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Rewiring cattle trade movements helps to control bovine paratuberculosis at a regional scale

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Abstract

Paratuberculosis is a worldwide disease mainly introduced through trade. Due to the low sensitivity of diagnostic tests, it is difficult to protect herds from purchasing infected animals. Our objective was to assess if rewiring trade networks to promote risk-based movements could reduce the spread of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) between dairy cattle herds at a regional scale. Two levels of control strategies were assessed. At the between-herd scale, trade rewiring aimed to prevent animals from high-risk herds moving into low-risk herds. At the within-herd scale, complementary additional measures were considered based on the herd infection status, aiming to limit the within-herd spread by reducing calf exposure to adult faeces and culling more rapidly after positive test results. We used a stochastic individual-based and between-herd mechanistic epidemiological model adapted to the 12,857 dairy cattle herds located in Brittany, western France. We compared the regional spread of MAP using observed trade movements against a rewiring algorithm rendering trade movements risk-based. All females over two years old were tested. Based on the results, and taking into account the low test sensitivity, herds were annually assigned one of three statuses: A if the estimated true prevalence was below 7%, B if it ranged from 7 to

21%, C otherwise. We also identified herds with a high probability of being MAP-free (AAA herds that had obtained an A status over three consecutive years) to assess the effect of decreasing their risk of purchasing infected animals on MAP regional spread. We showed that movement rewiring to prevent the sale of animals from high to low-prevalence herds reduces MAP regional spread. Targeting AAA herds made it possible to minimize the control effort to decrease MAP regional spread. However, animals purchased by AAA herds should have a moderate to high probability of being MAP-free, especially if the risk of purchasing animals from herds of unknown status cannot be managed. Improved hygiene and early culling of positive animals were relevant complementary on-farm control options to further decrease MAP spread. Future studies should identify how to define herd statuses to target optimal control measure combinations that could reduce the spread of MAP on a regional scale most effectively.

Keywords (6 max)

Johne’s disease, stochastic model, epidemiology, dairy cattle, network, control strategy

Introduction

Paratuberculosis is a worldwide endemic disease mainly introduced through trade (Barkema et al., 2018; McAloon et al., 2019). Movements of cattle among dairy herds maintain the regional circulation of *Mycobacterium avium* subsp. *paratuberculosis* (MAP), the pathogen which causes this disease (Beaunée et al., 2015). Once introduced into a herd, MAP also has a high probability of persisting over several years (Marcé et al., 2011), resulting in infected herds experiencing milk losses, early culling of animals, and increased mortality (Garcia & Shalloo, 2015).

The spread of MAP is hard to control in regions where the disease has become endemic (Beaunée et al., 2017). Indeed, detecting MAP-infected animals is difficult due to the low sensitivity of diagnostic tests (Barkema et al., 2018). The sensitivity of ELISA tests classically performed in serum varies from 0.15 for young or latently infected animals to over 0.70 for heavy shedders (Nielsen & Toft, 2008). Animals typically become infected at an early age (Windsor & Whittington, 2010). The infection often remains subclinical and undetectable for several years (Magombedze et al., 2013) before the animals eventually develop clinical signs (Mitchell et al., 2015). Shedding starts early and is intermittent, varying in levels between animals and over the lifetime of an infected animal. Given the poor sensitivity of diagnostic tests and the subclinical nature of the disease, it can be challenging to identify positive animals as part of test-and-cull programmes to reduce within-herd spread or pre-purchase testing measures to reduce between-herd spread (Camanes et al., 2018; More et al., 2015).

An alternative strategy to protect MAP-free herds and herds with a low prevalence is to promote risk-based trade movements (Gates et al., 2013; Gates & Woolhouse, 2015; Hidano et al., 2016). With such a strategy, animals from herds with a high-risk infection status, as determined by factors such as their testing history, geographical location, and movement patterns, should not be sold to herds with a low-risk infection status.

However, such a strategy can be undermined by how herd statuses are defined. If animals are not tested frequently, the herd status might not reflect the current within-herd prevalence. In Brittany, most herds are typically tested once a year, but even this may not accurately reflect the true herd status due to poor test sensitivity. Implementing additional within-herd control measures such as improving calf hygiene to reduce calf exposure to faeces from adult cows and culling test-positive cows as soon as possible after detection also may help to reduce the within-herd prevalence of disease, and therefore the risk of selling infected cattle. This also could help farmers to improve the health status of their herds, thus increasing their opportunities to sell their animals.

Our objective was to assess whether rewiring trade movements to be risk-based could reduce the spread of MAP between dairy cattle herds at a regional scale despite a low sensitivity and frequency of testing. Based on herd infection statuses, complementary additional measures were considered that aimed at either reducing calf exposure to adult faeces or shortening the delay before culling part of the test-positive animals.

Material and methods

We combined a regional epidemiological model of MAP spread between dairy cattle herds with a trade movement rewiring algorithm to manipulate observed trade movements between herds and render them risk-based. Animal movements and herd demography are derived from observed data in Brittany, western France. The model is stochastic, individual-based, and in discrete time, with a time-step of one week. The code is available under the Apache 2.0 license (Sup. Mat. §5). This model was used to compare the regional spread of MAP when using observed trade movements versus a rewiring algorithm rendering trade movements risk-based. We identified herds that had a very high probability of being MAP-free (i.e., with a very low-risk status). We assessed the extent to which decreasing the risk of these herds purchasing infected animals had an impact on the regional spread of MAP. Finally, we combined this risk-based trade with complementary within-herd control measures focusing on calves and test-positive animals to assess whether reducing the within-herd prevalence of MAP infected animals in high-risk herds further reduces between-herd spread.

Cattle demographic and movements

We used data from Brittany (western France) from 2005 to 2013. This area is characterized by a high density of dairy cattle (85% of cows are dairy cows). We focused on farms with over 15 dairy breeding females, assumed to be professional dairy farms. French dairy herds are mainly composed of females since breeding is based on artificial insemination instead of bulls. Thus, we considered only dairy or crossed-bred females, neglecting fattening activities often conducted in a different area of the farm. As a result, we selected 12,857 dairy cattle herds and 919,304 trade movements.

We calculated herd size and demographic parameters (calf mortality, culling rate per age group and per parity for cows, and births) using the comprehensive French database of cattle detention and trade movements (Table S3). This database records the life history of all dairy cattle from birth to death, including trade movements between farms. Each animal is defined by a unique ID number, breed, date and farm of birth, sex, and all the farms it has belonged to over its life, as well as the cause and date of entry into each farm (birth, purchase), and the cause and date of exit from each farm (death, sale). Herd size was calibrated to 1 January 2005. Births were calculated per week per herd. Other demographic parameters were calibrated for each herd-year.

We also used these data to build the trade network, in which nodes are farms and links are trade relationships. This network is directed (trade is not symmetric), weighted (the number of animals exchanged varies among pairs of farms) and time-varying (animal transactions occur at specific times). Fifty-four percent of the animals purchased come from outside the selected metapopulation (named external purchases hereafter).

Within-herd epidemiological model

At the within-herd scale, the epidemiological model is a stochastic discrete-time individual-based model of MAP spread in a structured dairy cattle herd with year-long calving. This model is fully described in Camanes et al. (2018). In brief, animals are defined by their age (in weeks), health status, parity (for cows), and possible test results (see section on herd statuses). Animals can be of six mutually exclusive age groups: newborns, unweaned calves, weaned calves, young heifers, bred heifers, and cows, each of these groups being reared in a specific environment of the farm. Animals change groups at a certain age or time of year. Animals also are defined by their age or parity for cows, as well as by their health status: 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). Susceptibility decreases exponentially with age, and the rare infection events that may occur after one year of age are neglected. Shedders belong to health statuses I_T, I_M, and I_H. Shedding during the latent phase can barely be detected and thus is neglected. Shedders can shed MAP in colostrum/milk (if they have calved) and in faeces. The quantity of MAP shed is heterogeneous and depends on the animal's health status. Five transmission routes are considered: *in utero*, via ingestion of contaminated colostrum, via ingestion of contaminated milk, via an indirect contact with the local environment where susceptible animals are raised and where infected animals of the same age group shed MAP, and finally via an indirect contact with the farm environment whose level of contamination is influenced by all shedders of the herd. MAP survives in the environment and thus indirect transmission is due to infected animals held in the same farm but not necessarily at the same time. Transmission from the farm environment is only considered indoors. Its probability is lower than the transmission due to the local environment. During the pasture season (from April to mid-November), animals older than six months of age are raised outdoors. They are only exposed to MAP shed by infected animals from their own age group. We assumed farmers manage calf hygiene so that - if the herd is infected – the true prevalence in adult females remains below 60%, as mostly observed in the field. Since male calves are sold within a few weeks after birth, they are not considered in the model. More details on the model and parameter values are provided in Sup. Mat. §1.

Between-herd epidemiological model

We applied the epidemiological model to the population and infection dynamics in each of the 12,857 herds selected in the data. Trade movements connect herds in a data-driven manner. When an animal is sold in the observed database, an animal in the same age group is picked at random in the selling herd and sent to the purchasing herd. Hence, only the infection status of the traded animal is random, but the date and type of movement are data-driven. External purchases also can be a source of MAP. We considered that these movements are associated with a similar risk as movements occurring among herds of the modelled metapopulation, assuming the modelled metapopulation belongs to a larger production area implementing similar control options. To do so, we considered that the probability of purchasing an infected animal from outside equals the average proportion in the modelled metapopulation of infected animals in the age group of the purchased animal. In a few cases, the simulated selling herd did not contain animals of the same age as observed in the database of real trade movements. We then selected an animal in the closest age group. If this was not possible, we assumed that the movement came from outside the modelled metapopulation.

Trade movement rewiring algorithm accounting for MAP herd statuses

The trade movement rewiring algorithm accounts for MAP herd statuses for connecting herds through trade, and modifies some of the observed movements. Herds can purchase animals only from herds of similar or lower risk infection statuses (e.g., with three statuses: Fig. 1, but the algorithm can work with a greater or smaller number of statuses). To do so, we first listed movements occurring over a 7-day time window (the model time step) in a given age group: less than 10 weeks, 11-26, 27-52, 53-91, 92-101, 102-111, 112-121, 122-130, and then per parity. We neglected the fact that batches of animals can be traded between two herds at a given date, as more than 85% of the weekly trade movements concerned only one or two animals. Comparing the observed and simulated distributions of the in and out-degree of the trade network showed that the impact of this simplification was low (Sup. Mat. §2, Fig. S1). In Brittany, dairy animals are mostly Holsteins, thus breed was not considered. Second, we distributed these movements according to the infection statuses of the selling and of the purchasing herds. Third, we identified high-risk movements (i.e., those from high-risk to low-risk herds). We switched them as much as possible with a relevant alternative. Unused low-risk movements were performed as observed. Fourth, for high-risk movements that cannot be switched (i.e., no relevant alternative available), the sold animal is culled and another animal is purchased from outside the modelled metapopulation with the same risk of being infected as in other movements coming from outside in the observed database. We assumed that movements coming from outside (external purchases) also are controlled. Thus, the probability of purchasing an infected animal from outside equals the average proportion of infected animals in the age group of the purchased animal in herds of similar or better infection statuses than the purchasing herd.

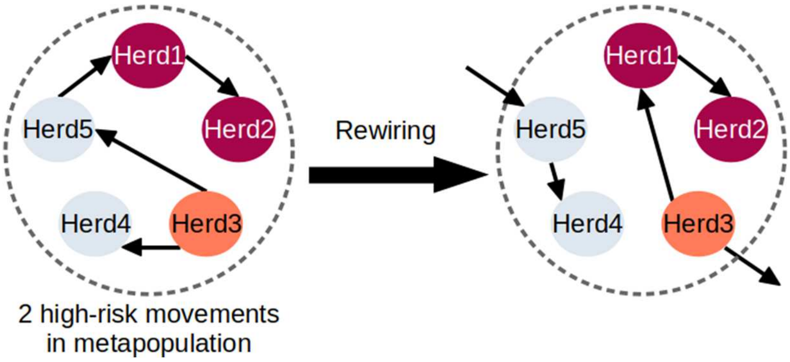


Figure 1. Principle of the rewiring algorithm (light grey: low-risk herd, orange: moderate-risk herd, scarlet: high-risk herd, arrows: trade movements). Movements from Herd3 to

Herd4 and Herd5 are high-risk movements and thus are modified by the algorithm, creating a new movement from Herd3 to Herd1, a purchase from outside the modelled metapopulation by Herd5, and a sale to outside by Herd3.

Definition of herd statuses in Brittany

In the model applied to Brittany, herd statuses were defined according to the capacity of diagnostic tests to detect infected herds. Herds with a true prevalence (proportion of infected animals among females older than 2 years) below 7% are in group A (can barely be detected as infected), herds with a true prevalence between 7 and 21% are in group B, and herds with a true prevalence above 21% are in group C (often have already had at least one animal detected as highly positive). These thresholds were chosen in agreement with field observations made by animal health services in Brittany. The chosen cut-offs enable the population of herds to be divided into three groups of operational size, compatible with trade organisation. In addition, unpublished preliminary work showed a good correlation between tests results (combination of ELISA on bulk tank milk and tests of two environmental samplings) and herd statuses. Herds with three negative tests had an apparent prevalence lower than 3.5%, while those with three positive tests had an apparent prevalence higher than 10.5%. The associated true prevalence was estimated as twice as high as the apparent one due to the sensitivity of the combined tests, leading to the chosen cut-offs.

To mimic a best-case situation, the herd statuses were based on the true and instantaneous prevalence at the time of trade, and used to modulate movements. To mimic a more realistic situation, herd statuses were defined once a year based on their apparent prevalence. A serum antibody ELISA test was performed on each female older than 2 years. Test specificity was assumed perfect. Test sensitivity varied among infection states: 0.15 for I_T and I_L, 0.47 for I_M, and 0.71 for I_H (Nielsen & Toft, 2008). The test was performed at a random date for each herd between January and April each year, i.e., before the grazing period. The same thresholds were used for herd statuses A, B, C as when defined based on true prevalence, but using the “estimated true prevalence”. We calculated the number of test-positive animals per health status, accounting for the status-specific test sensitivity. Then, we summed these numbers weighted by their associated test sensitivity, and we divided the result by the number of animals tested to have the estimated true prevalence. The misclassification rate was established in a “no control” scenario by comparing the apparent herd status defined once a year with the true herd status on the same date.

Finally, the number of trade movements to be rewired was expected to be considerable when accounting for herd statuses of all herds, potentially rendering risk-based trade unachievable in practice. We therefore focused on herds with three consecutive apparent low-risk annual statuses (herds labelled AAA) compared to all other herds. Managing only purchases and sales from AAA herds (other movements being kept as observed) was expected to be a good compromise between a high probability for herds to be MAP-free and the number of herds concerned to be sufficient so that AAA-related trade can be reorganised (enough relevant alternative movements). We assessed the impact of erroneously purchasing infected animals in AAA herds due to uncertainty about the status of selling herds. For that, we decreased this risk in the model by artificially assigning cattle that were purchased by AAA herds a set probability p of being MAP-free (5 cases: 0, 0.25, 0.5, 0.75, 1). This means that, in addition to preferentially purchase animals from AAA herds, each animal purchased by AAA herds is for sure not infected with probability p, and is picked at random among animals of the relevant age group in the AAA source herd attributed by the rewiring algorithm with probability $1-p$. In practice, this corresponds to implementing systematic tests before selling (sellers’ awareness raising) or purchasing (buyers’ awareness raising) an animal, and then combining this individual information with the knowledge of the status of the source herd to provide to the animal a guarantee of not being infected in the form of a negative predictive value. Movements among other herds are not modified, thus focusing the management effort at a regional scale on much fewer herds. To also consider the case where such a AAA herd status is not defined outside the modelled metapopulation, we compared two situations for AAA external purchases: one in which these external incoming movements are managed (same risk as if they were internal movements between AAA herds), and one in which they are not (same risk as on average in the metapopulation).

To assess how well the industry might already be doing in controlling movements from high-risk to low-risk farms, we compared the matrix distributing movements according the statuses of selling and purchasing herds in the "no control" scenario to the one in the scenarios using the rewiring algorithm (apparent A/B/C and apparent AAA/others). We could not account here for external purchases, as the status of the selling herd was unknown (not modelled). Thus, we looked only at internal movements, i.e., between modelled herds.

Complementary within-herd control measures

In addition, we combined the risk-based trade scenarios defining herd statuses using apparent prevalence with two complementary control measures: improved calf hygiene (ICH) and early culling (EC) part of the detected animals (Fig. 2).

First, calf hygiene was improved in herds of a given status (A, B, C, or AAA) when herds first reached the concerned infection status. For that, we modified the model parameter governing calf exposure to farm environment from its initial value ($e = 0.35$, Table S1) to 0.1. This mimics an incentive by collective animal health managers (such as regional animal health services) to improve calf hygiene in targeted herds (those with a low-risk status, or on the contrary those already encountering MAP issues) to help them control MAP spread locally. Introducing such a measure in A herds is counterintuitive. It accounts for the fact that some herds with an A status are indeed infected. Improving calf hygiene largely reduces the risk that these herds lose their A status if infected, increasing the probability of spontaneous fade-out of the infection.

Second, individual test results obtained once a year in each herd were associated with an early culling of part of the test-positive animals (within one month on average after the test result). Early culling was done irrespective of the herd status. We assumed that 10, 25, or 50% of detected I_M and I_H animals were randomly chosen to be culled early.

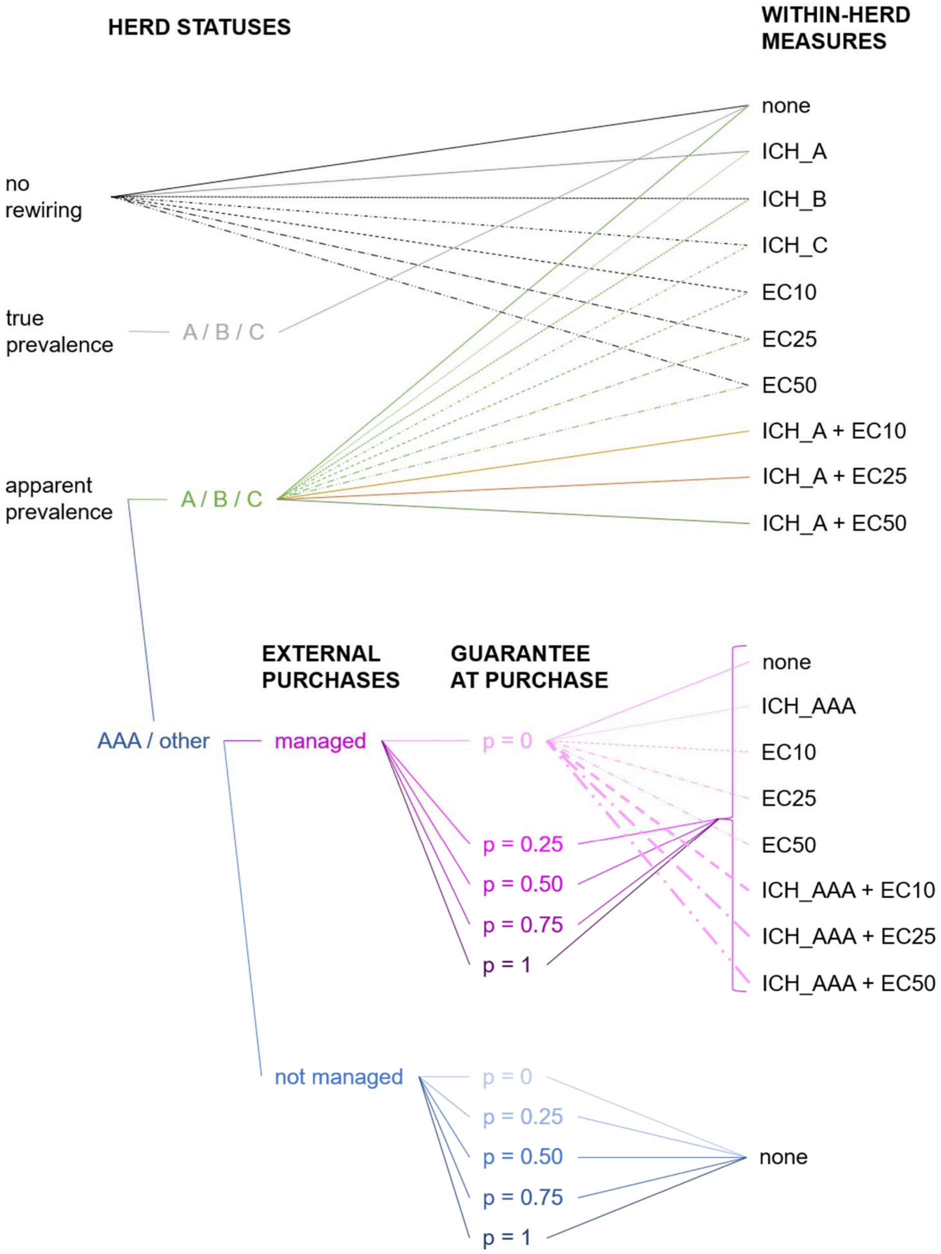


Figure 2. Scenario tree. Trade movement rewiring (using true or apparent prevalence and based on either A/B/C or AAA/other herd statuses) was combined with within-herd control measures (ICH_X: improved calf hygiene in herds of status X; ECn: early culling of a proportion *n* of detected shedders). For AAA herd status, we considered several cases: with or without managing external purchases, and an increasing probability *p* that purchased animals are MAP-free. The colour legend is the same as in the result figures.

We combined all of these scenarios and also assessed the effect of improved calf hygiene or/and early culling in scenarios without movement rewiring. We ended with 63 scenarios (Fig. 2): 1 dealing with A/B/C herd statuses based on true and instantaneous prevalence, 10 with A/B/C/ herd statuses based on apparent prevalence, 40 with AAA/other statuses where external purchases are managed, 5 with AAA/other statuses where external purchases are not managed, 6 with no rewiring but with within-herd control measures, and finally 1 without any control measures.

Model settings, initial conditions and model outputs

Animal health services consider that roughly 40%, 40% and 20% of the herds in Brittany are in statuses A, B, and C, respectively. To account for the heterogeneous probability for herds to be in one status or another, the initial conditions were defined in three steps. First, we randomly distributed herds in statuses to have 40% of herds in A, 40% in B, and 20% in C. Second, we simulated nine years of MAP spread, which provided the within-herd prevalence for each herd at the last time step. As a result, 33%, 43%, and 24% of the herds were in statuses A, B, and C, respectively, using the true prevalence to define the initial status. This new distribution is close to the initial one, but differs in that it better accounts for the infection probability of each herd. Third, as herd size can vary in nine years, we used within-herd simulations to associate each possible within-herd prevalence with a set of 100 realistic distributions of animals among health statuses and age groups, according to herd size. One distribution was drawn per simulated herd and kept similar among repetitions of the between-herd model. Herds were assigned into the AAA category after having obtained their third A status, including the initial one. This occurs before mid-year 2.

The model predicts over nine years (2005-2013), for each stochastic repetition and each scenario, the following: the proportion of infected herds in the metapopulation each week, the number of newly infected herds each week, the proportion of infected females older than 2 years per herd the first of January each year, and the number of herds per herd status each week if the true prevalence is used, once a year at a date between the 1st of January and the 30th of April (i.e., when the test is performed). In addition, we calculated the cumulative number of detected animals culled early, the cumulative number of herds improving calf hygiene, and the cumulative number of rewired purchases. These three indicators reflect the effort of control required for a given scenario. The model was developed in C++ Standard 11. We simulated 10 stochastic repetitions for each scenario.

Results

Regional MAP spread without control implementation

Starting from an endemic situation as observed in Brittany, 87% of the herds were consistently infected if no additional control measure was implemented (scenario “no control”, Fig. 3). New herds were regularly infected, indicating a regional circulation of MAP with fade-out / recolonization events (Fig. S2). Irrespective of the initial herd status, the proportion of infected females greater than two years of age progressively increased when no control was implemented (Fig. 4). Most of the herds nevertheless kept a within-herd prevalence lower than 60%, as observed in the area. In the observed trade network, there was no evidence that farmers were making trade decisions based on limiting MAP risk (Tab. 1), showing that the industry does not already control movements from high to low-risk farms with regards to paratuberculosis. Without risk-based trade, 26% of the purchases by AAA herds came from AAA herds, while AAA herds represented 33% of the herds on average.

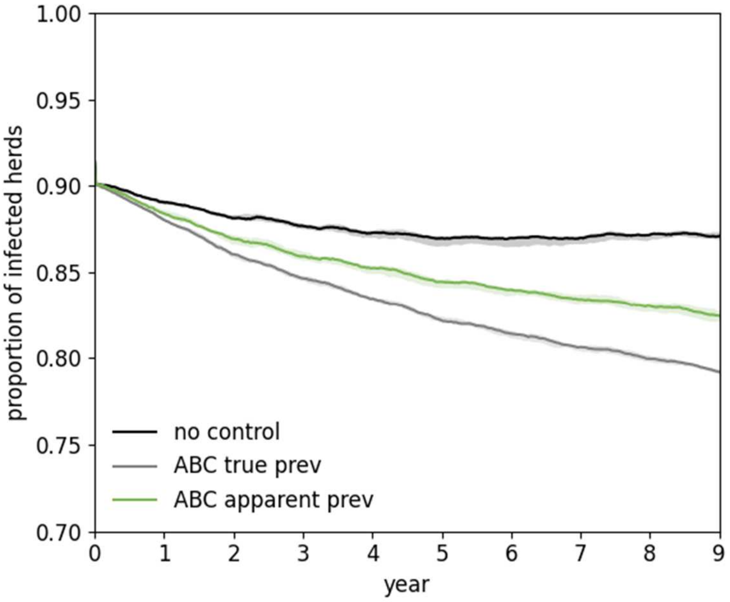


Figure 3. Proportion of MAP-infected herds in Brittany, western France, comparing a scenario without control measures and scenarios with risk-based movements based on A/B/C herd statuses. Herd statuses are defined based on the true and instantaneous prevalence at movement date (grey) or on the annual apparent prevalence (green) among females greater than 2 years of age. External purchases are managed. The distribution for 10 stochastic repetitions is shown.

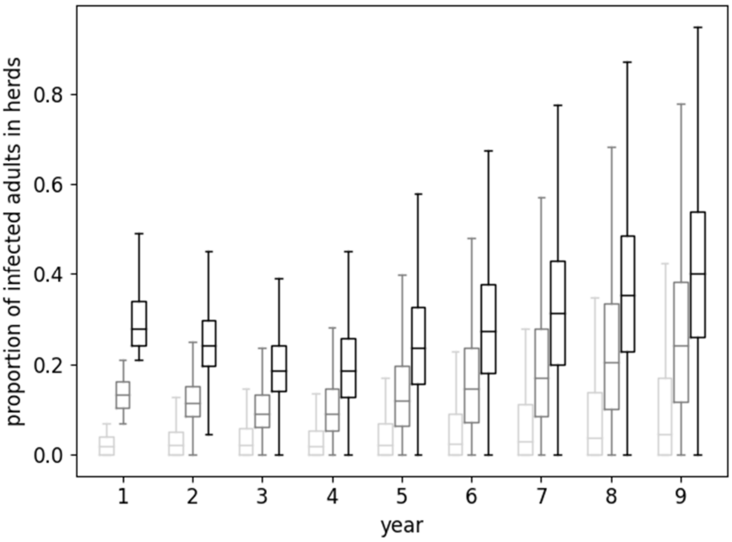


Figure 4. Annual distribution of the proportion of infected females greater than two years of age, the first of January of each year, according to the initial true prevalence in that age group when no control measure is implemented (light grey: initial herd status A (0-7% true prevalence), grey: initial herd status B (7-21%), black: initial herd status C (>21%)).

Table 1. Distribution of trade movements between pairs of herd statuses defined annually based on apparent prevalence in the no-control scenario. Herd statuses are either A/B/C or AAA/others, without crossing. "Others" thus represents all herds that are not AAA. Because of this definition of herd statuses, movements between AAA and A/B/C herds cannot be counted. For AAA/other herd statuses, movements in the first two years are not accounted for as statuses are not defined.

Purchasing herd Selling herd	AAA	Other	A	B	C
AAA	7 622	31 063			
Other	21 946				
A			32 487	26 021	24 387
B			22 300	19 447	18 585
C			22 069	20 359	25 667

Risk-based movements using A/B/C statuses decreased MAP regional spread

It should be noted that 63% of apparent A herds had a nil apparent prevalence. In this scenario, we assumed that all the movements could be controlled (Tab. S4). Table 2 highlights the misclassification of herds in apparent statuses due to the low test sensitivity. Among herds truly A, 91% were classified as such, and 71% of apparent A herds were truly A (Tab. 2).

Table 2. Misclassification among herd statuses. Comparison of the annual and apparent herd status with the status based on true prevalence at the same date, when no control measure is implemented. Herd statuses are compared for each herd-year-run.

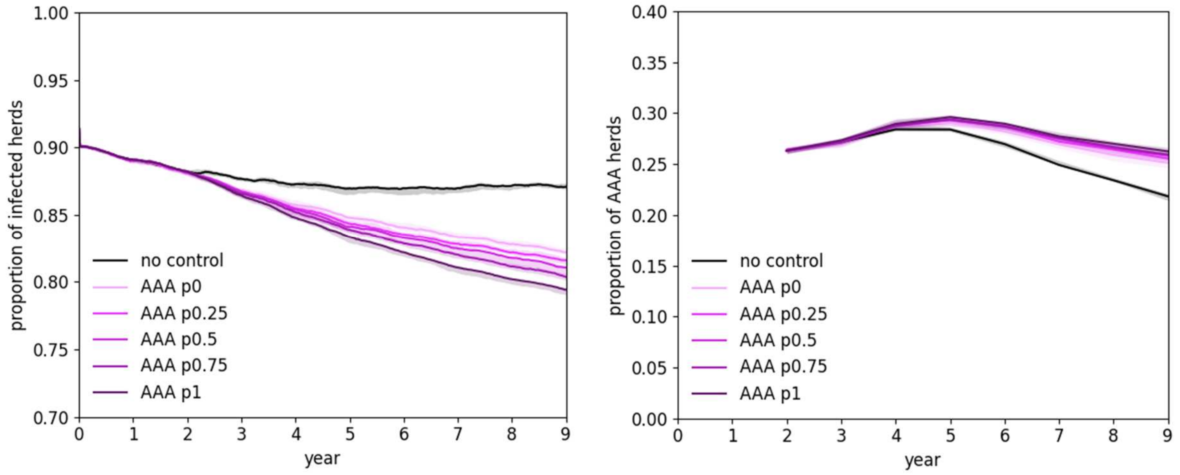
Apparent status True status	AAA	Other	A	B	C
AAA	192 823	31 629			
Other	41 916				
A			397 096	37 225	3 062
B			147 375	232 551	91 172
C			14 109	78 170	292 618

Trade movement rewiring to promote risk-based movements reduced MAP spread between dairy cattle herds at a regional scale when using A/B/C herd statuses. First, when herd statuses were defined based on the true and instantaneous prevalence the week the movement occurred (optimistic scenario, Fig. 3), herd prevalence decreased in nine years from 87% (no control) to 79%, and the cumulative herd incidence decreased from 1607 (no control) to 1052, i.e., a decrease of 35% (Fig. S2). Second, when herd statuses A/B/C were defined more realistically once a year based on apparent prevalence, the impact of rewiring decreased, with herd prevalence only decreasing from 87% (no control) to 82% in nine years (Fig. 3), and a cumulative herd incidence decrease of 17% (Fig. S2).

Risk-based movements using AAA/other statuses enable a focus on much fewer herds

Here, herd statuses were defined yearly on apparent prevalence but using three consecutive low-risk statuses (AAA vs. not AAA). It should be noted that 74% of AAA herds had a nil apparent prevalence. Among herds truly AAA, 86% were classified as such, and 82% of apparent AAA herds were truly AAA at status definition (Tab. 2).

When no MAP-free guarantee was provided to animals purchased by AAA herds (p=0, Fig. 5a), risk-based movements induced a similar decrease in herd prevalence (82%) compared to the scenario based on A/B/C herd statuses defined using apparent prevalence once a year (Fig. 3). However, it resulted in a higher decrease in herd incidence (of 36%, Fig. S3), a level comparable to the one obtained in the scenario based on true and instantaneous prevalence, thus counter-balancing the low test sensitivity. Results were further improved by increasing the probability for AAA herds to be sure not to purchase infected animals (parameter p). With this probability at 0.5 (one purchase over two is guaranteed, the other being chosen from a AAA herd with no further guarantee), herd prevalence after nine years was 81% while herd incidence decreased by 47% compared to the "no control" scenario. Herd incidence was halved if animals purchased by AAA herds were fully guaranteed as not infected (p=1), compared to when they were not (p=0, Fig. S3). This is a noticeable result, especially because AAA herds represent a moderate fraction (from 22 to 43%) of the herds in the modelled metapopulation (Fig. 5b). In this scenario, we assumed that all the movements could be controlled (Tab. S4).



(a) (b)

Figure 5. Proportion of MAP-infected herds (a) and of AAA herds (b) in Brittany, western France. The "no control" scenario is compared to five scenarios with risk-based movements based on AAA/other herd statuses, where the probability (*p*) that AAA herds purchased disease-free animals varies (0, 0.25, 0.5, 0.75, 1). Status AAA is given to herds having three successive annual A statuses based on apparent prevalence among females older than two years of age. External purchases are managed. The distribution for 10 stochastic repetitions is shown.

In the situation where external purchases by AAA herds could not be managed, the impact of movement rewiring was much lower, except when a perfect MAP-free guarantee could be provided to animals purchased by AAA herds (Fig. 6). Using the algorithm, 83% of the internal purchases by AAA herds came from AAA herds (Tab. 3), compared to 26% without the algorithm (Tab. 1), highlighting the performance of the algorithm in reducing at-risk movements also in this scenario.

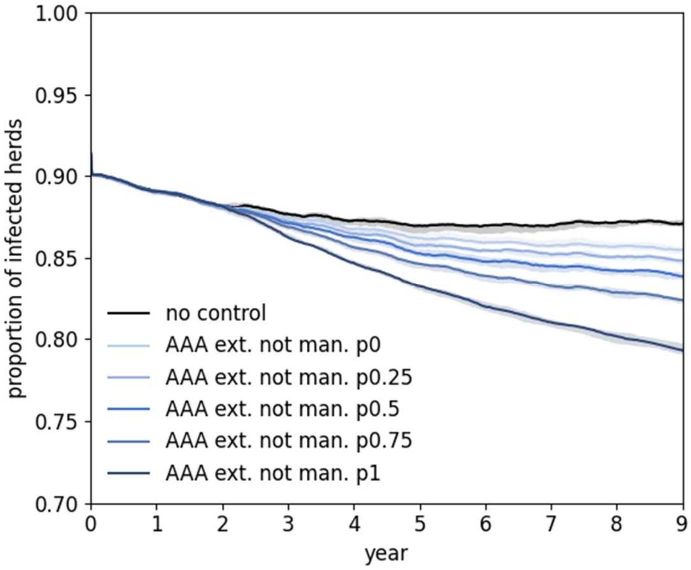


Figure 6. Proportion of MAP-infected herds in Brittany, western France, when movement control focuses on AAA herds but when external purchases are not managed. The scenario with no movement control (black) is compared to five scenarios where the probability (*p*) that AAA herds purchased disease-free animals varies (0, 0.25, 0.5, 0.75, 1). Status AAA is given to herds having three successive annual A statuses based on apparent prevalence among females over two years of age. The distribution for 10 stochastic repetitions is shown.

Table 3. Distribution of trade movements between pairs of herd statuses. Herd statuses are defined annually based on apparent prevalence in the AAA risk-based movement scenario (*p*=0), and external purchases are not managed.

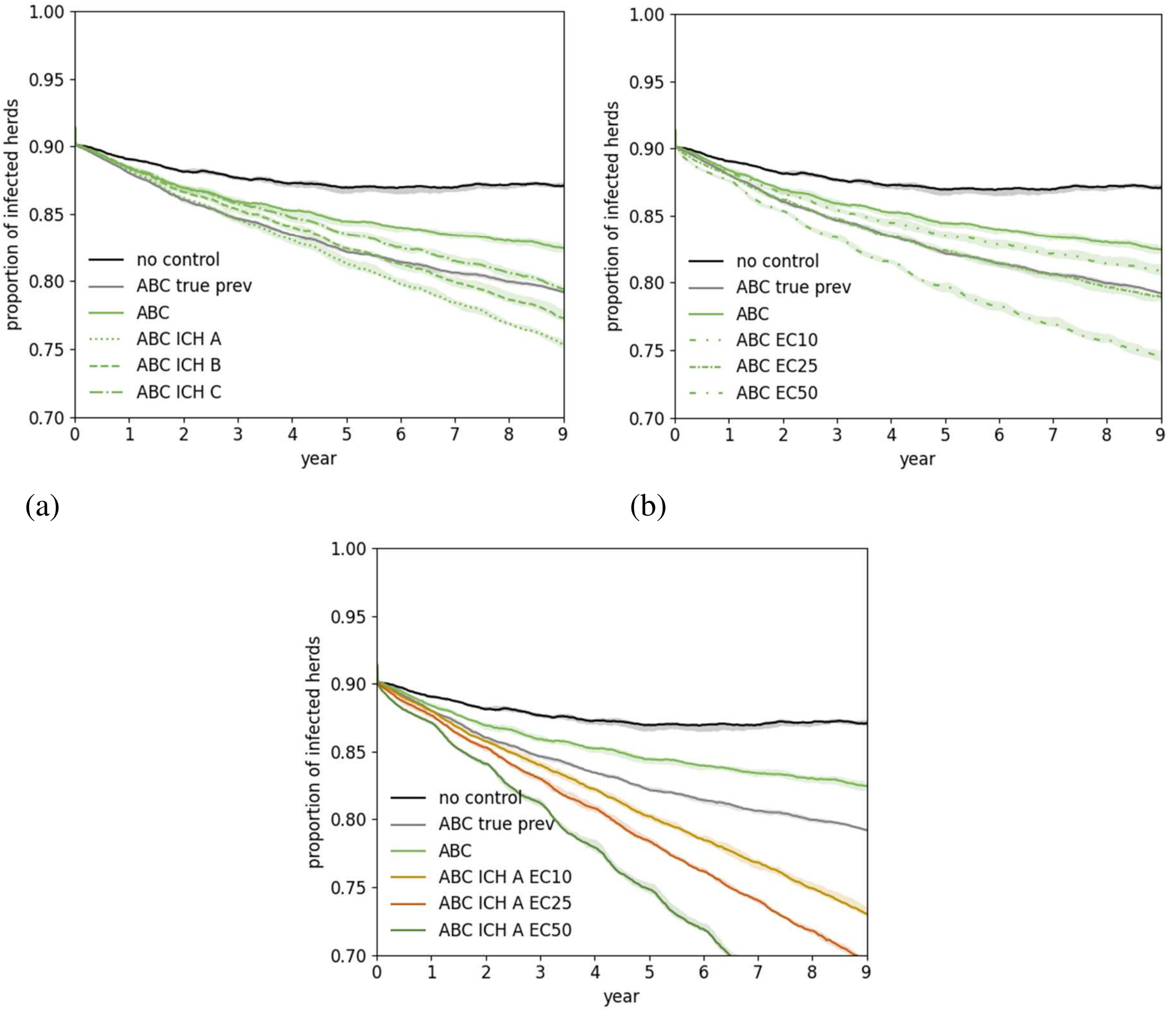
Purchasing herd Selling herd	AAA	Other
AAA	26 270	13 624
Other	5 388	124 451

Complementary on-farm control measures to enhance the effect of risk-based movements

The effect of movement rewiring was quite limited alone, but herd prevalence sharply decreased further when within-herd control measures also were implemented (Fig. 7-8, Fig. S2, S3, S5). The effect of movement rewiring and of within-herd measures was mostly additive (scenarios where within-herd control measures are applied alone are shown in Fig. S4 and S6).

Combining risk-based movements using A/B/C herd statuses with improved calf hygiene further reduced herd prevalence (Fig. 7a) but slightly increased herd incidence (Fig. S2). The main consequence was to stabilize the proportion of herds in status A. The proportion of herds classified as status A after nine years increased from 31-35% to 48-55% when calf hygiene was improved. The best option was to improve calf hygiene in herd status A, which stabilized the proportion of herds in status A after five years of control at 55% of the herds, while reaching the lower herd prevalence after nine years of control (75%). Targeting AAA herds was even better, as long as external purchases also were managed (Fig. 8a).

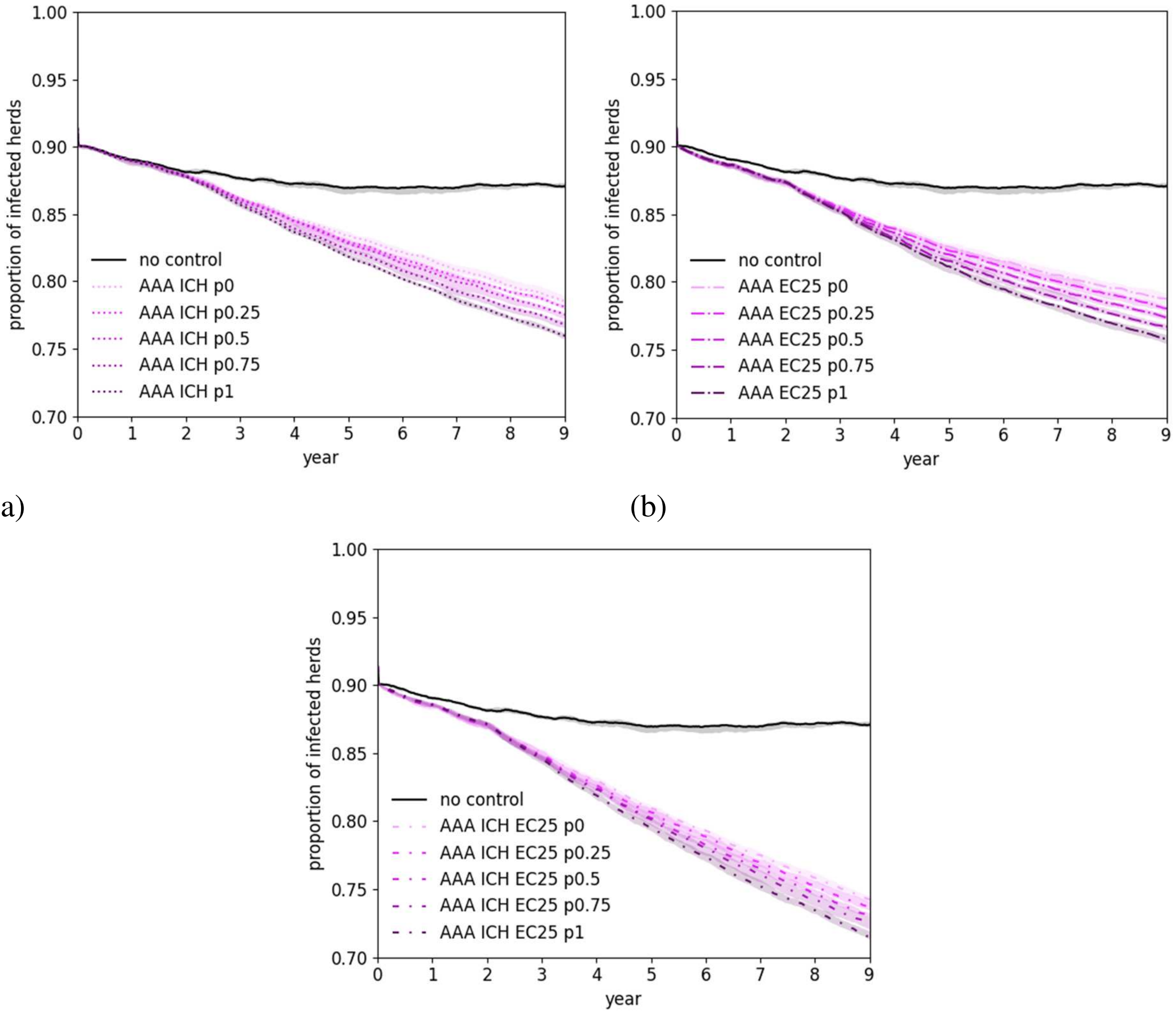
Combining risk-based movements using apparent A/B/C statuses with the early culling of part of the test-positive animals also improved herd prevalence (Fig. 7b), especially when half of the detected animals can be culled. When using AAA/other herd statuses, early culling 25% of test-positive animals gave comparable results to improving calf hygiene (Fig. 8a,b).



(a) (b)

(c)

Figure 7. Proportion of MAP-infected herds in Brittany, western France, according to the rewiring scenario, when using A/B/C herd statuses. The scenario without control is compared to scenarios with risk-based movements. External purchases are managed. MAP herd statuses are defined based on the true and instantaneous prevalence at movement date (grey) or on the annual apparent prevalence (coloured lines) among females over two years of age. Black, grey and light green solid lines are similar among panels to ease comparison. “ICH X” denotes improved calf hygiene in herds of status X. ECn denotes early culling n% of test-positive animals. The distribution for 10 stochastic repetitions is shown.



(a) (b)

(c)

Figure 8. Proportion of MAP-infected herds in Brittany, western France, according to the rewiring scenario, when using AAA/other herd statuses. The scenario without control (black, same among panels) is compared to five scenarios where the probability (*p*) that AAA herds purchased disease-free animals varies (0, 0.25, 0.5, 0.75, 1). Status AAA is given to herds having three successive annual A statuses based on apparent prevalence among females over two years of age. External purchases are managed. "ICH" denotes improved calf hygiene in AAA herds. ECn denotes early culling n% of test-positive animals. The distribution for 10 stochastic repetitions is shown.

Result synthesis

Combining all of the measures tested appeared to be the best way to improve the regional situation without needing to perfectly ensure that animals purchased by low-risk herds are MAP-free (Fig. 9). Focusing on AAA herds clearly reduced the number of movements to be managed (~10% of the movements were concerned) compared to scenarios involving A/B/C herd statuses (~40% of the movements were concerned), without impairing the decrease in herd prevalence. Managing external purchases by AAA herds was particularly valuable when only a poor guarantee could be provided for purchased animals, and did not significantly increase the number of movements to be managed. Improving calf hygiene in low-risk herds enhanced the decrease in herd prevalence for all scenarios considered. Even though tests were performed on an annual basis, the early culling of some test-positive animals also was useful as long as a sufficient proportion of test-positive animals could be culled (Fig. 9).

Several scenarios enabled a decrease in MAP herd prevalence to a similar extent (Fig. 9). The effort required to decrease herd prevalence from 87% in the no control scenario down to a lower value in nine years depended on herd status definition. For example, to decrease down to ~75% of herd prevalence using A/B/C apparent herd statuses, movement rewiring had to be combined with improved calf hygiene (ICH) in A herds or with the early culling (EC) of half the test-positive animals. To enable a similar decrease in herd prevalence while using AAA/other herd statuses, the number of movements to be rewired is divided by four. When managing external purchases in AAA herds, five scenarios gave close results, all combining movement rewiring with at least one additional measure (ensuring a proportion p of purchased animals by AAA herds are MAP-free, ICH or EC) implemented at various levels:

- p=0 + EC 50% of test-positive animals (no ICH);
- p=0 + ICH + EC 25% of test-positive animals;
- p=50% + ICH + EC of 10% of test-positive animals;

- *p*=100% + ICH (no EC);
- *p*=100% + EC 25% of test-positive animals (no ICH).

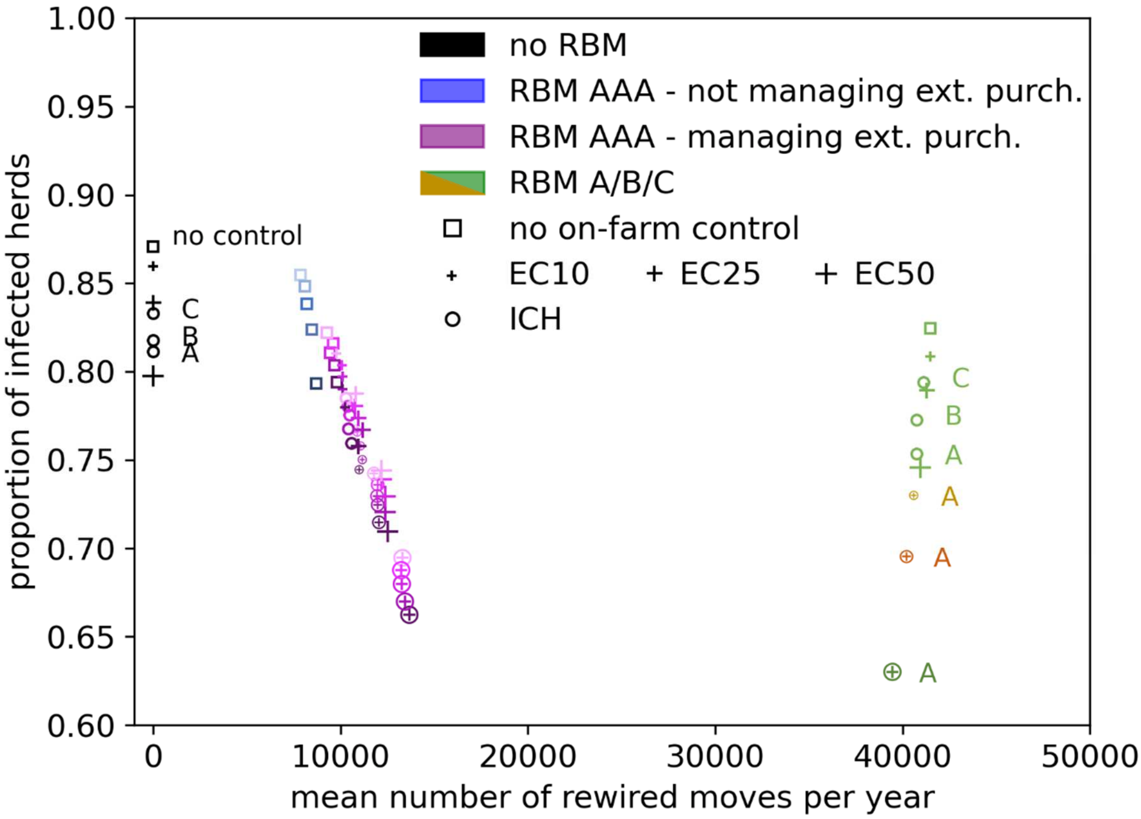


Figure 9. Control effort in terms of number of purchases to be rewired annually to decrease herd prevalence. Each symbol shows the x and y medians for one of the 62 scenarios (the scenario A/B/C based on true prevalence is not shown). Different colours are used to distinguished scenarios (same as in Fig. 2). Black: no movement rewiring; green/brown: A/B/C statuses based on apparent herd prevalence (the letter indicates which herd status is targeted for ICH), purple: AAA status with managing external purchases; blue: AAA status without managing external purchases. Colour intensity corresponds to variations in the probability that AAA herds purchased disease-free animals (from lighter *p*=0 to darker *p*=1). Shapes differ according to the within-herd measures: coloured square: only movement rewiring; dot: improved calf hygiene (ICH); cross: early culling (EC) of a proportion (10, 25

or 50%) of test-positive animals, shape size increasing with the proportion. Cross in dot indicates both within-herd measures are implemented.

Discussion

Manipulating trade movements to promote risk-based movements from dairy cattle herds of similar or better MAP statuses compared to destination herds is predicted to reduce the proportion of infected herds and the number of newly infected herds over a nine-year period. Such a control strategy has never been assessed before to decrease the spread of MAP at a regional scale. Risk-based movements are found to impact herd prevalence and incidence even when herd statuses are defined using the apparent prevalence, as determined by a herd-level serum ELISA performed yearly on cows over two years of age.

It is important to account for the variation in test sensitivity among animal health statuses (Nielsen & Toft, 2008) and to test all females over two years of age to define herd statuses in the model. Indeed, in a preliminary work (Ezanno et al., 2021), an average test sensitivity (0.20) was assumed and females 2.5 years old and over were tested. In this preliminary study, the impact of risk-based movements on MAP regional spread was smaller, while the average test sensitivity was the same. Indeed, herds with high shedders (I_M and I_H compared to I_L which do not shed) were not better identified than herds with I_L only. In addition, younger infected animals were missed.

Our modelling approach could help in the future to assess different testing schemes to define MAP herd statuses and mobilize these statuses in trade management at a large scale. Testing cows yearly using serum ELISA is frequently done in national and regional paratuberculosis control programmes (Whittington et al., 2019), and thus was retained for the present study. Together with milk ELISA and pooled faecal testing, serum ELISA was found to be one of the most cost-effective options (Sergeant et al., 2018). Combining individual ELISA results to classify herds as high and low risk based on the prevalence of infected animals with other parallel testing options, such as faecal testing and bulk milk testing, could reduce misclassifications due to poor test sensitivity (Sergeant et al., 2018). These testing options have different sensitivities from serum ELISA. Tests also can be conducted more frequently to make herd statuses more accurate.

Focusing on herds with a high probability to be MAP-free (AAA herds in our study) permitted a smaller proportion of herds to be targeted while reaching comparable results, as long as animals purchased from outside the modelled metapopulation (external purchases) also were managed. The practical implementation of trade rewiring would be eased as AAA herds represent around a third of the herds in Brittany and 13-20% of the purchases according to scenarios. Ensuring that at least half of the animals purchased by AAA herds are not infected should help reduce the regional herd prevalence and the number of newly infected herds. However, such a guarantee at purchase is difficult to achieve (Whittington et al., 2019). Further analyses are required to estimate more precisely the distribution of the risk of selling infected animals per herd status and to identify the largest population of herds that could be a source of animals for AAA herds.

Calf hygiene and management are known to impact MAP persistence in newly infected herds (Lu et al., 2010; Marcé et al., 2011; Konboon et al., 2018) and to be crucial control levers (Donat et al., 2016; Beaver et al., 2019; McAloon et al., 2019). Such measures also can target highly infected herds to decrease their prevalence, and thus the risk of spreading MAP to other herds (Whittington et al., 2019). However, there are many options to improve calf hygiene, and their choice may vary over time at the farm level (Nielsen and Toft, 2011), as well as between farms according to their characteristics (Donat et al., 2016). This is difficult to represent in epidemiological models. Some available options also cannot be easily implemented in the field in a large number of herds (Robinson et al., 2020). For example, improving calf hygiene often requires changing farming practices. While this has been highlighted as an important way to control MAP in infected herds (Doré et al., 2012, Camanes et al., 2018), it is sometimes considered too costly to be used in practice (Sorge et al., 2010).

Here, we assumed calf hygiene in all of the herds of the metapopulation was sufficient to prevent excessive within-herd prevalence. Indeed, only a few herds with a true prevalence higher than 60% are observed in the field. However, in the absence of quantitative data, calf hygiene was assumed similar among herds (similar exposure of calves to the farm environment possibly contaminated by shedding animals from other age-groups). Accounting for a variability in calf hygiene in epidemiological models at a large scale could impact model predictions. More data are needed to better characterize the variability of calf hygiene among farms and to quantify the associated calf exposure to contaminated environments of the farm.

Combining risk-based movement with on-farm improved calf hygiene in part of the herds in order to reduce calf exposure to MAP shed by other age-groups in these herds largely reduced herd prevalence and incidence, irrespective of the herd status targeted. In the model, this parameter directly impacts the within-herd transmission function in targeted herds. However, the control effort required to improve calf hygiene from moderate to high is unknown. More observational data would be useful to gain knowledge about what can be done on farms to improve hygiene, and to quantify its effectiveness in reducing MAP spread and the associated cost.

Early culling test-positive animals also could be an option. Focusing only on the detected highest shedders has been shown to have a small impact on herd prevalence and incidence, especially because these animals are not very numerous and animal testing is performed only once a year for practical reasons (More et al., 2015). This result was in line with previous farm-scale studies, indicating that a test-and-cull performed on a yearly basis was not sufficient to impact MAP spread in a herd, especially in herds with poor hygiene (Lu et al., 2008, 2010; Robins et al., 2015; Konboon et al., 2018; Verteramo Chiu et al., 2018). In addition, only test-positive females are culled. Animals born to these females detected as positive also could be targeted by an early culling strategy, but this was previously shown as not having a high impact on within-herd prevalence (Camanes et al., 2018). On the other hand, we showed that early culling half of the detected animals irrespective of their shedding level had a large impact despite the yearly testing, but it could jeopardize herd productivity by sharply reducing herd size. Another option could be to intensify testing in a subpopulation of herds. However, while testing facilitates the definition of herd statuses and the implementation of early culling, it also is expensive and voluntary participation is difficult to sustain (Geraghty et al., 2014). More reliable diagnostic tests at animal and herd levels are still needed, as are an assessment of alternative testing schemes (Barkema et al., 2018). Finally, early culling could be preferentially performed in specific herds, especially accounting for herd location along the trade network and thus of their risk to (re)introduce MAP. Other criteria such as genomics data providing information on animal susceptibility to MAP infection also could be used to prioritize animals to be culled in addition to test results.

In conclusion, a focus on herds that have been accorded a low-risk status three years in a row has been shown to be a good solution to minimize the effort required to decrease MAP spread at a regional scale. These herds have a high probability of being MAP-free. However, animals purchased and introduced into these herds should have a high probability of being MAP-free, especially if purchases from outside the modelled metapopulation cannot be managed to limit the risk that the purchased animals are infected. Future studies should focus on identifying how to optimally target herds to combine as efficiently as possible at a regional scale risk-based animal trade, early culling of positive animals, and calf hygiene improvement, depending on the testing scheme implemented.

Conflict of interest statement

Declarations of interest: none.

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