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## Modelling transmission and control of *Mycobacterium avium* subspecies *paratuberculosis* within Irish dairy herds with compact spring calving

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### ABSTRACT

Paratuberculosis is a chronic bacterial infection of the intestine in cattle caused by *Mycobacterium avium* subspecies *paratuberculosis* (*Map*). To better understand *Map* transmission in Irish dairy herds, we adapted the French stochastic individual-based epidemiological simulation model to account for seasonal herd demographics. We investigated the probability of *Map* persistence over time, the within-herd prevalence over time, and the relative importance of transmission pathways, and assessed the relative effectiveness of test-and-cull control strategies. We investigated the impact on model outputs of calf separation from cows (calves grazed on pasture adjacent to cows vs. were completely separated from cows) and test-and-cull. Test-and-cull scenarios consisted of highly test-positive cows culled within 13 or 4 weeks after detection, and calf born to highly test-positive cows kept vs removed. We simulated a typical Irish dairy herd with on average 82 lactating cows, 112 animals in total. Each scenario was iterated 1000 times to adjust variation caused by stochasticity. *Map* was introduced in the fully naive herd through the purchase of a moderately infectious primiparous cow. Infection was considered to persist when at least one infected animal remained in the herd or when *Map* was present in the environment.

The probability of *Map* persistence 15 years after introduction ranged between 32.2–42.7 % when calves and cows had contact on pasture, and between 18.9–29.4 % when calves and cows were separated on pasture. The most effective control strategy was to cull highly test-positive cows within four weeks of detection (absolute 10 % lower persistence compared to scenarios without control). Removing the offspring of highly test-positive dams did not affect either *Map* persistence or within-herd prevalence of *Map*.

Mean prevalence 15 years after *Map* introduction was highest (63.5 %) when calves and cows had contact on pasture. Mean prevalence was 15 % lower (absolute decrease) when cows were culled within 13 weeks of a high test-positive result, and 28 % lower when culled within 4 weeks.

Around calving, the infection rate was high, with calves being infected *in utero* or via the general indoor environment (most important transmission routes). For the remainder of the year, the incidence rate was relatively low with most calves being infected on pasture when in contact with cows. Testing and culling was an effective control strategy when it was used prior to the calving period to minimize the number of highly infectious cows present when calves were born.

### 1. Introduction

Paratuberculosis is a chronic bacterial infection of the intestine in cattle caused by *Mycobacterium avium* subspecies *paratuberculosis* (*Map*). Paratuberculosis is endemic within the dairy sector worldwide (McAloon et al., 2019). It has an economic impact due to milk losses, early

culling and increased mortality (Garcia and Shalloo, 2015).

There are many challenges with paratuberculosis, for example, related to diagnosis and control (Barkema et al., 2018). Susceptibility reduces with age, and older animals are assumed to be resistant (Windsor and Whittington, 2010). Clinical signs (e.g., decreased milk production, weight loss, diarrhoea) usually do not appear until later in

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life (after first calving), or are sometimes never observed (Mitchell et al., 2015). Infected animals without clinical signs are difficult to diagnose because diagnostic tests have a poor test performance with 15–71 % sensitivity depending on the stage of infection (More et al., 2015; Bar-kema et al., 2018). Thus, infected animals can be undetected in a herd while contributing to *Map* transmission within the herd. Transmission occurs *in utero* or via ingestion of milk or faeces containing *Map*. However, the relative importance of the main transmission pathways at farm level, and the drivers of transmission in different farming systems, are not yet fully understood.

Simulation models are useful tools to study *Map* transmission and evaluate control options (Marcé et al., 2010). Previous modelling results have highlighted a large effect of farm management on *Map* transmission for French herds with all-year-round calving; the level of exposure of calves to contaminated environments and the age at which calves are exposed to adults are especially important for transmission (Marcé et al., 2011a).

In Ireland, the dairy system is pasture-based to optimally use grazed grass as the primary feed source for lactating cattle (Ramsbottom et al., 2015). Therefore, more than 90 % of herds adhere to a compact spring calving period (Butler et al., 2010; Ramsbottom et al., 2015). Because of these seasonal herd demographics, the results of modelling *Map* transmission in an all-year-round production system cannot be directly extrapolated to the Irish seasonal production system.

To better understand *Map* transmission in Irish dairy herds, we used a stochastic individual-based epidemiological model accounting for seasonal herd demographics. We used this model to investigate the probability of *Map* persistence in a herd over time, the within-herd prevalence over time, and the relative importance of transmission pathways. We also assessed the relative effectiveness of various test-and-cull control strategies under two options for calf management on pasture.

## 2. Material and methods

To simulate *Map* transmission within an Irish dairy herd and to assess the relative impact of control strategies, we adapted the stochastic and

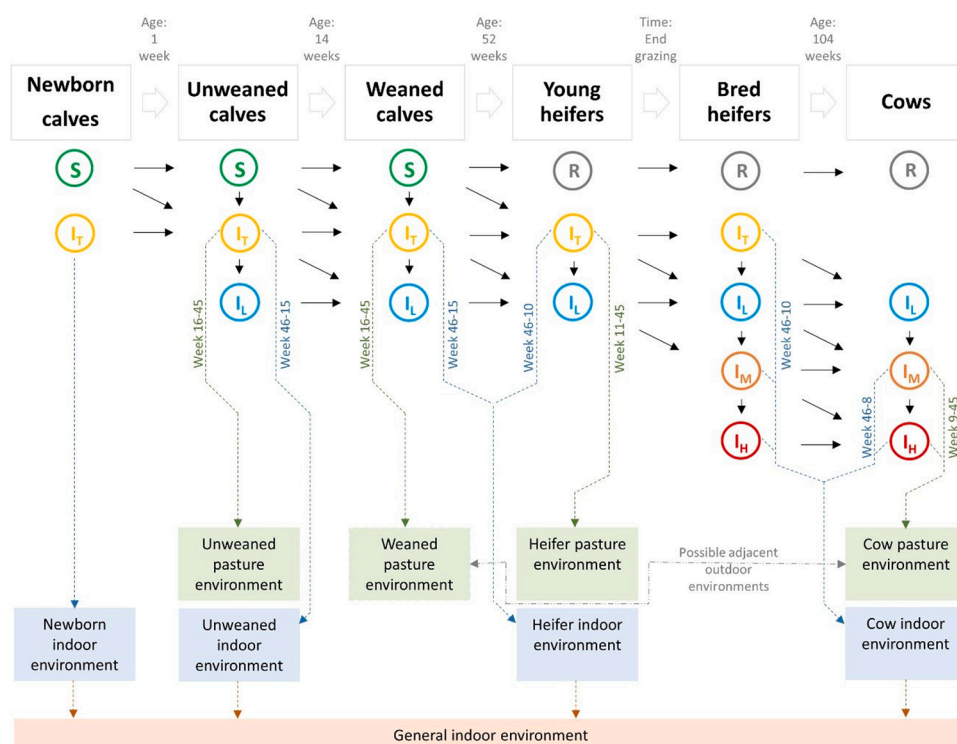
individual-based model developed to simulate *Map* transmission within French dairy herds (Camanes et al., 2018). Both herd demographics and infection dynamics are considered in the model, which is fully described in Camanes et al. (2018).

### 2.1. Herd demography

Animals in a herd are divided into six age groups: newborn calves, unweaned calves, weaned calves, young heifers, bred heifers, and cows (Fig. 1). An animal moves to the next group at a defined age or time in the year.

Adaptations were made to allow the model to represent a typical Irish spring calving dairy farm with associated management (Fig. 2) (Teagasc, 2016). Herd demographics were seasonal, with cows calving early in the year (February – beginning of April) (Supplementary material, Figure S4) (Tratalos et al., 2017). The 50 % of calves born during the first three weeks of the calving season were assumed to be calves from dams bred to dairy bulls; the 50 % born later (*i.e.* after the 6th week of the year (from week 7)) were assumed to be calves from dams bred to beef bulls, these animals were sold at three weeks of age together with all the male calves (Shalloo et al., 2004). Milk production increased after calving and reached its peak around eight weeks in lactation (Quinn, 2005) (Supplementary material, Figure S2). Cows that had calved were turned out to pasture from week 9 onwards (Bloemhoff et al., 2014; Ramsbottom et al., 2015). Heifers were turned out to pasture in week 11 and calves in week 16. Cows were dried off and housed again at the end of November in week 45 (Bloemhoff et al., 2014; Ramsbottom et al., 2015). Cows and heifers that were not in-calf were assumed to be culled after the grazing period (week 47) together with other cows and heifers destined for culling (Maher et al., 2008). Table 1 gives an overview of the parameter values for a typical Irish spring calving dairy herd. Details of all model parameters related to herd dynamics and management are in Supplementary material, Table S3.

We simulated a typical Irish dairy herd with on average 82 lactating cows. We sampled the number of lactating cows from a normal distribution with a mean of 82 and standard deviation of 4.1. At the start of the simulation, the herd (*i.e.*, total number of stock on the farm)



**Fig. 1.** Transmission model for Johne's disease in an Irish spring calving dairy herd. Health states include susceptible (S), resistant (R), transiently infectious ( $I_T$ ), latently infected ( $I_L$ ), moderately infectious ( $I_M$ ), and highly infectious ( $I_H$ ). Solid lines represent transitions between health states and dashed lines represent the contribution of *Mycobacterium avium* sub-species *paratuberculosis* (*Map*) shed by infectious animals to their respective local environment. Together, the amounts of *Map* in the local indoor environments make up the total amount of *Map* in the general indoor environment.

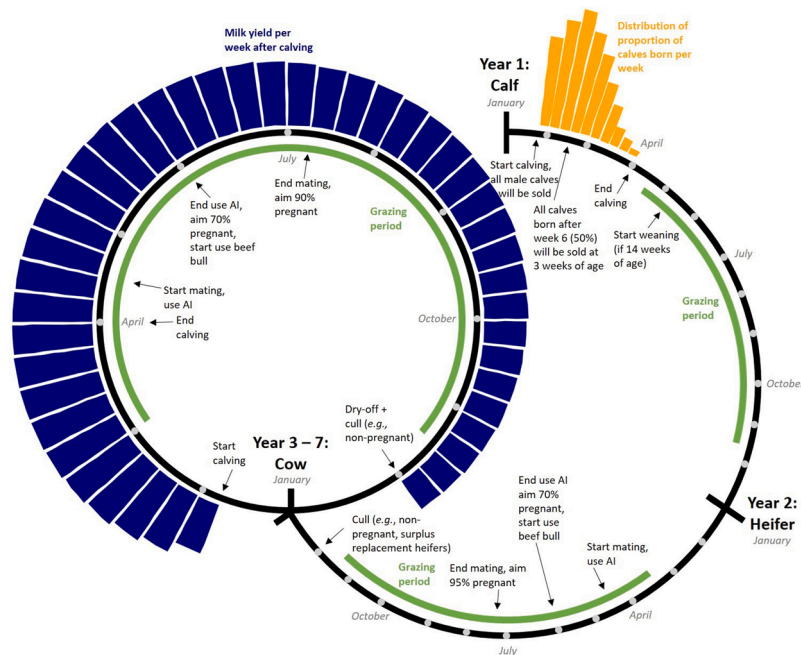


Fig. 2. Schematic overview of herd management in a typical Irish spring calving dairy herd.

consisted of 62.8 % cows, 17.6 % bred heifers, and 19.6 % weaned calves.

## 2.2. *Map* transmission

Six health states are modelled: susceptible (S), resistant (R), transiently infectious ( $I_T$ ), latently infected ( $I_L$ ), moderately infectious ( $I_M$ ), and highly infectious and possibly clinically affected ( $I_H$ ). Cattle up to one year of age are assumed to be susceptible to infection, with susceptibility decreasing exponentially with age (Supplementary material, Figure S1). Uninfected calves are assumed to be resistant to infection after one year. Animals in health states  $I_T$ ,  $I_M$ , and  $I_H$  are infectious and shed *Map* in their colostrum/milk and faeces, with the quantity shed depending on health state (Supplementary material, Figures S3 and S5). *Map* is transmitted via ingestion of colostrum/milk that is contaminated directly or indirectly with faeces, via an environment contaminated with faeces, or *in utero* which includes transmission during parturition. Two environment types were modelled, the local environment which can be either indoor or on pasture and the general indoor environment. Fig. 1 gives an overview of the different animal groups and their contribution to the local and general indoor environments. Transmission via the local environment is defined as the risk posed by other animals held in the same place, indoors or on pasture, but not necessarily at the same time. Transmission via the general indoor environment is defined as the risk posed by other animals held indoors but not necessarily at the same place or time. The total amount of *Map* present in the general indoor environment is the sum of the amount of *Map* present in all local indoor environments, thus all infectious animals that reside indoors contribute to the contamination of the general indoor environment (Marcé et al., 2011a, 2011b). For every week, 40.0 % of the *Map* load was removed from the indoor environment to represent the effect of cleaning manure. Similarly, *Map* load on pastures was reduced by 7.1 % per week to mimic the natural reduction. Indoor environments were additionally cleaned once after all animals had left their respective environments, e.g., the newborn environment was cleaned once after all calves have been born. This cleaning removed an additional 16.7 % of *Map* present in the environment. Details of all model parameters for processes related to *Map* transmission are in Supplementary material, Table S1.

## 2.3. *Map* control

We investigated the impact of three factors on *Map* persistence and transmission: calf separation (calves grazed on pasture in contact with cows, or calves grazed on pasture completely separated from cows), test-and-cull (highly test-positive cows culled within 13 weeks, or these cows culled within 4 weeks after detection), and calf disposal (keeping all calves from highly test-positive dams, or removing these calves). When there was contact between cows and calves on pasture, they were on adjacent pastures and while physically separated (Fig. 1), exchange of bacteria between their environments was considered possible. Under the programme of ‘testing and culling’, a serum ELISA to detect *Map* antibodies was performed on all animals older than 2 years of age. The specificity of the test assumed was 0.985 and the sensitivity assumed was 0.15 for  $I_T$  and  $I_L$ , 0.47 for  $I_M$  and 0.71 for  $I_H$  animals (More et al., 2015). Test-and-cull was performed yearly on all animals >2 years of age (cows) during week 1 of the year (reference scenario), just prior to the calving season. To assess the effect of timing of testing, two alternative test dates were considered: 1) shortly after calving in week 14, and 2) towards the end of the grazing period in week 35. Given the absence of precise knowledge, test-positive  $I_H$  cows were assumed to be highly positive (Camanes et al., 2018). Highly test-positive cows were removed from the farm within 4 or 13 weeks after testing to assess the effect of rapid and late removal. The sale of offspring was based on adaptations from the French model (Camanes et al., 2018) because no clear information was available on which age offspring are sold in Ireland. Therefore, we assumed that offspring younger than 21 weeks were sold at 21 weeks of age and offspring older than 21 weeks were sold at 90 weeks of age. Details of all model parameters for processes related to *Map* control are in Supplementary material Table S2. All control strategy combinations were explored (Table 2).

## 2.4. Simulations

The simulation time step was one week, 52 weeks made up one year, and 15 years were simulated. Each scenario was iterated 1000 times to adjust for variation caused by stochasticity. At the start of each simulation (in the first week of the first year), *Map* was introduced into a fully naive herd through the purchase of a moderately infectious ( $I_M$ )

**Table 1**  
Overview of parameter values for a typical Irish spring calving dairy herd.

Parameter definition	Value	Source
Weaning age (weeks)	14	<sup>a</sup>
Age weaned calf becomes young heifer (weeks)	52	<sup>b</sup>
Time young heifer becomes bred heifer (week)	45	<sup>b</sup>
Age at first calving (weeks)	104	(Teagasc, 2016)
Calf mortality rate at birth (fraction)	0.043	(Mee, 2013; Mee et al., 2008)
Exit rate (week <sup>-1</sup> ):		
1 and 2 weeks of age	0.018	<sup>d</sup>
Week 3 to weaning	0.0025	<sup>d</sup>
Weaning to first calving	0.00024	<sup>d</sup>
Parity 1	0.00047	(Maher et al., 2008)
Parity 2	0.00043	(Maher et al., 2008)
Parity 3	0.00043	(Maher et al., 2008)
Parity 4	0.00044	(Maher et al., 2008)
Parity 5(+)	0.00229	(Maher et al., 2008)
Replacement rate	0.22	<sup>a</sup>
Culled fraction (once per year):		
Bred heifers	0.1800	<sup>a</sup>
Parity 1	0.1120	<sup>a</sup>
Parity 2	0.0588	<sup>a</sup>
Parity 3	0.0700	<sup>a</sup>
Parity 4	0.2184	<sup>a</sup>
Parity 5(+)	0.5796	<sup>a</sup>
Cull bred heifers and cows in week	47	(Butler et al., 2010; Maher et al., 2008)
Start grazing (week):		
Unweaned and weaned calves	16	(Bloemhoff et al., 2014)
Young heifers	11	(Bloemhoff et al., 2014)
Cows	9	(Bloemhoff et al., 2014; Ramsbottom et al., 2015)
End grazing all animals (week)	45	(Bloemhoff et al., 2014; Ramsbottom et al., 2015)
Faeces produced by (kg/day):		
Newborn calf / unweaned calf	0.4	<sup>a</sup>
Weaned calf	4.1	<sup>a</sup>
Young heifer	7.5	<sup>a</sup>
Bred heifer	22.5	<sup>a</sup>
Cow	22.5	<sup>a</sup>

<sup>a</sup> Expert opinion.

<sup>b</sup> Model assumption.

<sup>c</sup> The rate with which animals leave the herd. This can have several reasons: death, culling, selling, etc.

<sup>d</sup> Agricultural statistics.

**Table 2**  
Simulated control strategies.

Scenario	Calf separation (pasture)	Test and cull implemented (week 1)	Time until culling cow after detected as high positive (I <sub>H</sub> ) (weeks)	Calves from dam detected as high positive (I <sub>H</sub> ) removed (%)
1	Contact	No	–	–
2	Separate	No	–	–
3	Contact	Yes	13	0
4	Separate	Yes	13	0
5	Contact	Yes	13	100
6	Separate	Yes	13	100
7	Contact	Yes	4	0
8	Separate	Yes	4	0
9	Contact	Yes	4	100
10	Separate	Yes	4	100

primiparous cow. Except for this purchase, we assumed that the herd was closed for the simulation period of 15 years. *Map* persistence, prevalence, incidence, age at infection, and the main transmission routes were assessed. Infection was considered to persist when at least one infected animal was present in the herd or when *Map* was present in the environment.

The model was developed in C++ Standard 14 (Stroustrup, 2000). Outputs were analysed in R version 3.6.1 (R Core Team, 2018) using packages viridis (Garnier, 2018) and ggplot2 (Wickham, 2016).

### 3. Results and discussion

#### 3.1. Persistence of *Map* infection

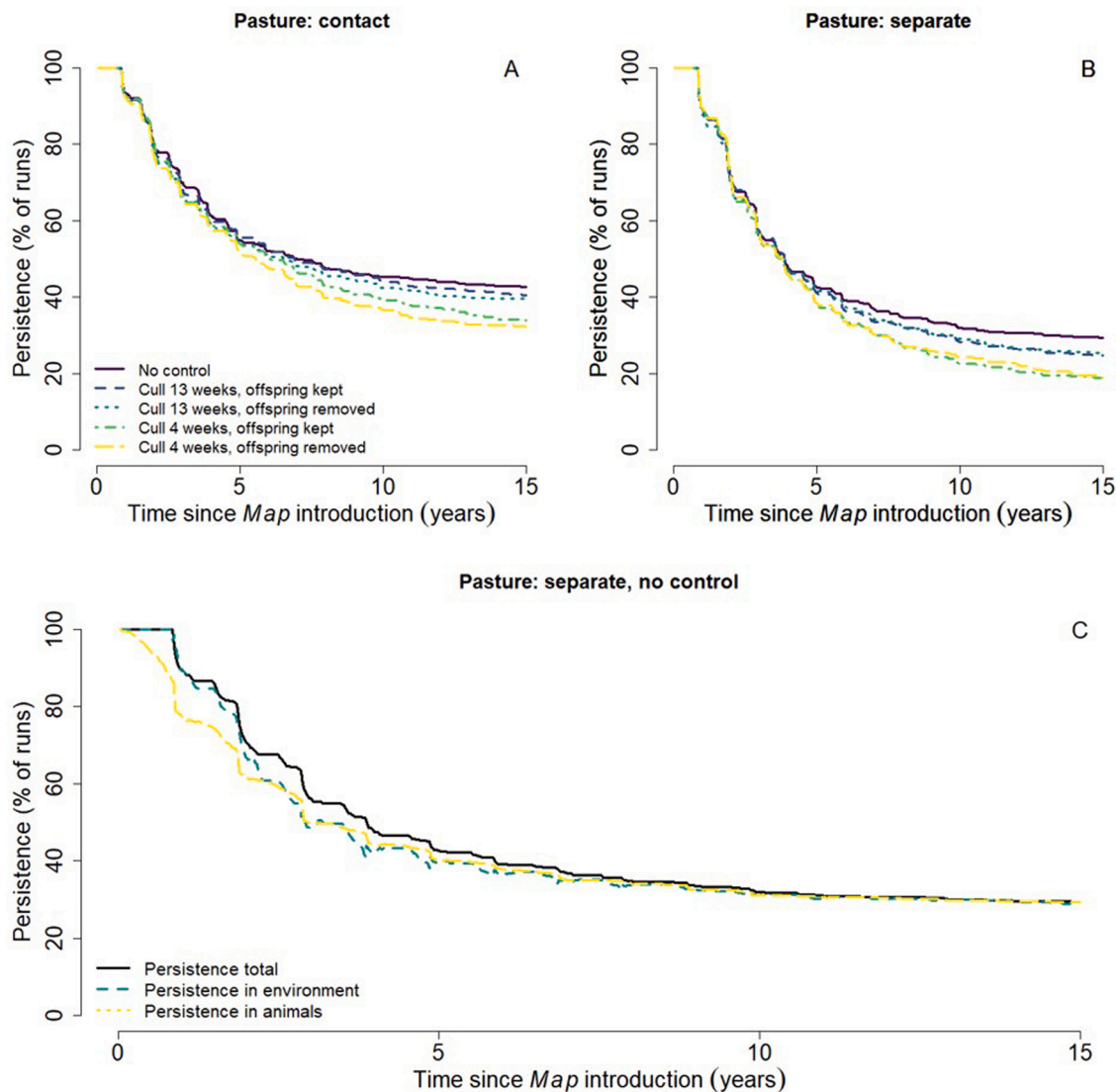
Extinction is defined as disease clearance, *i.e.*, the opposite of persistence. The probability of extinction 15 years after *Map* introduction ranged between 57.3 and 67.8 % for a typical Irish dairy herd with seasonal calving when calves and cow had contact on pasture, and between 70.6 and 81.1 % when calves and cows were separated on pasture (Fig. 3A,B). In a typical medium-size French dairy herd with all-year round calving and no control strategy, a similar probability of extinction within 15 years of 66 % was predicted (Marcé et al., 2011b). Early extinction (within the first two years following introduction) occurred in about 20 % of the cases when calves and cows had contact on pasture, and in about 30 % of the cases when they were separated. In France, the probability of early extinction was higher at 43 % (Marcé et al., 2011b). Calving and related herd management practices are seasonal in Ireland and mainly all-year-round in western France. Therefore, the exit pattern of cows from a herd is different. In Ireland, as presented in the model, cows are usually culled once a year, after dry-off at the end of the grazing season (week 47). At this time, around 22 % of the cows are culled to be replaced by in-calf heifers at the beginning of the following year. Exit rates of cows during the rest of the year are low, meaning that the first infectious cow introduced into the herd has a high probability of remaining in the herd for almost a year until culling. Even if the cow were removed from the herd, it has already contaminated the environment for some weeks. It takes some time before *Map* disappears from the environment even when no infectious animal is present, thus infection persists (Fig. 3C). When cows are culled all-year-round, as is often the case in France, they have a higher chance of being removed from the herd over the course of a year and before heavily contaminating the environment. These differences could explain the greater probability of early extinction in France compared to Ireland.

Control strategies did not affect the probability of extinction within the first five years after *Map* introduction (Fig. 3A,B). Thereafter, culling of highly test-positive cows increased the probability of extinction in a herd. Culling highly test-positive cows within four weeks of detection in week 1 was most effective, with an absolute 10 % greater probability of extinction compared to scenarios with no control strategy. Removing offspring of highly test-positive cows did not affect the probability of *Map* extinction.

#### 3.2. Prevalence within persistently infected herds

For herds in which infection persisted for at least 15 years, the mean prevalence at the end of the simulated period (15 years) was highest when calves and cows had contact on pasture (63.5 % infected (I<sub>T</sub>, I<sub>L</sub>, I<sub>M</sub>, and I<sub>H</sub>), 27.6 % infectious (I<sub>T</sub>, I<sub>M</sub>, and I<sub>H</sub>), and 4.4 % highly infectious (I<sub>H</sub>) animals; Fig. 4A). Fig. 4 shows the prevalence averaged over all stochastic repetitions in which *Map* infection persisted for 15 years. Note, however, that despite the same initial conditions the change in prevalence over time can be very different from one replicate to another, therefore a large range of prevalences was observed (Supplementary material, Figure S11). In Ireland, the prevalence of infected animals within infected herds was estimated to be 13.7 % (McAloon et al., 2016). According to our model, this prevalence level could be reached on average five years after *Map* introduction in a herd, irrespective of the control strategy.

Five years after *Map* introduction, control strategies started to have a positive effect on the within-herd prevalence. Compared to herds with no control strategy, the average prevalence after fifteen years was ~15 % lower (absolute decrease) when cows were culled within 13 weeks



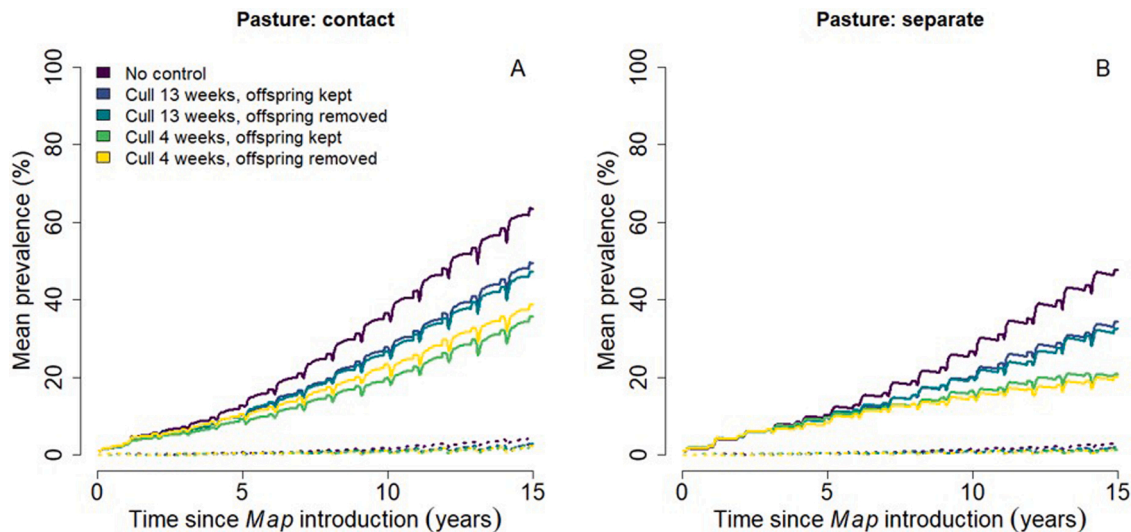
**Fig. 3.** Percentage of herds in which *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) infection persisted over time. Infection was considered to persist when at least one infected animal was present in the herd or when *Map* was present in the environment. Cows that tested highly positive in week 1 were culled within 13 or 4 weeks and offspring of these cows was either kept or removed. A) Cows and calves could have contact on pasture, B) Cows and calves were separated on pasture, C) The proportion of herds in which *Map* persisted, in total (black solid line), in at least one infected animal (yellow dotted line), and in the environment (green dashed line), for herds where cows and calves were separated on pasture and no control strategy was implemented. Other simulated control scenarios showed similar patterns. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

after testing highly positive in week 1 and ~28 % lower when cows were culled within 4 weeks after testing highly positive in week 1 (Fig. 4). In simulated French all-year-round calving dairy herds, a short interval (4 weeks) between testing and culling was important when the within-herd prevalence was between 7% and 21 %. For higher prevalences, the interval between testing and culling was no longer relevant (Camanes et al., 2018). In contrast, in simulated Danish dairy herds, immediate culling of repeatedly ELISA-positive cows was an effective strategy to reduce the prevalence, while delayed culling kept the prevalence constant at 5, 25, or 50 % depending on the scenario (Kudahl et al., 2008). For the scenarios that we simulated, mean prevalences increased over a 15-year time period even with calf separation and culling of test positive  $I_H$  cows albeit at a lower rate of increase compared to herds that did not implement control strategies. Furthermore, in herds practicing calf separation and the culling of high test-positive cows within 4 weeks, mean prevalence stabilized at around 20 % towards the end of the 15-year simulation period (Fig. 4B).

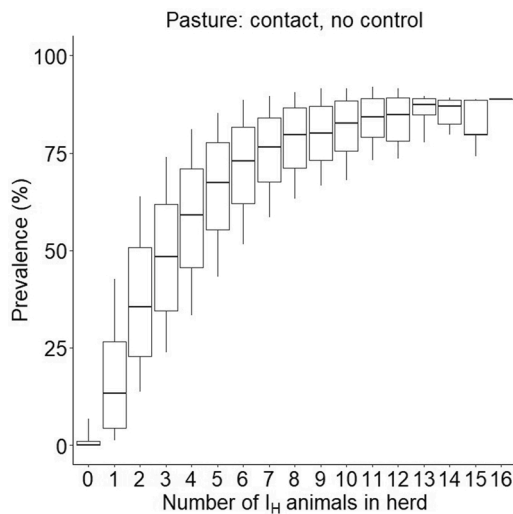
For all tested scenarios, mean prevalence of highly infectious cows

( $I_H$ ) remained relatively low over time (4.4 % maximum after 15 years). Thus, with an average herd size of 112 animals, on average there will be five highly infectious and possibly affected (that is, presenting clinical signs) cows in a herd. Fig. 5 shows the distribution of the within-herd prevalence according to the number of  $I_H$  cows present in the herd. When the number of  $I_H$  cows in a herd was low, a broad range of prevalences was observed (Fig. 5). Thus, based on the number of clinical cases observed, the within-herd prevalence could be even higher than a farmer is expecting, the so-called “Iceberg effect” (Magombedze et al., 2013).

Mean within-herd prevalence was not different in herds where offspring were removed compared to herds where offspring were kept.  $I_H$  cows have a high probability (0.65) of giving birth to *Map*-positive offspring (compared to 0.149 for  $I_T$ ,  $I_L$ , and  $I_M$  cows). Therefore, one might expect that  $I_H$  cows would contribute substantially to *Map* dispersion in a herd and that removing their offspring would be an effective control measure. However, when the within-herd prevalence is low (e.g., when infection does not persist in the long run), the number of



**Fig. 4.** Mean prevalence of all infected animals ( $I_T$ ,  $I_L$ ,  $I_M$ , and  $I_H$ ; solid line) and of only highly infectious animals ( $I_H$ ; dotted line) over time in herds where *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) infection persisted for 15 years. Cows and calves could either have contact on pasture (A) or be separated on pasture (B). Cows that tested highly positive were culled within 13 or 4 weeks and the offspring of these cows was either kept or removed.



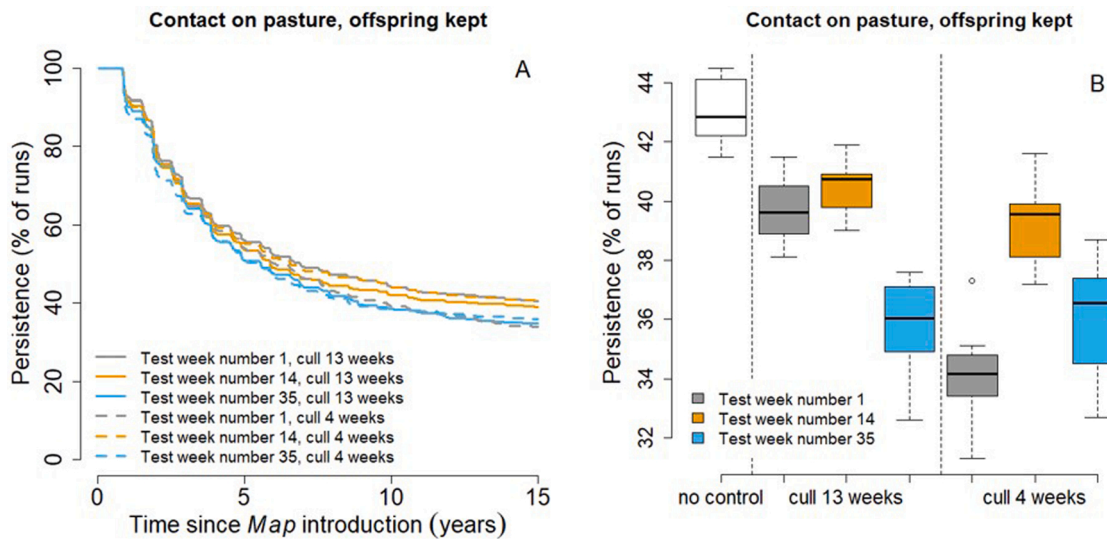
**Fig. 5.** Variation of the within-herd prevalence with regards to the number of highly infectious animals ( $I_H$ ) in the herd, without any control and when calves and cows had contact on pasture. Each box contains values between the first and the third quartiles, the horizontal line corresponding to the median. Vertical lines outside the boxes extend to 10th and 90th percentiles.

$I_H$  cows in the herd is also low (Fig. 5). Because there are few  $I_H$  cows, the number of *Map*-positive offspring born to  $I_H$  cows is also low. In such a situation, removing offspring of test positive  $I_H$  cows has no additional effect on the probability of extinction nor on the prevalence compared to removing the dam only, because the number of calves removed is low or even zero. In contrast, when the within-herd prevalence is high (e.g., when infection has already persisted for a long period of time), the number of  $I_H$  cows in the herd is also relatively high (Fig. 5). Because there are many  $I_H$  cows, the number of *Map*-positive offspring born to an  $I_H$  cow is also high. However, the removal of the offspring of test positive  $I_H$  cows in these situations has no effect on the within herd prevalence because the infection pressure from other transmission routes, for example from the contaminated environment, is also high. This means that calves that are *Map*-negative at birth have a high chance of being infected within their first year of life. Removing offspring of  $I_H$  test positive cows will only marginally reduce within-herd prevalence. This

was also observed in France where, irrespective of the starting prevalence, culling calves born to infected cows detected as infected had no effect on within-herd prevalence over the longer term (Camanes et al., 2018).

### 3.3. Effect of test date on *Map* persistence

To assess the impact of timing of testing, we considered three alternatives: testing yearly in week 1 (the reference scenario), testing yearly in week 14 shortly after calving, and testing yearly in week 35 towards the end of the grazing period. Fig. 6 presents the proportion of repetitions in which *Map* persists by timing of testing, for the scenario where calves and cows could have contact on pasture and the offspring of test positive cows were kept. For other scenarios (variations of contact/separation on pasture, offspring kept/removed), similar patterns were observed (Supplementary material, Figure S12). The first five years after *Map* introduction, test date does not have an effect on the probability of persistence (Fig. 6A). However, over a longer period of time, the probability of persistence differs with different timing of testing, after accounting for the stochasticity of the model results (Fig. 6B). Persistence after 15 years of simulation was higher when animals were tested in week 14, or in week 1 and culled 13 weeks later, compared to when animals were tested in week 35, or in week 1 and culled 4 weeks later. These differences can be attributed to the timing of the calving season which commences in Ireland in week 4 and ends in week 13 (Supplementary material, Figure S4). Cows that test high positive in week 1 followed by rapid removal are culled in week 5, i.e., at the beginning of the calving season. Therefore, they neither give birth to a possibly infected calf nor contribute to the infection pressure during the calving period when young, highly susceptible calves are present on the farm. In contrast, cows identified in week 1 followed by delayed removal will be culled in week 14, immediately after the calving season ends. Therefore, they may both give birth to an infected calf and contribute to the infection pressure during the calving period. Cows that test high positive in week 14 are, irrespective of the culling strategy, present during the calving season at the beginning of the year and have a high probability of being a high shedder at that time. Cows that test high positive in week 35 are, with rapid removal, culled in week 39, i.e., before cows are housed again in week 45. Therefore, they do not contribute to the infection pressure of the general indoor environment. With delayed culling, they are culled in week 48, thereby contributing to the infection pressure of the general indoor environment for only a short period of



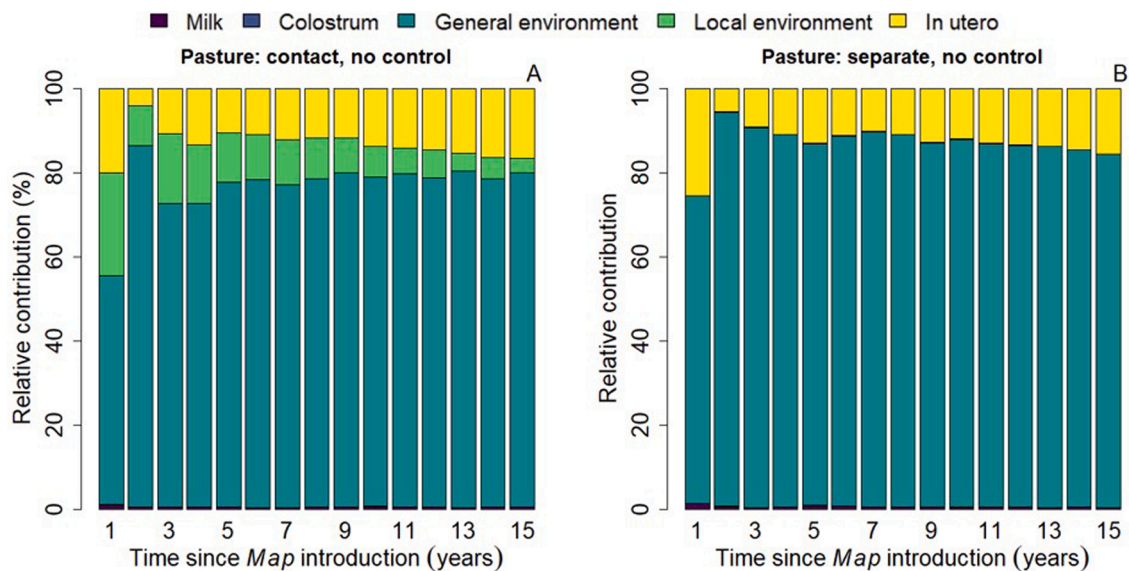
**Fig. 6.** Comparison of the proportion of herds in which *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) infection persisted among 6 test-and-cull scenarios: variation over time (A), and distributions over 10 repetitions of 1000 stochastic runs 15 years after *Map* introduction (B). In all scenarios, calves and cows had contact on pasture and offspring of cows that tested highly positive was kept. Cows that tested highly positive were culled within 13 or 4 weeks. Cows were tested in week 1 (grey), 14 (orange), or 35 (blue). Each box contains values between the first and third quartiles, the horizontal line corresponding to the median. Whiskers extend to lower observed point that falls within the first quartile – 1.5x interquartile range and the largest observed point that falls within the third quartile + 1.5x interquartile range. Points represent outliers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

time. When testing and culling is performed towards the end of the year, the number of highly infectious cows present during the subsequent calving season is also low.

These results highlight the need for farmers to consider the optimal time to testing and culling, with the aim to minimize the number of highly infectious cows that might be present when calves are being born. Other factors to consider when determining the optimal time to test for paratuberculosis are the interval between calving and testing, and the interval between testing for bovine tuberculosis and testing. Test specificity is reduced during the first week after calving (Nielsen and Toft, 2012) and within three months of testing for tuberculosis (Picasso-Risso et al., 2019).

### 3.4. Relative importance of transmission routes

The most important transmission route was the general indoor environment, followed by *in utero* transmission (Fig. 7). However, when calves and cows had contact on pasture, the second most important transmission route during the first four years after *Map* introduction was the local environment, thereafter, it was *in utero* transmission. The local environment did not contribute significantly to transmission when calves and cows grazed separately on pasture. For all herds, colostrum and milk were minor transmission routes. The relative contribution of transmission routes over time in scenarios with control strategies in place showed similar patterns. These results are in contrast with farmers' perceptions that transmission via milk, not the environment, was the most important transmission route (McAloon et al., 2017). However, in this model, transmission via colostrum/milk is defined



**Fig. 7.** Relative contribution of *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) transmission routes over time and without any control. Calves and cows had contact on pasture (A) or were separated on pasture (B).



strictly as transmission via ingestion of colostrum or milk that is contaminated directly or indirectly with faeces in the liquid itself (Marcé et al., 2011b). Thus, for example, transmission via faecally contaminated buckets used to feed calves is considered to be part of the transmission via the general indoor environment (Marcé et al., 2011b). These results are similar to those found for a typical all-year-round calving dairy herd in France, where after 15 years ~80 % of transmission occurred via the general indoor environment and ~20 % *in utero* (Marcé et al., 2011b).

### 3.5. Incidence

Fig. 8 shows the relative incidence over the course of an average year with transmission routes specified. Highest incidences were observed between weeks 4 and 14, when calves were infected *in utero* or via the general indoor environment. A drop in incidence was observed after week 9, noting at this point that cows go to pasture and do not subsequently contribute to the general indoor environment. Later, when calves were sent to pasture and came into contact with cows, transmission via the local pasture environment was observed (Fig. 8A). At the end of the grazing season (week 45), there was a slight increase in incidence because of transmission via the general indoor environment. The incidence of infection over the course of a year in scenarios with control strategies in place showed similar patterns. Thus, there is seasonality in the incidence over the course of a year. Around calving, incidences are high, with calves being infected *in utero* or via the general indoor environment, the remainder of the year incidences are relatively low with calves infected on pasture when there is contact with cows.

When looking at the age at infection (Fig. 9), most of the infected animals were newborns infected *in utero* or via the general indoor environment. Infections became less frequent as calves aged. For calves that had contact with cows on pasture, a slight increase in incidence was observed at 14 weeks of age (weaning). In scenarios with control strategies in place, similar incidence patterns were observed. These results show, similar to France, that exposure of especially young calves to an environment contaminated with faeces from adult cows should be avoided (Marcé et al., 2011a, 2011b; Camanes et al., 2018).

### 3.6. Herd demographics

We adapted a stochastic individual-based epidemiological model to

study *Map* transmission in a typical Irish dairy cattle herd under the hypothesis that results from an all-year-round production system could not be directly extrapolated to a seasonal production system. In French all-year-round calving herds, the level of exposure of calves to contaminated environments and the age of calves when exposed to adults each had a large effect on *Map* transmission (Marcé et al., 2011a). Although there is seasonality in incidence, conclusions for Ireland are similar. *Map* is mainly transmitted during the first weeks of life and via environments contaminated by adult cows, e.g., the general indoor environment and, when cows and calves are kept adjacent to each other, the local pasture environment.

### 3.7. Model assumptions

We modelled *Map* transmission in dairy herds that did not introduce animals, except for the infected primiparous cow that initiated the infection. More frequent introductions of (infected) animals would likely increase both the probability of *Map* persistence and the within-herd prevalence. In Brittany (France), introducing a second infected animal increased the probability of persistence 5 years after the first introduction from 30 % to 60 %, while introducing five or more infected animals resulted in a probability of persistence of 90 % (Beaunée et al., 2015). Furthermore, within-herd prevalences five years after introduction increased with the number of infected animals introduced, albeit less rapidly compared to the probability of persistence (Beaunée et al., 2015). These results were obtained with a spatio-temporal model that accounts for herd demographics, within-herd *Map* transmission, and between-farm *Map* transmission through animal trade (Beaunée et al., 2015, 2017). Adapting this model to the Irish farming setting where animal trade patterns might be different from Brittany, would give insight into whether conclusions derived from this model are applicable also in Ireland.

## 4. Conclusion

We adapted the French stochastic individual-based epidemiological simulation model to account for seasonal herd demographics, and used it to investigate the probability that *Map* persists in a typical Irish dairy cattle herd over time, the within-herd prevalence over time, and the relative importance of transmission pathways. We assessed the relative effectiveness of test-and-cull control strategies under two options of calf

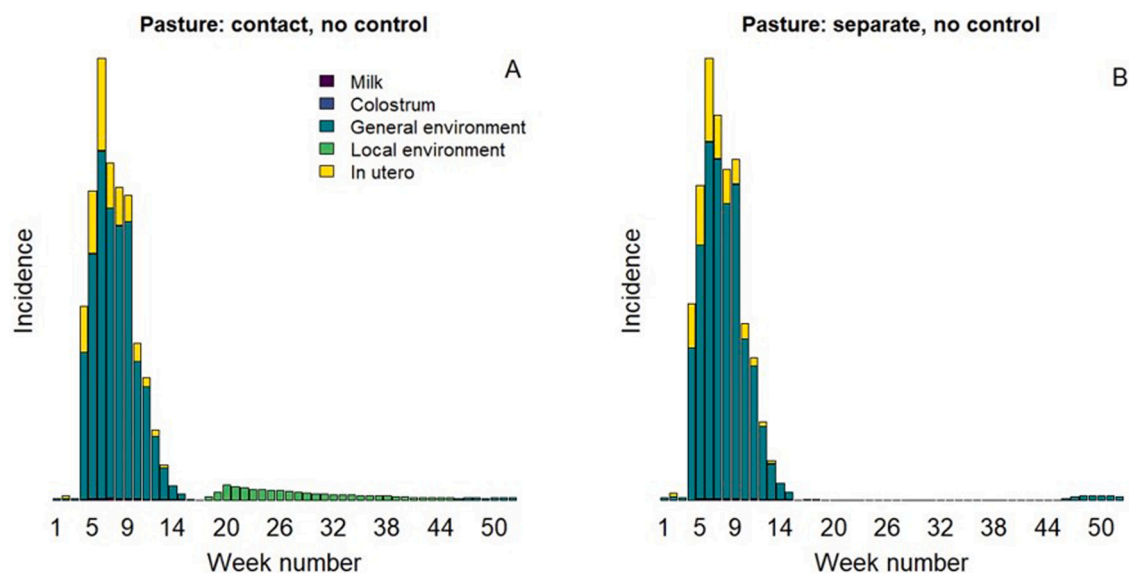


Fig. 8. Relative *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) incidence per week of an average year with contribution of transmission routes specified for herds in the absence of control. Calves and cows had contact on pasture (A) or were separated on pasture (B).

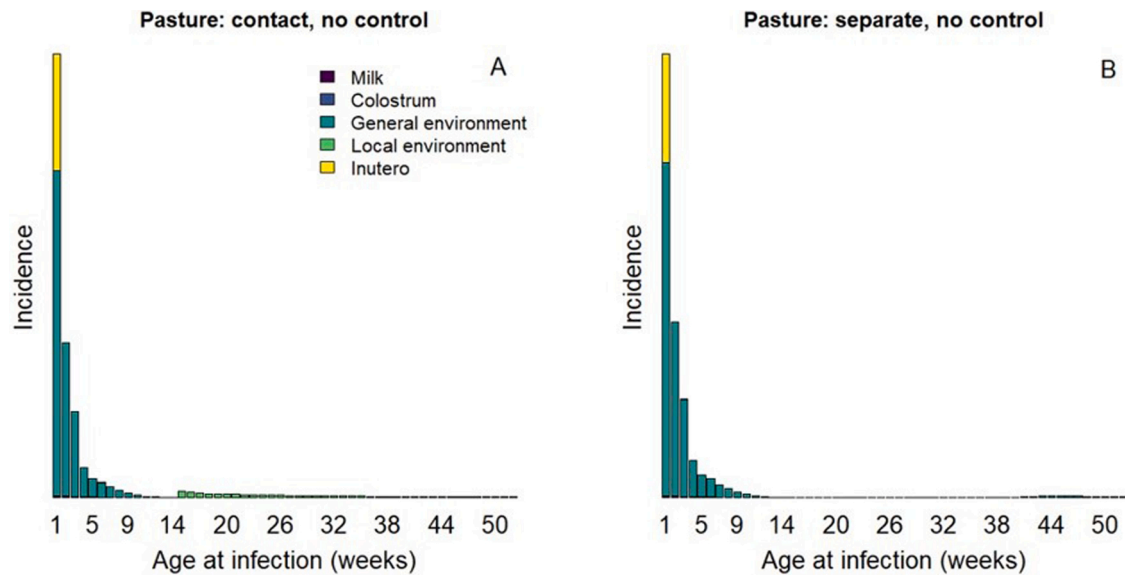


Fig. 9. Relative incidence per age in weeks with contribution of transmission routes specified for herds in the absence of control. Calves and cows had contact on pasture (A) or were separated on pasture (B).

management on pasture. We found that extinction within 2 years after *Map* introduction is lower when compared to herds with all-year-round calving, possibly because the initial infectious cow has a higher probability of remaining in the herd for almost a year. However, extinction before 15 years after initial introduction is not different from a non-seasonal calving herd. The general indoor environment is the most important transmission route followed by *in utero* transmission. Similar to herds without seasonal demographics, calf exposure to environments contaminated by cows should be avoided, especially for young calves which are the most susceptible. Separating cows and calves on pasture is an effective control strategy that reduces persistence and within-herd prevalence. Testing and culling is an effective control strategy when it is used prior to the calving period, to minimize the number of highly infectious cows present when calves are being born.

#### Declaration of Competing Interest

None.

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#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.prevetmed.2020.10.5228>.

#### References

- Barkema, H.W., Orsel, K., Nielsen, S.S., Koets, A.P., Rutten, V.P.M.G., Bannantine, J.P., Keefe, G.P., Kelton, D.F., Wells, S.J., Whittington, R.J., Mackintosh, C.G., Manning, E.J., Weber, M.F., Heuer, C., Forde, T.L., Ritter, C., Roche, S., Corbett, C.S., Wolf, R., Griebel, P.J., Kastelic, J.P., De Buck, J., 2018. Knowledge gaps that hamper prevention and control of *Mycobacterium avium* subspecies *paratuberculosis* infection. *Transbound. Emerg. Dis.* 65, 125–148. <https://doi.org/10.1111/tbed.12723>.
- Beaunée, G., Vergu, E., Ezanno, P., 2015. Modelling of paratuberculosis spread between dairy cattle farms at a regional scale. *Vet. Res.* 46, 1–13. <https://doi.org/10.1186/s13567-015-0247-3>.
- Beaunée, G., Vergu, E., Joly, A., Ezanno, P., 2017. Controlling bovine paratuberculosis at a regional scale: towards a decision modelling tool. *J. Theor. Biol.* 435, 157–183. <https://doi.org/10.1016/j.jtbi.2017.09.012>.
- Bloemhoff, Y., Danaher, M., Forbes, A., Morgan, E., Mulcahy, G., Power, C., Sayers, R., 2014. Veterinary Parasitology Parasite control practices on pasture-based dairy farms in the Republic of Ireland. *Vet. Parasitol.* 204, 352–363. <https://doi.org/10.1016/j.vetpar.2014.05.029>.
- Butler, S.T., Shalloo, L., Murphy, J.J., 2010. Extended lactations in a seasonal-calving pastoral system of production to modulate the effects of reproductive failure. *J. Dairy Sci.* 93, 1283–1295. <https://doi.org/10.3168/jds.2009-2407>.
- Camanes, G., Joly, A., Fourichon, C., Ben Romdhane, R., Ezanno, P., 2018. Control measures to prevent the increase of paratuberculosis prevalence in dairy cattle herds: an individual-based modelling approach. *Vet. Res.* 49, 60. <https://doi.org/10.1186/s13567-018-0557-3>.
- García, A.B., Shalloo, L., 2015. Invited review: the economic impact and control of paratuberculosis in cattle. *J. Dairy Sci.* 98, 5019–5039. <https://doi.org/10.3168/JDS.2014-9241>.
- Garnier, S., 2018. *Viridis: Default Color Maps From "matplotlib" (No. 0.5.1)*.
- Kudahl, A.B., Nielsen, S.S., Østergaard, S., 2008. Economy, efficacy, and feasibility of a risk-based control program against paratuberculosis. *J. Dairy Sci.* 91, 4599–4609. <https://doi.org/10.3168/jds.2008-1257>.
- Magombedze, G., Ngonhala, C.N., Lanzas, C., 2013. Evaluation of the "Iceberg phenomenon" in Johnne's disease through mathematical modelling. *PLoS One* 8. <https://doi.org/10.1371/journal.pone.0076636>.
- Maher, P., Good, M., More, S.J., 2008. Trends in cow numbers and culling rate in the Irish cattle population, 2003 to 2006. *Ir. Vet. J.* 61, 455–463.
- Marcé, C., Ezanno, P., Weber, M.F., Seegers, H., Pfeiffer, D.U., Fourichon, C., 2010. Invited review: modeling within-herd transmission of *Mycobacterium avium* subspecies *paratuberculosis* in dairy cattle: a review. *J. Dairy Sci.* 93, 4455–4470. <https://doi.org/10.3168/jds.2010-3139>.
- Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U., Fourichon, C., 2011a. Within-herd contact structure and transmission of *Mycobacterium avium* subspecies *paratuberculosis* in a persistently infected dairy cattle herd. *Prev. Vet. Med.* 100, 116–125. <https://doi.org/10.1016/j.prevetmed.2011.02.004>.
- Marcé, C., Ezanno, P., Seegers, H., Pfeiffer, D.U., Fourichon, C., 2011b. Predicting fadeout versus persistence of paratuberculosis in a dairy cattle herd for management and control purposes: a modelling study. *Vet. Res.* 42, 36. <https://doi.org/10.1186/1297-9716-42-36>.
- McAloon, C.G., Doherty, M.L., Whyte, P., O'Grady, L., More, S.J., Messam, L.L.M., Good, M., Mullowney, P., Strain, S., Green, M.J., 2016. Bayesian estimation of prevalence of paratuberculosis in dairy herds enrolled in a voluntary Johnne's Disease

- Control Programme in Ireland. *Prev. Vet. Med.* 128, 95–100. <https://doi.org/10.1016/j.prevetmed.2016.04.014>.
- McAloon, C.G., Macken-Walsh, Á., Moran, L., Whyte, P., More, S.J., O'Grady, L., Doherty, M.L., 2017. Johne's disease in the eyes of Irish cattle farmers: a qualitative narrative research approach to understanding implications for disease management. *Prev. Vet. Med.* 141, 7–13. <https://doi.org/10.1016/J.PREVETMED.2017.04.001>.
- McAloon, C.G., Roche, S., Ritter, C., Barkema, H.W., Whyte, P., More, S.J., O'Grady, L., Green, M.J., Doherty, M.L., 2019. A review of paratuberculosis in dairy herds — part 1: epidemiology. *Vet. J.* <https://doi.org/10.1016/j.tvjl.2019.01.010>.
- Mee, J.F., 2013. Why Do So Many Calves Die on Modern Dairy Farms and What Can We Do about Calf Welfare in the Future? *Anim.* 1036–1057. <https://doi.org/10.3390/ani3041036>.
- Mee, J.F., Berry, D.P., Cromie, A.R., 2008. Prevalence of, and risk factors associated with, perinatal calf mortality in pasture-based Holstein-Friesian cows. *Anim.* 2 (4), 613–620. <https://doi.org/10.1017/S1751731108001699>.
- Mitchell, R.M., Schukken, Y., Koets, A., Weber, M., Bakker, D., Stabel, J., Whitlock, R.H., Louzoun, Y., 2015. Differences in intermittent and continuous fecal shedding patterns between natural and experimental *Mycobacterium avium* subspecies paratuberculosis infections in cattle Modeling Johne's disease: From the inside out Dr Ad Koets and Prof Yrjo Grohn. *Vet. Res.* 46, 1–10. <https://doi.org/10.1186/s13567-015-0188-x>.
- More, S.J., Cameron, A.R., Strain, S., Cashman, W., Ezanno, P., Kenny, K., Fourichon, C., Graham, D., 2015. Evaluation of testing strategies to identify infected animals at a single round of testing within dairy herds known to be infected with *Mycobacterium avium* ssp. paratuberculosis. *J. Dairy Sci.* 98, 5194–5210. <https://doi.org/10.3168/jds.2014-8211>.
- Nielsen, S.S., Toft, N., 2012. Effect of days in milk and milk yield on testing positive in milk antibody ELISA to *Mycobacterium avium* subsp. Paratuberculosis in dairy cattle. *Vet. Immunol. Immunopathol.* 149, 6–10. <https://doi.org/10.1016/j.vetimm.2012.05.013>.
- Picasso-Risso, C., Grau, A., Bakker, D., Nacar, J., Mínguez, O., Perez, A., Alvarez, J., 2019. Association between results of diagnostic tests for bovine tuberculosis and Johne's disease in cattle. *Vet. Rec.* 185, 693. <https://doi.org/10.1136/vr.105336>.
- Quinn, N., 2005. *Modelling Lactation and Liveweight Curves in Irish Dairy Cows*. Dublin City University.
- R Core Team, 2018. *R: A Language and Environment for Statistical Computing*.
- Ramsbottom, G., Horan, B., Berry, D.P., Roche, J.R., 2015. Factors associated with the financial performance of spring-calving, pasture-based dairy farms. *J. Dairy Sci.* 98, 3526–3540. <https://doi.org/10.3168/jds.2014-8516>.
- Shalloo, L., Dillon, P., Rath, M., Wallace, M., 2004. Description and validation of the moorepark dairy system model. *J. Dairy Sci.* 1945–1959. [https://doi.org/10.3168/jds.S0022-0302\(04\)73353-6](https://doi.org/10.3168/jds.S0022-0302(04)73353-6).
- Stroustrup, B., 2000. *The C++ Programming Language, 3rd ed.* Addison-Wesley Longman Publishing Co.
- Teagasc, 2016. *Dairy Manual*.
- Tratalos, J.A., Graham, D.A., More, S.J., 2017. Patterns of calving and young stock movement in Ireland and their implications for BVD serosurveillance. *Prev. Vet. Med.* 142, 30–38. <https://doi.org/10.1016/J.PREVETMED.2017.04.005>.
- Wickham, H., 2016. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag, New York.
- Windsor, P.A., Whittington, R.J., 2010. Evidence for age susceptibility of cattle to Johne's disease. *Vet. J.* 184, 37–44. <https://doi.org/10.1016/j.tvjl.2009.01.007>.