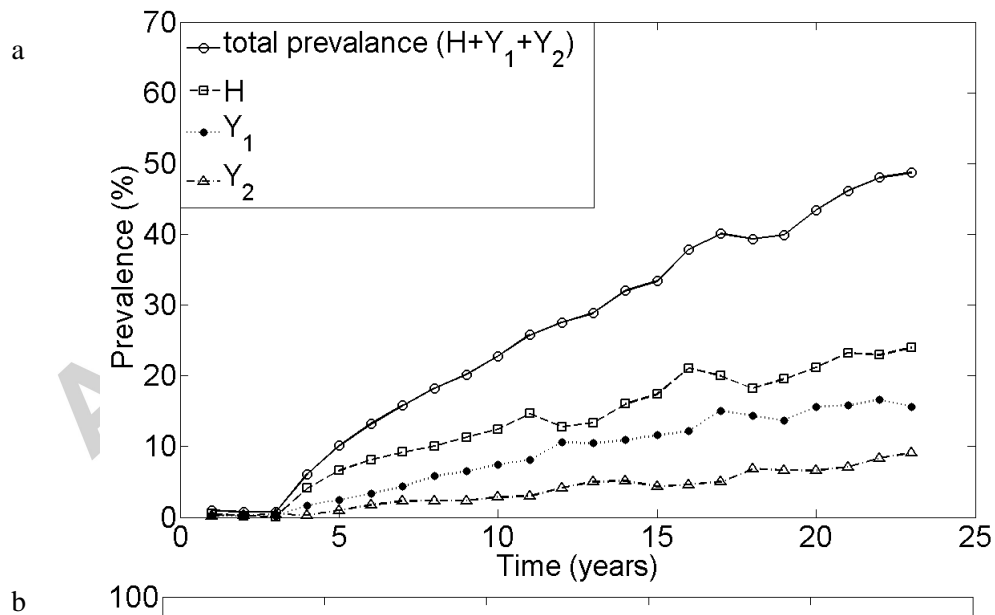


Figure 6. MAP endemic simulation after 1% initial infected animals over 22 years of simulation: (a) total adult prevalence (open circles) and the prevalence of latent animals (H, open squares), low shedders (Y_1 , closed circles) and high shedders (Y_2 , open triangles) without any control strategy; (b) number of infection in calves and heifers, where S_{calves} (open circle), I_{calves} (solid circle), $S_{heifers}$ (downward triangle) and $I_{heifers}$ (upward triangle) are susceptible and infected calves and heifers, respectively.

3.5 Sensitivity analysis

Maintaining a closed herd without bringing replacements from outside requires the herd to be well managed, maintaining constant replacements from within the herd. We performed a local sensitivity analysis, in which some parameters were kept constant to measure the impact of changes in other parameters on herd size and demographics. For all analyses, we assumed that all heifers transitioned to the milking herd at 24 months of age and that there would be no miscarriages from heifer replacements. According to our results, the average pregnancy (annually) of 71.1% (95% CI: 70.8% to 71.5%) was sufficient to maintain constant herd size. However, as culling was dependent on parity stochastic in nature, we tested adult culling rate and yearly pregnancy percentage while keeping calf-heifer culling constant. Figure 7 shows changes in average herd size at year 10 (the midpoint of the simulation) for different annual pregnancy percentage (69-73%) and different adult culling rates. The black line shows the average herd size with base model parameters. As expected, a high yearly pregnancy percentage and lower culling increased the herd size and vice versa. Herd size was more sensitive to culling rate than to pregnancy percentage.

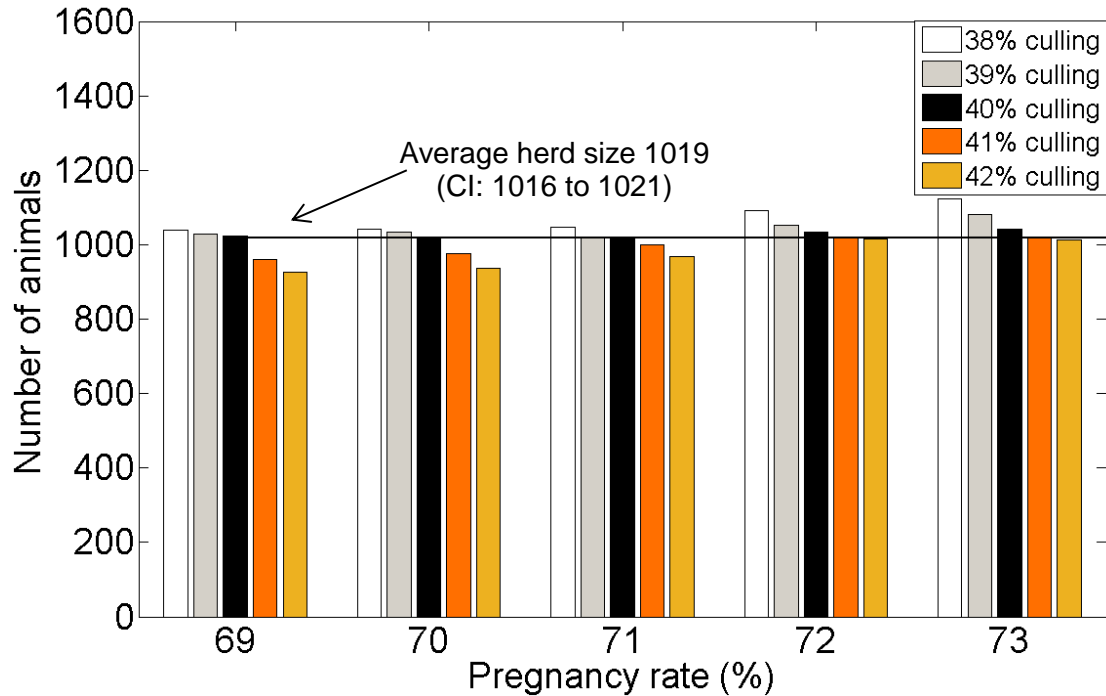


Figure 7. Demonstration of impact of annual pregnancy percentage and adult culling rate on herd size after 10 years while keeping the calf-heifer culling and first calving date constant.

Stochastic models are capable of simulating stochastic behavior in populations, such as the likelihood of persistence and fade-out of infection. In this model, MAP persistence was defined as at least 1 infected animal in the herd throughout the simulation period, while a fadeout occurred if the number of infected animals fell to 0 at any time point. Figure 8 presents the result of two separate example simulation runs where fade out (a) and persistence (b) can be seen. In this study, 24% of all runs resulted in fadeout between 10-17 years of simulation time, but no fadeout was observed among herds persisting before 10 years.

Several previous models have discussed fadeout and persistence for MAP infection (Groenendaal et al., 2002; Pouillot et al., 2004; Kudahl et al., 2007; Lu et al., 2010; 2013; Marce et al., 2011). All these models considered a 100 animal herd where 1 infected animal was introduced to study the chance of fadeout of the disease versus persistence probability; when the number of total infected animals within a herd is small, fadeout becomes more likely. In Marce et al., (2011), it was shown that fadeout occurred 66% of the time. In our model, fadeout was less likely because of herd size. Moreover, special characteristics of our model impact our evaluation of fadeout. In Figure 8a, we can see that in year 14 there were no infected animals in the milking herd, but true fadeout did not occur until year 17, when there were no infected animals in any age group.

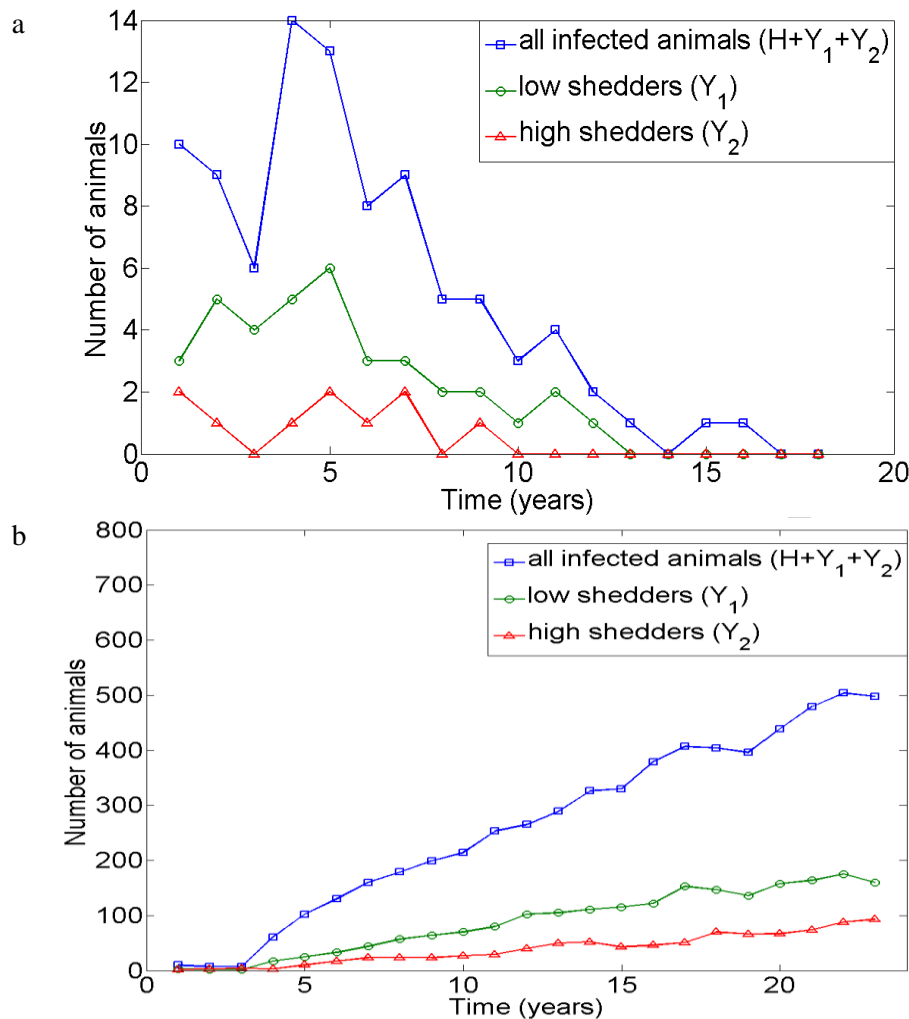


Figure 8. Illustration of MAP fadeout and persistence over time in two simulation runs without any control, (a) fadeout occurred at 17 years, when all infected animals disappeared from all the three loops (milking/adult, calf and heifer) of a dairy herd and (b) MAP persistence over the whole simulation period.

In Figure 9, the importance of model parameters was sorted by the PRCC from highest to lowest by order. The transmission rate of high shedders (β_{y_2}) to susceptible is the most influential parameter for prevalence, while adult-to-calf transmission via horizontally (β_a) and colostrum (β_m) are medium influential parameters. In reality, high shedders contribute high MAP load in the feces and which contaminate the herd environment and give back the infection to the susceptibles. So, β_{y_2} plays an important role to simulate the model prevalence. But also β_a and β_m play significant role to make MAP persisted. Vertical transmission from latent (V_h) and low shedders (V_{y_1}) have minimal influence on

prevalence, but vertical transmission from high shedders(V_{y2}) plays sufficient role to maintain the infection in calves.

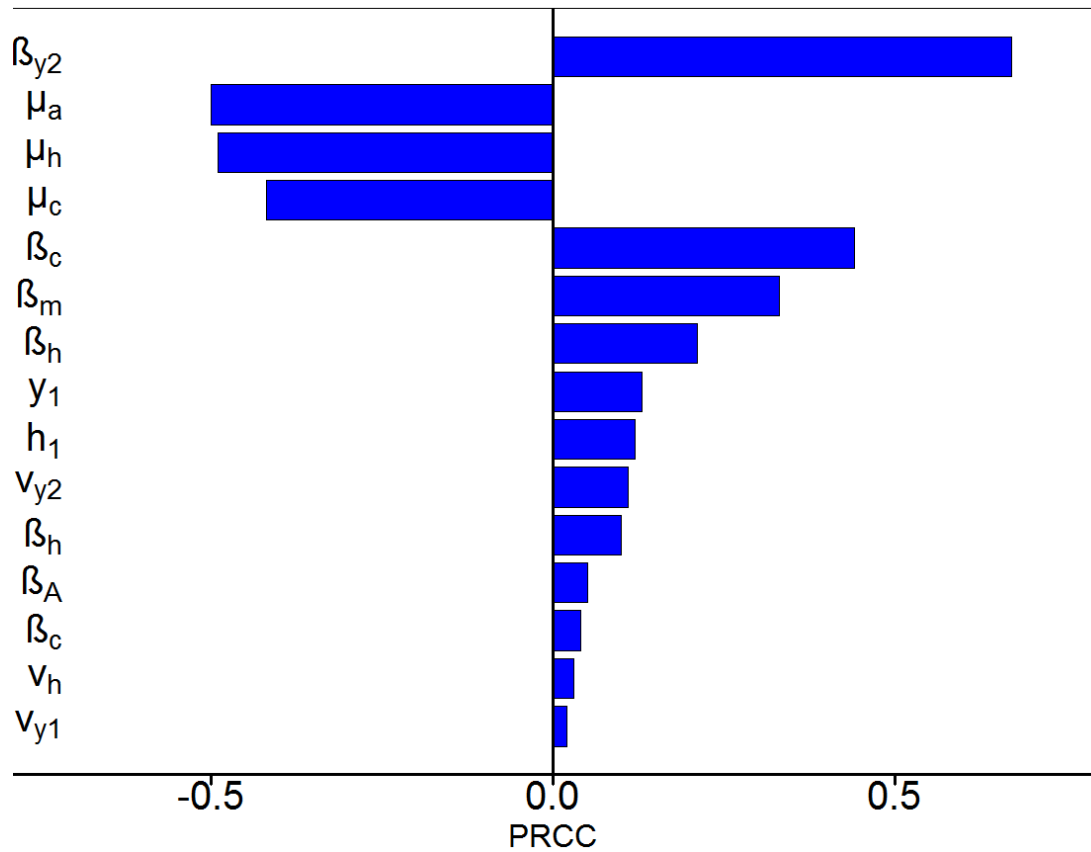


Figure 9. Parameter sensitivity analysis is given by the partial rank correlation coefficient (PRCC) with no additional culling due to MAP infection.

3.6 Evaluation of individual information in infection transmission

One advantage of building an IBM is to track individual animals through birth to death. For understanding MAP dynamics, the model should investigate all the key factors from individual point of view, i.e., horizontal and vertical routes of transmission to calves, adult-to-adult transmission, calf-to-calf and heifer-to-heifer transmission. The model should also store all relevant individual information necessary for following farm policy. This individual information may contain, for example, information on the parity distribution of each infection category, the infection status of the dam to determine probability of vertical infection, and the lactation status of infected animals. All these data points can carry important messages to the farmer about the endemic condition of the herd and what measures should be taken to mitigate the infection. The IBM can supply all this information about both MAP

infection and individual animals. The IBM collected all data for each individual animal after every year of simulation.

Figure 10a illustrates the contribution of each MAP transmission path to overall infection transmission with the absolute number of infections occurring by each path during every year of the simulation. Adult-to-calf (horizontal) and infection via milk/colostrum were the key routes of MAP infection, but vertical and heifer-to-heifer infection paths also contributed to the growth in infections. Adult-to-adult infection was minimal but did contribute to the persistence of MAP infection in milking herd category. Figure 10b demonstrates the number of animals progressing from H to Y_1 and Y_1 to Y_2 each year. Recently Smith et al., (2015) investigated the role of adult infection in the dynamics of MAP prevalence in a herd; the authors also used RDQMA data to identify dual infection paths: intermittently low-shedding that do not progress to clinical disease, and continuously shedding animals that quickly progress to high shedding and, eventually, clinical disease (Mitchell et al., 2015a, b; Schukken et al., 2015). In our current IBM model we have not implemented dual infection pathways for simplicity, but the information extracted about separate infections routes from this model can be used to understand the MAP infection more deeply, including the impact of super-shedder or high MAP loaded animals (Pradhan et al., 2011).

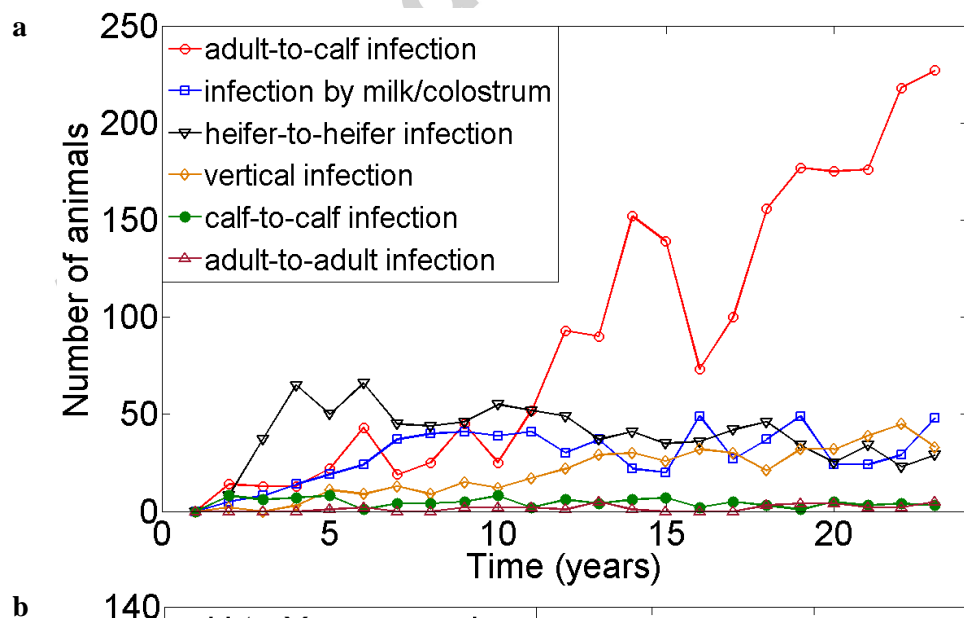


Figure 10. Infections transmission in herd area, (a) presents different infection paths contribution over 22 years of simulation: adult-to-calf transmission (open circle), infection by milk/colostrum (rectangle), heifer-to-heifer transmission (downward triangle), vertical transmission (diamond), calf-to-calf infection (solid circle) and adult-to-adult transmission (upward triangle), and (b) the number of animals progress the disease from latent to low shedders (downward triangle) and then low shedders to high shedders (upward triangle). All the results are presented in absolute numbers.

Figure 11 shows the source of vertically infected calves presented as the absolute number from each class of infected dam: latent, low shedding and high shedding dams. The absolute number of vertically infected calves from latent dams is greatest, but the percentage of calves vertically infected by high shedding dams was higher. According Whittington & Sergeant, (2001), approximately 30% of an endemically infected herd is latently infected cattle at any point of time. This indicates the importance of vertical infection, which should be considered before adopting any control strategy.

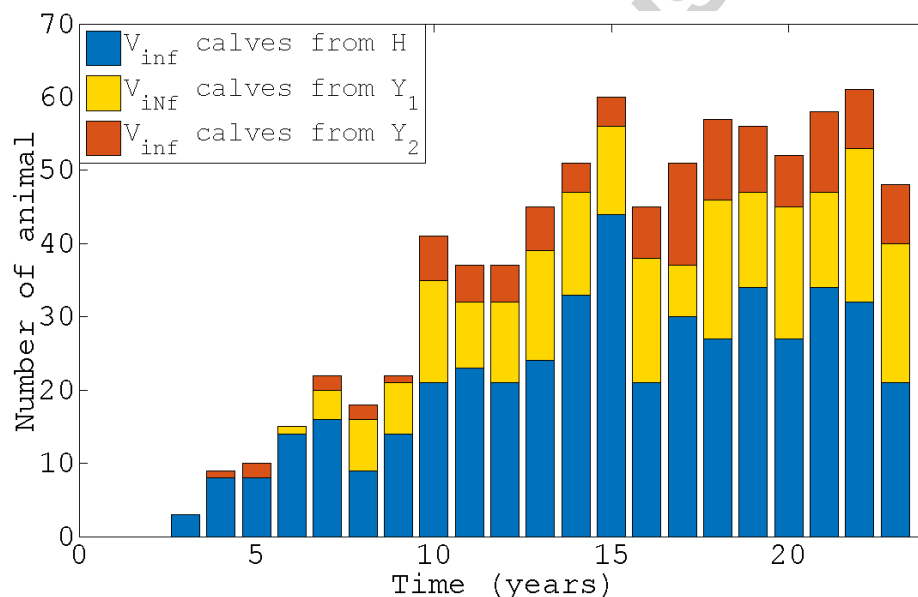


Figure 11. Vertical transmission of MAP from dam to daughter by dam infection status: latent (H, blue), low shedders (Y₁, yellow) and high shedders (Y₂, red).

For implementing a control strategy, it can be useful to know the percentage of high and low shedders and the age stratification and lactation status of infected animals. Figure 12a illustrates the parity distribution for animals in each infected category; latently infected animals are mostly young (between parity 1 and 3), while low shedding animals ranged from parity 2 to 5 and high shedders ranged from parity 3 to 6. In field situations, the parity distribution of infected animals can be identified only for low and high shedding animals, as no testing method can clearly identify the latent animals (Lu et al., 2008; Schukken

et al., 2015). Most farmers do not cull the low shedders as it is not economically justified by milk loss, but culling of high shedders is generally desirable because of lower milk yield (Smith et al., 2009).

Figure 12b shows the distribution of stage of lactation (VWP, waiting to be inseminated and pregnant) for infected animals of different categories. No large differences in lactation status were noted between infection categories. This is vital information for the farmer's decision on when to cull an animal with a high-positive test result. As culling decisions are made for economic reasons and a farmer may choose to retain a positive cow for the length of her lactation before culling her, lactation status is important. The farmer may implement different control measures, such as not to inseminate the test positive cow to avoid vertical transmission, or culling the calf immediately to avoid horizontal transmission.

3.7 Importance of individual information for herd management

Previous compartmental models (Mitchell et al., 2008; Lu et al., 2008; Lu et al., 2010) gave different average dynamics of MAP infections, but did not consider the individual information of the dairy animal's life events such as age, lactation cycle, parity, calving interval, insemination trials, pregnancy. One of the contributions of our IBM model is that it reveals individual information about infected animals after every simulation interval. Mitchell et al., (2008) was the first to include calf-to-calf transmission in compartmental modeling to allow susceptible calves to be infected through one of two direct transmission routes: calf-calf transmission, and adult-calf transmission. We included these transmission dynamics and measured the individual contribution after every year of the simulation period (Figure 9). The success of MAP control strategies, which aim to reduce infections by blocking infection routes, relies on the importance of individual components, such as immediate separation of new born calves to decrease horizontal transmission from dam-to-daughter. As our model tracks infection routes (9a & 9b), we can understand which route contributes more to the prevalence. Our model can also identify which category of infected dams (H, Y₁ and Y₂) contributed most to vertically infected calves (Figure 10), identifying the role of animals that are considered less infectious in maintaining MAP infection in the herd. Another contribution of our model is that we separated true vertical infection through in utero infection from horizontal infection by infectious adult animals, allowing us to understand the limitations of calving pen hygiene. Our model also demonstrates the separate infection routes in both calf and heifer rearing loops: calf-to-calf and heifer-to-heifer infection (Figure 9b). This information may help the farmer to improve calf and heifer rearing managing at the individual pen level.

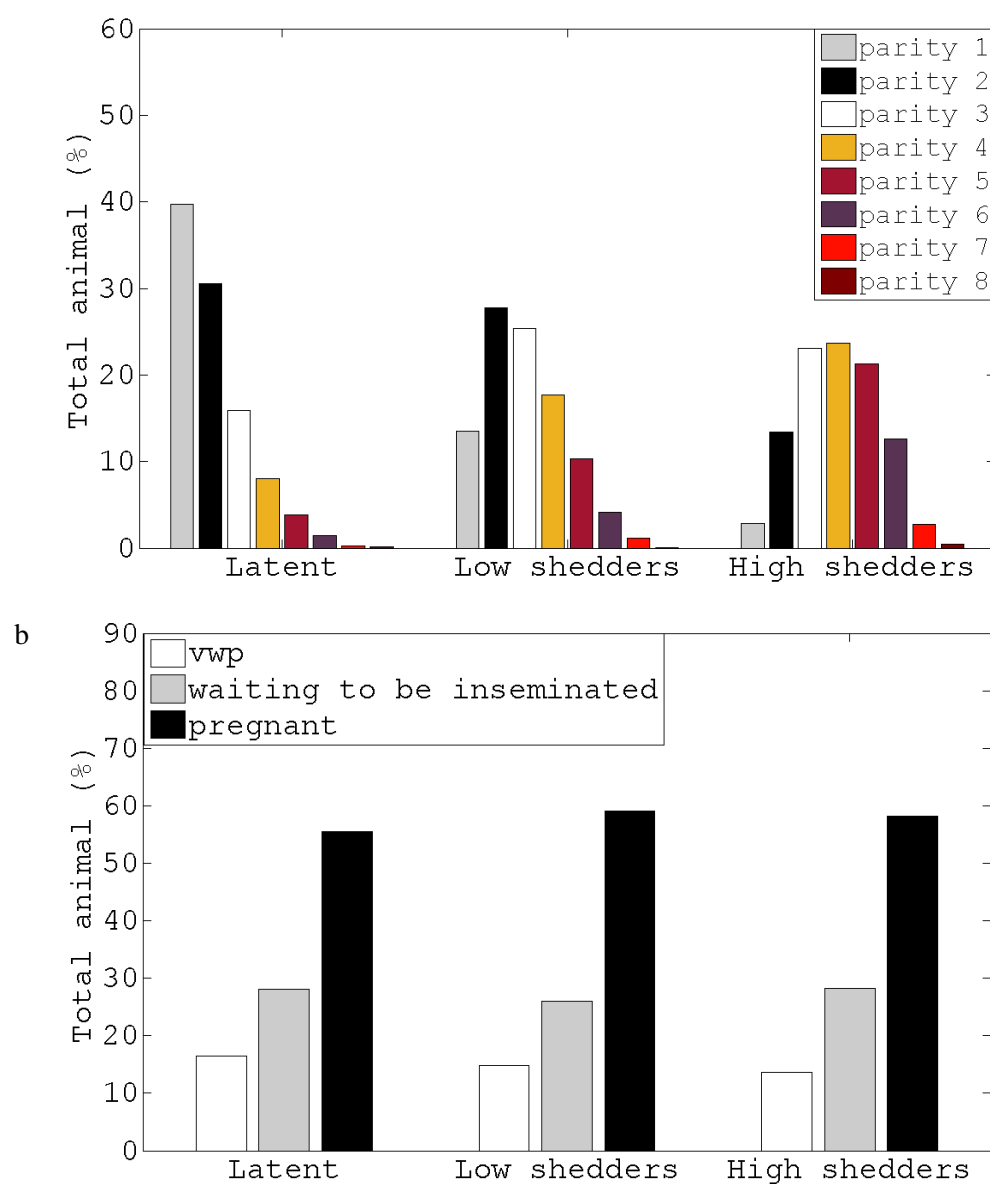


Figure 12. Parity (a) and reproductive status (b) information for individual animals in each infection category: latent, low shedders and high shedders

Our uninfected herd model provides a parameterization adequate to sustain constant herd size over long periods. The uninfected herd model gives a basic framework that can be integrated with different disease models to evaluate their dynamics. Simulated results from the MAP-infected IBM model resemble the results of previous non-IBM models (Mitchell et al., 2008; Marce et al., 2011). In addition our model added individual information of value to the farmer as to how MAP transmits and progresses. This understanding will make it easier to understand the true impact of different control strategies. Also based on the herd endemic status, this individual information about age, parity, and lactation status may give different motivation to different producers.

Current MAP control strategies presented in different models (Kudahl et al., 2007; Kudahl et al., 2008; Lu et al., 2008, 2010; 2013; Marce et al., 2011; Robins et al., 2015) have one common difficulty from the MAP biologic point of view: MAP has an extremely long subclinical phase. It is thus extremely difficult to identify infected animals and manage them according to the selected control strategy. Our current model can observe the impact of this subclinical phase in individual animals. This model did not include any control strategies, as our main objective of this attempt was to build a MAP infection model by considering daily processes at the individual cow level. We also did not consider any subclinical and clinical effects of JD, as accurate parameterization for these is lacking in current data (Schukken et al., 2015). However, our model is adaptive; future studies will incorporate control and clinical disease impacts.

4. Conclusion

This paper presents an individual based model of MAP transmission in a dairy herd. Prior to building the MAP transmission model, we constructed an individual based model of uninfected dairy herd dynamics containing relevant individual processes involved in life cycle of a dairy animal. The model considered three groups of animals depending on individual age: milking/adult herd, calves and heifers. The relevant life cycle processes: calving, VWP, insemination, pregnancy, dry-off period, open cows and death/cull were included. The model was simulated with 1000 adult animals and the results showed that herd size was stable for 20 years.

MAP infection dynamics were integrated with the existing model. All current understanding of MAP transmission except dual path infections (Smith et al., 2015; Schukken et al., 2015, Mitchell et al., 2015a,b) were adopted in our MAP model. The MAP model was simulated over 22 years. The results showed that infection information about MAP transmission paths can provide useful information to better

understand disease dynamics. This work facilitates improved understanding of MAP infection transmission and progression by using individual animal information for each infected category. The IBM model can be adapted with different parameterizations to understand herd-specific MAP dynamics. The presented results indicate that herd management can be driven by a number of parameters, giving flexibility to the IBM model. Individual animal information may provide decision support to farmers choosing a control strategy. Overall, this paper provides a unique tool to understand MAP infection from an individual point of view where all the relevant within-herd processes have been taken into consideration. The current model is adaptive in nature, so that it can be extended in different ways, e.g., economic analysis of an infected herd by including milk yield.

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Highlight

- Individual based model of *Mycobacterium Avium* Subsp. *Paratuberculosis* is developed
- MAP infection framework is integrated on top a stable uninfected dairy herd
- Key life cycle processes of a cow are included simultaneously with MAP infection
- Both uninfected and MAP infected models are parameterized and simulated
- Daily information of infected cow can influence the choice of control strategy