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

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9

10 **Abstract**

11 Paratuberculosis is a worldwide disease mainly introduced through trade. Due to the low
12 sensitivity of diagnostic tests, it is difficult to protect herds from purchasing infected animals.

13 Our objective was to assess if rewiring trade networks to promote risk-based movements
14 could reduce the spread of *Mycobacterium avium* subsp. *paratuberculosis* (MAP) between

15 dairy cattle herds at a regional scale. Two levels of control strategies were assessed. At the
16 between-herd scale, trade rewiring aimed to prevent animals from high-risk herds moving

17 into low-risk herds. At the within-herd scale, complementary additional measures were
18 considered based on the herd infection status, aiming to limit the within-herd spread by

19 reducing calf exposure to adult faeces and culling more rapidly after positive test results. We
20 used a stochastic individual-based and between-herd mechanistic epidemiological model

21 adapted to the 12,857 dairy cattle herds located in Brittany, western France. We compared the
22 regional spread of MAP using observed trade movements against a rewiring algorithm

23 rendering trade movements risk-based. All females over two years old were tested. Based on
24 the results, and taking into account the low test sensitivity, herds were annually assigned one

25 of three statuses: A if the estimated true prevalence was below 7%, B if it ranged from 7 to

26 21%, C otherwise. We also identified herds with a high probability of being MAP-free (AAA
27 herds that had obtained an A status over three consecutive years) to assess the effect of
28 decreasing their risk of purchasing infected animals on MAP regional spread. We showed
29 that movement rewiring to prevent the sale of animals from high to low-prevalence herds
30 reduces MAP regional spread. Targeting AAA herds made it possible to minimize the control
31 effort to decrease MAP regional spread. However, animals purchased by AAA herds should
32 have a moderate to high probability of being MAP-free, especially if the risk of purchasing
33 animals from herds of unknown status cannot be managed. Improved hygiene and early
34 culling of positive animals were relevant complementary on-farm control options to further
35 decrease MAP spread. Future studies should identify how to define herd statuses to target
36 optimal control measure combinations that could reduce the spread of MAP on a regional
37 scale most effectively.

38

39 **Keywords (6 max)**

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

41

42 **Introduction**

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

50 The spread of MAP is hard to control in regions where the disease has become endemic
51 (Beaunée et al., 2017). Indeed, detecting MAP-infected animals is difficult due to the low
52 sensitivity of diagnostic tests (Barkema et al., 2018). The sensitivity of ELISA tests
53 classically performed in serum varies from 0.15 for young or latently infected animals to over
54 0.70 for heavy shedders (Nielsen & Toft, 2008). Animals typically become infected at an
55 early age (Windsor & Whittington, 2010). The infection often remains subclinical and
56 undetectable for several years (Magombedze et al., 2013) before the animals eventually
57 develop clinical signs (Mitchell et al., 2015). Shedding starts early and is intermittent,
58 varying in levels between animals and over the lifetime of an infected animal. Given the poor
59 sensitivity of diagnostic tests and the subclinical nature of the disease, it can be challenging to
60 identify positive animals as part of test-and-cull programmes to reduce within-herd spread or
61 pre-purchase testing measures to reduce between-herd spread (Camanes et al., 2018; More et
62 al., 2015).

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

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

75 could help farmers to improve the health status of their herds, thus increasing their
76 opportunities to sell their animals.

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

82

83 **Material and methods**

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

97

98 *Cattle demographic and movements*

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

106 We calculated herd size and demographic parameters (calf mortality, culling rate per age
107 group and per parity for cows, and births) using the comprehensive French database of cattle
108 detention and trade movements (Table S3). This database records the life history of all dairy
109 cattle from birth to death, including trade movements between farms. Each animal is defined
110 by a unique ID number, breed, date and farm of birth, sex, and all the farms it has belonged to
111 over its life, as well as the cause and date of entry into each farm (birth, purchase), and the
112 cause and date of exit from each farm (death, sale). Herd size was calibrated to 1 January
113 2005. Births were calculated per week per herd. Other demographic parameters were
114 calibrated for each herd-year.

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

120

121 *Within-herd epidemiological model*

122 At the within-herd scale, the epidemiological model is a stochastic discrete-time individual-
123 based model of MAP spread in a structured dairy cattle herd with year-long calving. This

124 model is fully described in Camanes et al. (2018). In brief, animals are defined by their age
125 (in weeks), health status, parity (for cows), and possible test results (see section on herd
126 statuses). Animals can be of six mutually exclusive age groups: newborns, unweaned calves,
127 weaned calves, young heifers, bred heifers, and cows, each of these groups being reared in a
128 specific environment of the farm. Animals change groups at a certain age or time of year.
129 Animals also are defined by their age or parity for cows, as well as by their health status:
130 susceptible (S), resistant (R), transiently infectious (I_T), latently infected (I_L), moderately
131 infectious (I_M), and highly infectious and possibly clinically affected (I_H). Susceptibility
132 decreases exponentially with age, and the rare infection events that may occur after one year
133 of age are neglected. Shedders belong to health statuses I_T , I_M , and I_H . Shedding during the
134 latent phase can barely be detected and thus is neglected. Shedders can shed MAP in
135 colostrum/milk (if they have calved) and in faeces. The quantity of MAP shed is
136 heterogeneous and depends on the animal's health status. Five transmission routes are
137 considered: *in utero*, via ingestion of contaminated colostrum, via ingestion of contaminated
138 milk, via an indirect contact with the local environment where susceptible animals are raised
139 and where infected animals of the same age group shed MAP, and finally via an indirect
140 contact with the farm environment whose level of contamination is influenced by all shedders
141 of the herd. MAP survives in the environment and thus indirect transmission is due to
142 infected animals held in the same farm but not necessarily at the same time. Transmission
143 from the farm environment is only considered indoors. Its probability is lower than the
144 transmission due to the local environment. During the pasture season (from April to mid-
145 November), animals older than six months of age are raised outdoors. They are only exposed
146 to MAP shed by infected animals from their own age group. We assumed farmers manage
147 calf hygiene so that - if the herd is infected - the true prevalence in adult females remains
148 below 60%, as mostly observed in the field. Since male calves are sold within a few weeks

149 after birth, they are not considered in the model. More details on the model and parameter
150 values are provided in Sup. Mat. §1.

151

152 *Between-herd epidemiological model*

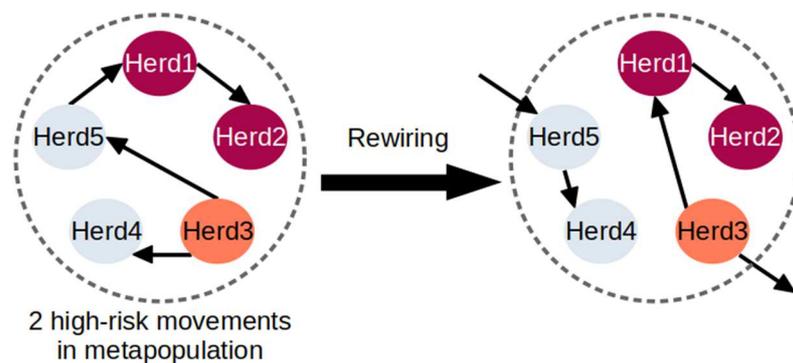
153 We applied the epidemiological model to the population and infection dynamics in each of
154 the 12,857 herds selected in the data. Trade movements connect herds in a data-driven
155 manner. When an animal is sold in the observed database, an animal in the same age group is
156 picked at random in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

168

169 *Trade movement rewiring algorithm accounting for MAP herd statuses*

170 The trade movement rewiring algorithm accounts for MAP herd statuses for connecting herds
171 through trade, and modifies some of the observed movements. Herds can purchase animals
172 only from herds of similar or lower risk infection statuses (e.g., with three statuses: Fig. 1, but
173 the algorithm can work with a greater or smaller number of statuses). To do so, we first listed

174 movements occurring over a 7-day time window (the model time step) in a given age group:
 175 less than 10 weeks, 11-26, 27-52, 53-91, 92-101, 102-111, 112-121, 122-130, and then per
 176 parity. We neglected the fact that batches of animals can be traded between two herds at a
 177 given date, as more than 85% of the weekly trade movements concerned only one or two
 178 animals. Comparing the observed and simulated distributions of the in and out-degree of the
 179 trade network showed that the impact of this simplification was low (Sup. Mat. §2, Fig. S1).
 180 In Brittany, dairy animals are mostly Holsteins, thus breed was not considered. Second, we
 181 distributed these movements according to the infection statuses of the selling and of the
 182 purchasing herds. Third, we identified high-risk movements (i.e., those from high-risk to low-
 183 risk herds). We switched them as much as possible with a relevant alternative. Unused low-
 184 risk movements were performed as observed. Fourth, for high-risk movements that cannot be
 185 switched (i.e., no relevant alternative available), the sold animal is culled and another animal
 186 is purchased from outside the modelled metapopulation with the same risk of being infected
 187 as in other movements coming from outside in the observed database. We assumed that
 188 movements coming from outside (external purchases) also are controlled. Thus, the
 189 probability of purchasing an infected animal from outside equals the average proportion of
 190 infected animals in the age group of the purchased animal in herds of similar or better
 191 infection statuses than the purchasing herd.



192

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

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

198

199 *Definition of herd statuses in Brittany*

200 In the model applied to Brittany, herd statuses were defined according to the capacity of
201 diagnostic tests to detect infected herds. Herds with a true prevalence (proportion of infected
202 animals among females older than 2 years) below 7% are in group A (can barely be detected
203 as infected), herds with a true prevalence between 7 and 21% are in group B, and herds with a
204 true prevalence above 21% are in group C (often have already had at least one animal
205 detected as highly positive). These thresholds were chosen in agreement with field
206 observations made by animal health services in Brittany. The chosen cut-offs enable the
207 population of herds to be divided into three groups of operational size, compatible with trade
208 organisation. In addition, unpublished preliminary work showed a good correlation between
209 tests results (combination of ELISA on bulk tank milk and tests of two environmental
210 samplings) and herd statuses. Herds with three negative tests had an apparent prevalence
211 lower than 3.5%, while those with three positive tests had an apparent prevalence higher than
212 10.5%. The associated true prevalence was estimated as twice as high as the apparent one due
213 to the sensitivity of the combined tests, leading to the chosen cut-offs.

214 To mimic a best-case situation, the herd statuses were based on the true and instantaneous
215 prevalence at the time of trade, and used to modulate movements. To mimic a more realistic
216 situation, herd statuses were defined once a year based on their apparent prevalence. A serum
217 antibody ELISA test was performed on each female older than 2 years. Test specificity was
218 assumed perfect. Test sensitivity varied among infection states: 0.15 for I_T and I_L , 0.47 for I_M ,
219 and 0.71 for I_H (Nielsen & Toft, 2008). The test was performed at a random date for each

220 herd between January and April each year, i.e., before the grazing period. The same
221 thresholds were used for herd statuses A, B, C as when defined based on true prevalence, but
222 using the “estimated true prevalence”. We calculated the number of test-positive animals per
223 health status, accounting for the status-specific test sensitivity. Then, we summed these
224 numbers weighted by their associated test sensitivity, and we divided the result by the
225 number of animals tested to have the estimated true prevalence. The misclassification rate
226 was established in a “no control” scenario by comparing the apparent herd status defined
227 once a year with the true herd status on the same date.

228 Finally, the number of trade movements to be rewired was expected to be considerable when
229 accounting for herd statuses of all herds, potentially rendering risk-based trade unachievable
230 in practice. We therefore focused on herds with three consecutive apparent low-risk annual
231 statuses (herds labelled AAA) compared to all other herds. Managing only purchases and
232 sales from AAA herds (other movements being kept as observed) was expected to be a good
233 compromise between a high probability for herds to be MAP-free and the number of herds
234 concerned to be sufficient so that AAA-related trade can be reorganised (enough relevant
235 alternative movements). We assessed the impact of erroneously purchasing infected animals
236 in AAA herds due to uncertainty about the status of selling herds. For that, we decreased this
237 risk in the model by artificially assigning cattle that were purchased by AAA herds a set
238 probability p of being MAP-free (5 cases: 0, 0.25, 0.5, 0.75, 1). This means that, in addition
239 to preferentially purchase animals from AAA herds, each animal purchased by AAA herds is
240 for sure not infected with probability p , and is picked at random among animals of the
241 relevant age group in the AAA source herd attributed by the rewiring algorithm with
242 probability $1-p$. In practice, this corresponds to implementing systematic tests before selling
243 (sellers’ awareness raising) or purchasing (buyers’ awareness raising) an animal, and then
244 combining this individual information with the knowledge of the status of the source herd to

245 provide to the animal a guarantee of not being infected in the form of a negative predictive
246 value. Movements among other herds are not modified, thus focusing the management effort
247 at a regional scale on much fewer herds. To also consider the case where such a AAA herd
248 status is not defined outside the modelled metapopulation, we compared two situations for
249 AAA external purchases: one in which these external incoming movements are managed
250 (same risk as if they were internal movements between AAA herds), and one in which they
251 are not (same risk as on average in the metapopulation).

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

258

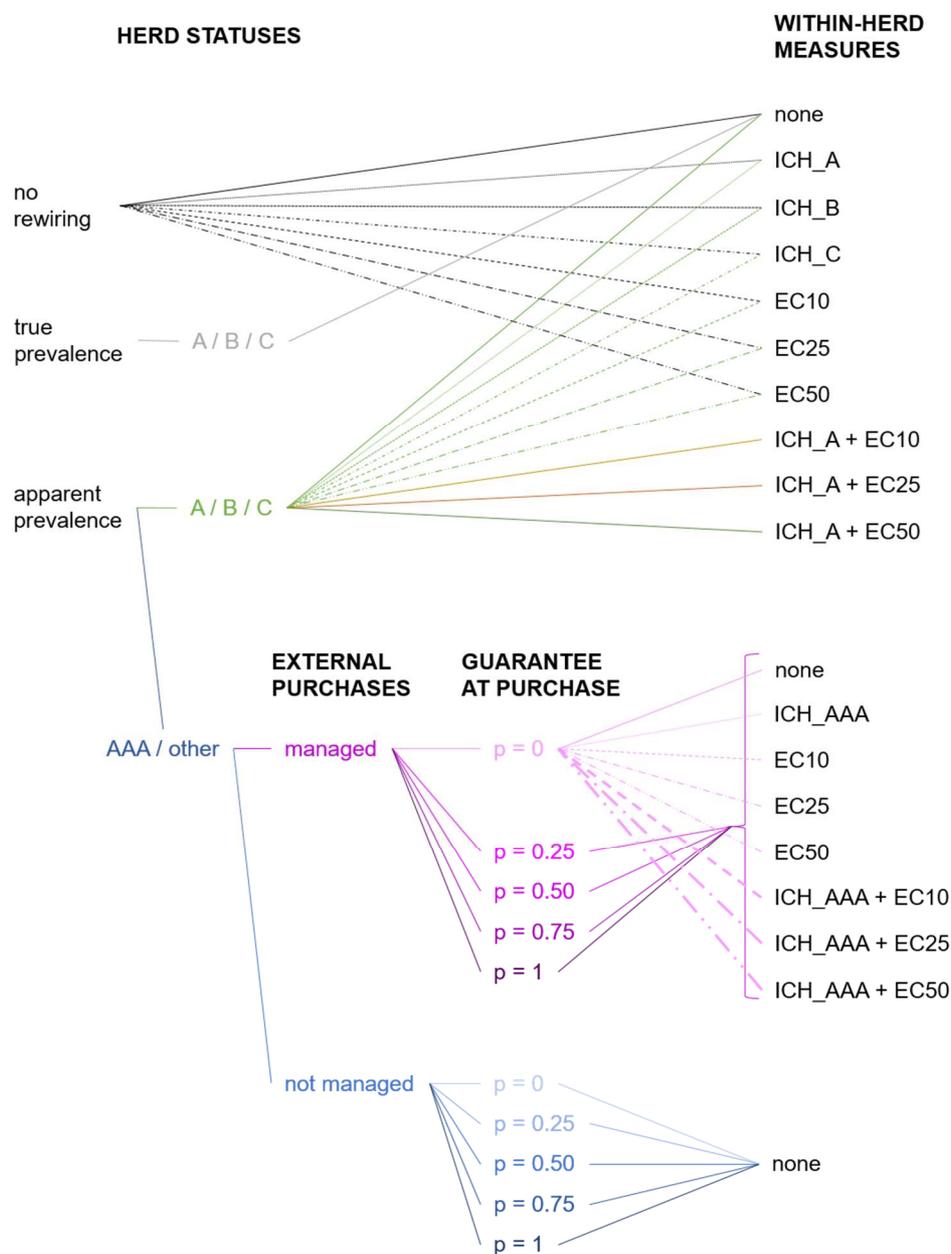
259 *Complementary within-herd control measures*

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

263 First, calf hygiene was improved in herds of a given status (A, B, C, or AAA) when herds
264 first reached the concerned infection status. For that, we modified the model parameter
265 governing calf exposure to farm environment from its initial value ($e = 0.35$, Table S1) to 0.1.
266 This mimics an incentive by collective animal health managers (such as regional animal
267 health services) to improve calf hygiene in targeted herds (those with a low-risk status, or on
268 the contrary those already encountering MAP issues) to help them control MAP spread
269 locally. Introducing such a measure in A herds is counterintuitive. It accounts for the fact that

270 some herds with an A status are indeed infected. Improving calf hygiene largely reduces the
 271 risk that these herds lose their A status if infected, increasing the probability of spontaneous
 272 fade-out of the infection.

273 Second, individual test results obtained once a year in each herd were associated with an
 274 early culling of part of the test-positive animals (within one month on average after the test
 275 result). Early culling was done irrespective of the herd status. We assumed that 10, 25, or
 276 50% of detected I_M and I_H animals were randomly chosen to be culled early.



277

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

284

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

292

293 *Model settings, initial conditions and model outputs*

294 Animal health services consider that roughly 40%, 40% and 20% of the herds in Brittany are
295 in statuses A, B, and C, respectively. To account for the heterogeneous probability for herds
296 to be in one status or another, the initial conditions were defined in three steps. First, we
297 randomly distributed herds in statuses to have 40% of herds in A, 40% in B, and 20% in C.
298 Second, we simulated nine years of MAP spread, which provided the within-herd prevalence
299 for each herd at the last time step. As a result, 33%, 43%, and 24% of the herds were in
300 statuses A, B, and C, respectively, using the true prevalence to define the initial status. This
301 new distribution is close to the initial one, but differs in that it better accounts for the
302 infection probability of each herd. Third, as herd size can vary in nine years, we used within-

303 herd simulations to associate each possible within-herd prevalence with a set of 100 realistic
304 distributions of animals among health statuses and age groups, according to herd size. One
305 distribution was drawn per simulated herd and kept similar among repetitions of the between-
306 herd model. Herds were assigned into the AAA category after having obtained their third A
307 status, including the initial one. This occurs before mid-year 2.

308 The model predicts over nine years (2005-2013), for each stochastic repetition and each
309 scenario, the following: the proportion of infected herds in the metapopulation each week, the
310 number of newly infected herds each week, the proportion of infected females older than 2
311 years per herd the first of January each year, and the number of herds per herd status each
312 week if the true prevalence is used, once a year at a date between the 1st of January and the
313 30th of April (i.e., when the test is performed). In addition, we calculated the cumulative
314 number of detected animals culled early, the cumulative number of herds improving calf
315 hygiene, and the cumulative number of rewired purchases. These three indicators reflect the
316 effort of control required for a given scenario. The model was developed in C++ Standard 11.
317 We simulated 10 stochastic repetitions for each scenario.

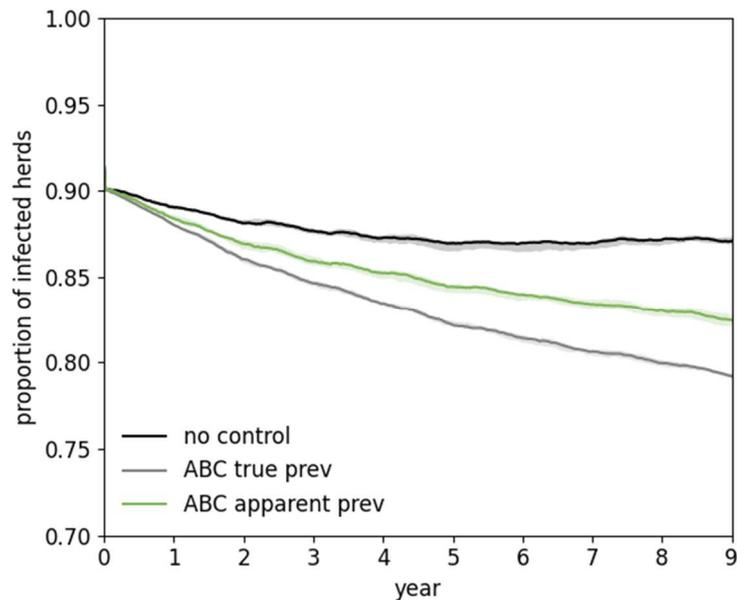
318

319 **Results**

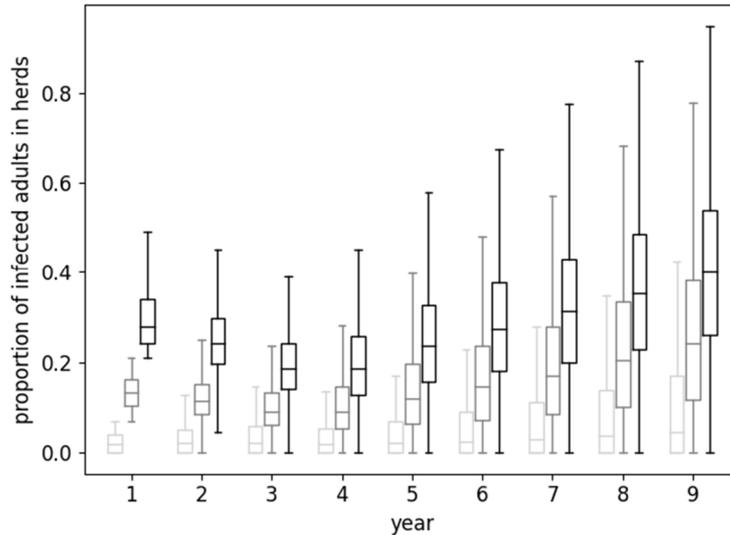
320 *Regional MAP spread without control implementation*

321 Starting from an endemic situation as observed in Brittany, 87% of the herds were
322 consistently infected if no additional control measure was implemented (scenario “no
323 control”, Fig. 3). New herds were regularly infected, indicating a regional circulation of MAP
324 with fade-out / recolonization events (Fig. S2). Irrespective of the initial herd status, the
325 proportion of infected females greater than two years of age progressively increased when no
326 control was implemented (Fig. 4). Most of the herds nevertheless kept a within-herd
327 prevalence lower than 60%, as observed in the area. In the observed trade network, there was

328 no evidence that farmers were making trade decisions based on limiting MAP risk (Tab. 1),
329 showing that the industry does not already control movements from high to low-risk farms
330 with regards to paratuberculosis. Without risk-based trade, 26% of the purchases by AAA
331 herds came from AAA herds, while AAA herds represented 33% of the herds on average.



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



339
 340 **Figure 4. Annual distribution of the proportion of infected females greater than two**
 341 **years of age, the first of January of each year, according to the initial true prevalence in**
 342 **that age group when no control measure is implemented** (light grey: initial herd status A
 343 (0-7% true prevalence), grey: initial herd status B (7-21%), black: initial herd status C
 344 (>21%)).

345
 346 **Table 1. Distribution of trade movements between pairs of herd statuses defined**
 347 **annually based on apparent prevalence in the no-control scenario.** Herd statuses are
 348 either A/B/C or AAA/others, without crossing. “Others” thus represents all herds that are not
 349 AAA. Because of this definition of herd statuses, movements between AAA and A/B/C herds
 350 cannot be counted. For AAA/other herd statuses, movements in the first two years are not
 351 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

352

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

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

359

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

True status \ Apparent status	Apparent 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

363

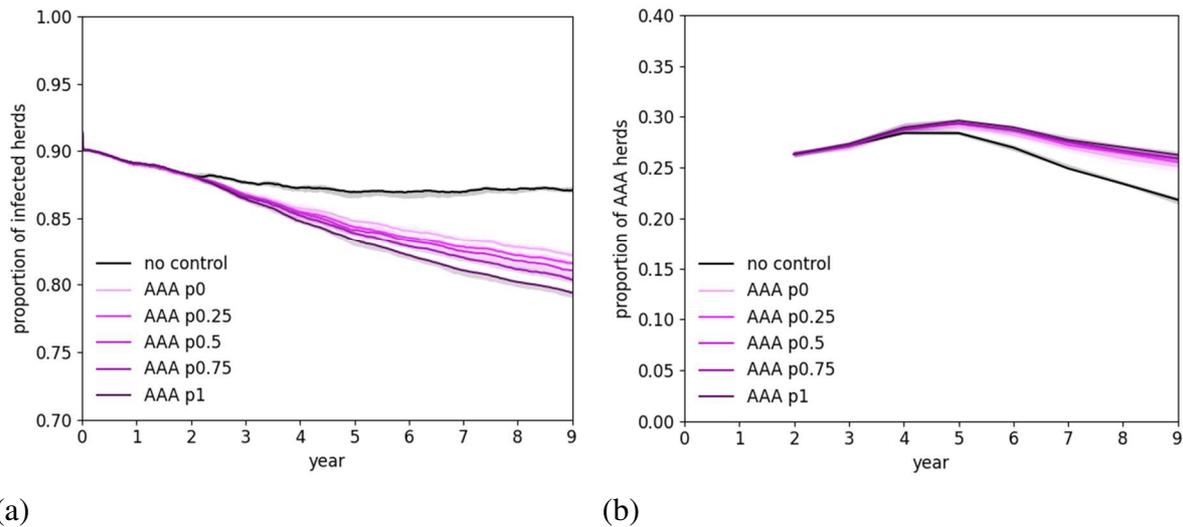
364 Trade movement rewiring to promote risk-based movements reduced MAP spread between
 365 dairy cattle herds at a regional scale when using A/B/C herd statuses. First, when herd
 366 statuses were defined based on the true and instantaneous prevalence the week the movement
 367 occurred (optimistic scenario, Fig. 3), herd prevalence decreased in nine years from 87% (no
 368 control) to 79%, and the cumulative herd incidence decreased from 1607 (no control) to
 369 1052, i.e., a decrease of 35% (Fig. S2). Second, when herd statuses A/B/C were defined more
 370 realistically once a year based on apparent prevalence, the impact of rewiring decreased, with
 371 herd prevalence only decreasing from 87% (no control) to 82% in nine years (Fig. 3), and a
 372 cumulative herd incidence decrease of 17% (Fig. S2).

373

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

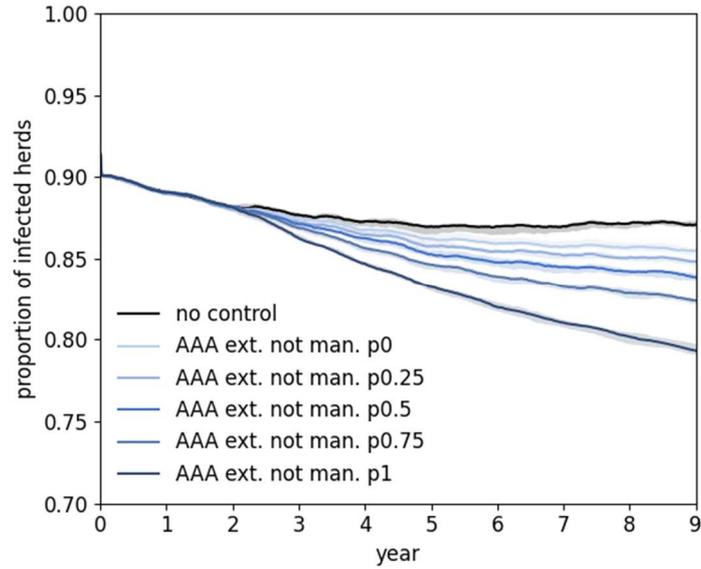
375 Here, herd statuses were defined yearly on apparent prevalence but using three consecutive
376 low-risk statuses (AAA vs. not AAA). It should be noted that 74% of AAA herds had a nil
377 apparent prevalence. Among herds truly AAA, 86% were classified as such, and 82% of
378 apparent AAA herds were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

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



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

403
404 In the situation where external purchases by AAA herds could not be managed, the impact of
405 movement rewiring was much lower, except when a perfect MAP-free guarantee could be
406 provided to animals purchased by AAA herds (Fig. 6). Using the algorithm, 83% of the
407 internal purchases by AAA herds came from AAA herds (Tab. 3), compared to 26% without
408 the algorithm (Tab. 1), highlighting the performance of the algorithm in reducing at-risk
409 movements also in this scenario.



410 **Figure 6. Proportion of MAP-infected herds in Brittany, western France, when**
 411 **movement control focuses on AAA herds but when external purchases are not managed.**
 412
 413 The scenario with no movement control (black) is compared to five scenarios where the
 414 probability (p) that AAA herds purchased disease-free animals varies (0, 0.25, 0.5, 0.75, 1).
 415 Status AAA is given to herds having three successive annual A statuses based on apparent
 416 prevalence among females over two years of age. The distribution for 10 stochastic
 417 repetitions is shown.

418
 419 **Table 3. Distribution of trade movements between pairs of herd statuses.** Herd statuses
 420 are defined annually based on apparent prevalence in the AAA risk-based movement scenario
 421 ($p=0$), and external purchases are not managed.

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

422
 423 *Complementary on-farm control measures to enhance the effect of risk-based movements*

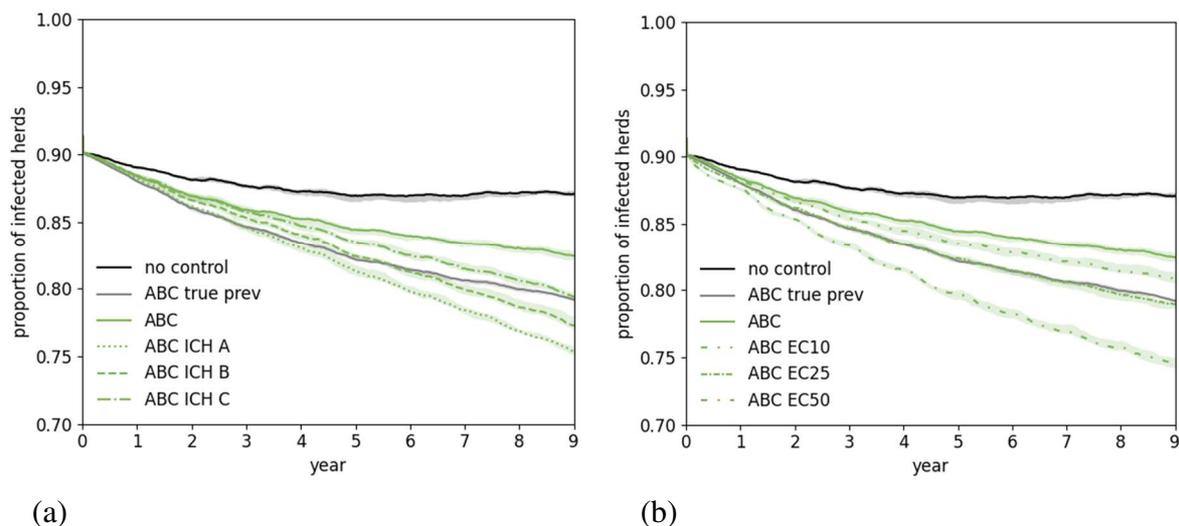
424 The effect of movement rewiring was quite limited alone, but herd prevalence sharply
425 decreased further when within-herd control measures also were implemented (Fig. 7-8, Fig.
426 S2, S3, S5). The effect of movement rewiring and of within-herd measures was mostly
427 additive (scenarios where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

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

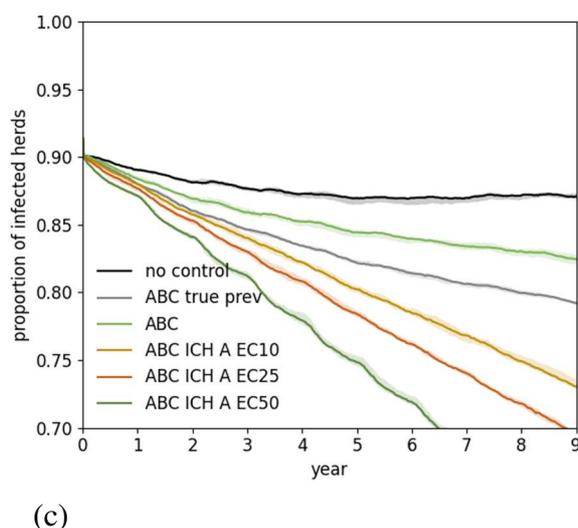
437 Combining risk-based movements using apparent A/B/C statuses with the early culling of
438 part of the test-positive animals also improved herd prevalence (Fig. 7b), especially when
439 half of the detected animals can be culled. When using AAA/other herd statuses, early culling
440 25% of test-positive animals gave comparable results to improving calf hygiene (Fig. 8a,b).

441

442



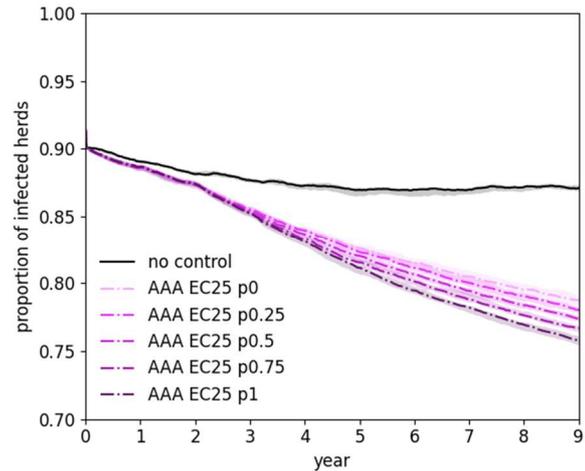
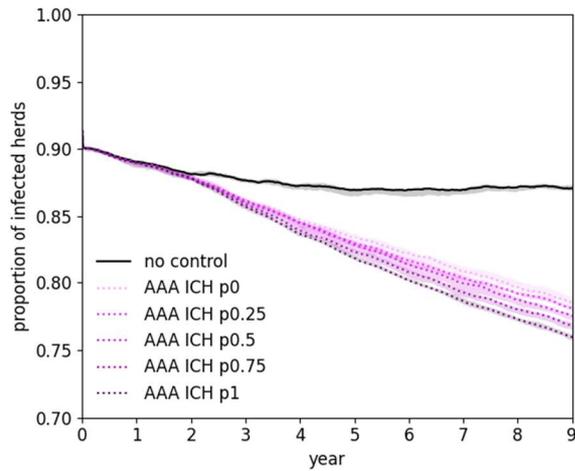
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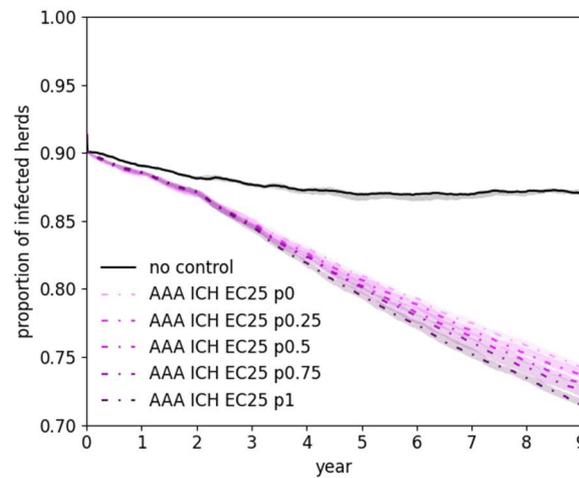
447 **Figure 7. Proportion of MAP-infected herds in Brittany, western France, according to**
 448 **the rewiring scenario, when using A/B/C herd statuses.** The scenario without control is
 449 compared to scenarios with risk-based movements. External purchases are managed. MAP
 450 herd statuses are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

455



456
457 (a)

(b)



458
459 (c)

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

468

469

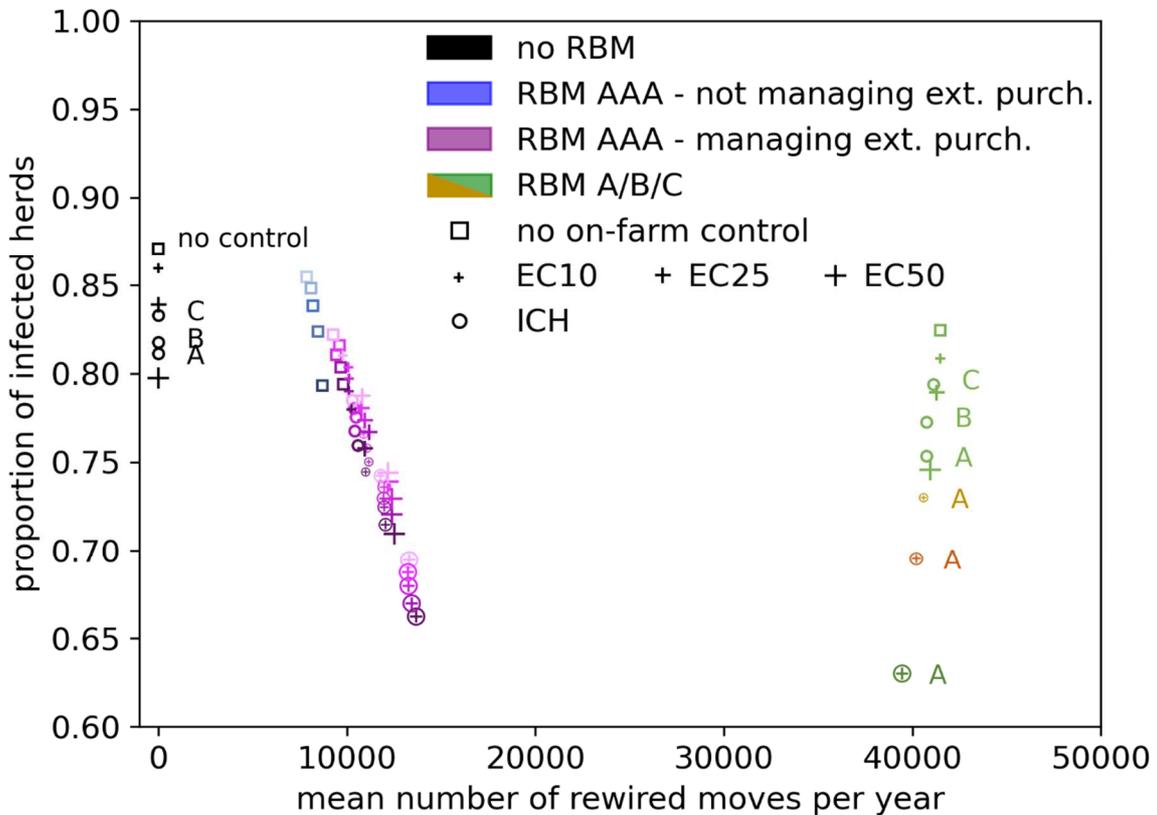
470 *Result synthesis*

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

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

- 492 • $p=0$ + EC 50% of test-positive animals (no ICH);
- 493 • $p=0$ + ICH + EC 25% of test-positive animals;
- 494 • $p=50%$ + ICH + EC of 10% of test-positive animals;

- 495 • $p=100%$ + ICH (no EC);
- 496 • $p=100%$ + EC 25% of test-positive animals (no ICH).



497

498 **Figure 9. Control effort in terms of number of purchases to be rewired annually to**

499 **decrease herd prevalence.** Each symbol shows the x and y medians for one of the 62

500 scenarios (the scenario A/B/C based on true prevalence is not shown). Different colours are

501 used to distinguished scenarios (same as in Fig. 2). Black: no movement rewiring;

502 green/brown: A/B/C statuses based on apparent herd prevalence (the letter indicates which

503 herd status is targeted for ICH), purple: AAA status with managing external purchases; blue:

504 AAA status without managing external purchases. Colour intensity corresponds to variations

505 in the probability that AAA herds purchased disease-free animals (from lighter $p=0$ to darker

506 $p=1$). Shapes differ according to the within-herd measures: coloured square: only movement

507 rewiring; dot: improved calf hygiene (ICH); cross: early culling (EC) of a proportion (10, 25

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

510

511 **Discussion**

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

519 It is important to account for the variation in test sensitivity among animal health statuses
520 (Nielsen & Toft, 2008) and to test all females over two years of age to define herd statuses in
521 the model. Indeed, in a preliminary work (Ezanno et al., 2021), an average test sensitivity
522 (0.20) was assumed and females 2.5 years old and over were tested. In this preliminary study,
523 the impact of risk-based movements on MAP regional spread was smaller, while the average
524 test sensitivity was the same. Indeed, herds with high shedders (I_M and I_H compared to I_L
525 which do not shed) were not better identified than herds with I_L only. In addition, younger
526 infected animals were missed.

527 Our modelling approach could help in the future to assess different testing schemes to define
528 MAP herd statuses and mobilize these statuses in trade management at a large scale. Testing
529 cows yearly using serum ELISA is frequently done in national and regional paratuberculosis
530 control programmes (Whittington et al., 2019), and thus was retained for the present study.
531 Together with milk ELISA and pooled faecal testing, serum ELISA was found to be one of
532 the most cost-effective options (Sergeant et al., 2018). Combining individual ELISA results

533 to classify herds as high and low risk based on the prevalence of infected animals with other
534 parallel testing options, such as faecal testing and bulk milk testing, could reduce
535 misclassifications due to poor test sensitivity (Sergeant et al., 2018). These testing options
536 have different sensitivities from serum ELISA. Tests also can be conducted more frequently
537 to make herd statuses more accurate.

538 Focusing on herds with a high probability to be MAP-free (AAA herds in our study)
539 permitted a smaller proportion of herds to be targeted while reaching comparable results, as
540 long as animals purchased from outside the modelled metapopulation (external purchases)
541 also were managed. The practical implementation of trade rewiring would be eased as AAA
542 herds represent around a third of the herds in Brittany and 13-20% of the purchases according
543 to scenarios. Ensuring that at least half of the animals purchased by AAA herds are not
544 infected should help reduce the regional herd prevalence and the number of newly infected
545 herds. However, such a guarantee at purchase is difficult to achieve (Whittington et al.,
546 2019). Further analyses are required to estimate more precisely the distribution of the risk of
547 selling infected animals per herd status and to identify the largest population of herds that
548 could be a source of animals for AAA herds.

549 Calf hygiene and management are known to impact MAP persistence in newly infected herds
550 (Lu et al., 2010; Marcé et al., 2011; Konboon et al., 2018) and to be crucial control levers
551 (Donat et al., 2016; Beaver et al., 2019; McAloon et al., 2019). Such measures also can target
552 highly infected herds to decrease their prevalence, and thus the risk of spreading MAP to
553 other herds (Whittington et al., 2019). However, there are many options to improve calf
554 hygiene, and their choice may vary over time at the farm level (Nielsen and Toft, 2011), as
555 well as between farms according to their characteristics (Donat et al., 2016). This is difficult
556 to represent in epidemiological models. Some available options also cannot be easily
557 implemented in the field in a large number of herds (Robinson et al., 2020). For example,

558 improving calf hygiene often requires changing farming practices. While this has been
559 highlighted as an important way to control MAP in infected herds (Doré et al., 2012,
560 Camanes et al., 2018), it is sometimes considered too costly to be used in practice (Sorge et
561 al., 2010).

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

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

579 Early culling test-positive animals also could be an option. Focusing only on the detected
580 highest shedders has been shown to have a small impact on herd prevalence and incidence,
581 especially because these animals are not very numerous and animal testing is performed only
582 once a year for practical reasons (More et al., 2015). This result was in line with previous

583 farm-scale studies, indicating that a test-and-cull performed on a yearly basis was not
584 sufficient to impact MAP spread in a herd, especially in herds with poor hygiene (Lu et al.,
585 2008, 2010; Robins et al., 2015; Konboon et al., 2018; Verteramo Chiu et al., 2018). In
586 addition, only test-positive females are culled. Animals born to these females detected as
587 positive also could be targeted by an early culling strategy, but this was previously shown as
588 not having a high impact on within-herd prevalence (Camanes et al., 2018). On the other
589 hand, we showed that early culling half of the detected animals irrespective of their shedding
590 level had a large impact despite the yearly testing, but it could jeopardize herd productivity
591 by sharply reducing herd size. Another option could be to intensify testing in a subpopulation
592 of herds. However, while testing facilitates the definition of herd statuses and the
593 implementation of early culling, it also is expensive and voluntary participation is difficult to
594 sustain (Geraghty et al., 2014). More reliable diagnostic tests at animal and herd levels are
595 still needed, as are an assessment of alternative testing schemes (Barkema et al., 2018).
596 Finally, early culling could be preferentially performed in specific herds, especially
597 accounting for herd location along the trade network and thus of their risk to (re)introduce
598 MAP. Other criteria such as genomics data providing information on animal susceptibility to
599 MAP infection also could be used to prioritize animals to be culled in addition to test results.

600 In conclusion, a focus on herds that have been accorded a low-risk status three years in a row
601 has been shown to be a good solution to minimize the effort required to decrease MAP spread
602 at a regional scale. These herds have a high probability of being MAP-free. However,
603 animals purchased and introduced into these herds should have a high probability of being
604 MAP-free, especially if purchases from outside the modelled metapopulation cannot be
605 managed to limit the risk that the purchased animals are infected. Future studies should focus
606 on identifying how to optimally target herds to combine as efficiently as possible at a

607 regional scale risk-based animal trade, early culling of positive animals, and calf hygiene
608 improvement, depending on the testing scheme implemented.

609

610 **Conflict of interest statement**

611 Declarations of interest: none.

612

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620

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